ALTACE® ramipril

PHARMACOLOGIC CLASSIFICATION:
Angiotensin Converting Enzyme Inhibitor

ACTION AND CLINICAL PHARMACOLOGY
ALTACE (ramipril) is an angiotensin converting enzyme (ACE) inhibitor.

Following oral administration, ALTACE is rapidly hydrolyzed to ramiprilat, its principal active metabolite.

INDICATIONS AND CLINICAL USE: *Essential Hypertension.* ALTACE (ramipril) is indicated in the treatment of essential hypertension. It may be used alone or in association with thiazide diuretics. ALTACE should normally be used in patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects. ALTACE can also be tried as an initial agent in those patients in whom use of diuretics and/or beta-blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. The safety and efficacy of ALTACE in renovascular hypertension have not been established and therefore, its use in this condition is not recommended. The safety and efficacy of concurrent use of ALTACE with antihypertensive agents other than thiazide diuretics have not been established.

Treatment Following Acute Myocardial Infarction
ALTACE is indicated following acute myocardial infarction in clinically stable patients with signs of left ventricular dysfunction to improve survival and reduce hospitalizations for heart failure. Sufficient experience in the treatment of patients with severe (NYHA class IV) heart failure immediately after myocardial infarction is not yet available. (See WARNINGS – Hypotension.)

MANAGEMENT OF PATIENTS AT INCREASED RISK OF CARDIOVASCULAR EVENTS: ALTACE may be used to reduce the risk of myocardial infarction, stroke or cardiovascular death in patients over 55 years of age who are at high risk of cardiovascular events because of a history of coronary artery disease, stroke, peripheral artery disease, or diabetes that is accompanied by at least one other cardiovascular risk factor such as hypertension, elevated total cholesterol levels, low high density lipoprotein levels, cigarette smoking, or documented microalbuminuria. The incidence of the primary outcome (composite of myocardial infarction, stroke and death from cardiovascular causes) was reduced from 17.8% in the placebo-treated group to 14.0% in the ramipril-treated group.

GENERAL: In using ALTACE consideration should be given to the risk of angioedema (see WARNINGS). **When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected ALTACE should be discontinued as soon as possible (see WARNINGS – Use in Pregnancy, and INFORMATION FOR THE PATIENT).**

CONTRAINDICATIONS: ALTACE (ramipril) is contraindicated in patients who are hypersensitive to this drug, or to any ingredient in the formulation, or in those patients who have a history of angioedema.

WARNINGS: *Angioedema:* Angioedema has been reported in patients with ACE inhibitors, including ALTACE (ramipril). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ALTACE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: Symptomatic hypotension has occurred after administration of ALTACE, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ALTACE should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ALTACE is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response may not be a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion in hypertensive patients. However, lower doses of ALTACE and/or reduced concomitant diuretic therapy should be considered. *In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of ALTACE (see ADVERSE REACTIONS – Treatment Following Acute Myocardial Infarction, DOSAGE AND ADMINISTRATION – Treatment Following Acute Myocardial Infarction).*

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ALTACE cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease. Use in Pregnancy: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ALTACE should be discontinued as soon as possible.

PRECAUTIONS: Renal Impairment: *As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Use of ALTACE should include appropriate assessment of renal function. ALTACE should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.*

Anaphylactoid Reactions during Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ALTACE. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS – Drug Interactions).

Surgery/Anesthesia: In patients undergoing surgery or anesthesia with agents producing hypotension, ALTACE may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume repletion.

Aortic Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Patients with Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with ALTACE (see ADVERSE REACTIONS). Should the patient receiving ALTACE experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of ALTACE should be considered when appropriate. There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ALTACE should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Pediatric Use: The safety and effectiveness of ALTACE in children have not been established; therefore use in this age group is not recommended.

Use in Elderly: Although clinical experience has not identified differences in response between the elderly (>65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Patient Alertness: ALTACE may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ALTACE, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Drug Interactions: Concomitant Diuretic Therapy: Hypotension may result but can be minimized by discontinuing diuretic or increasing salt intake prior to ramipril treatment and/or reducing initial dose. Agents increasing serum potassium: Use potassium sparing diuretics with caution and monitor frequently. Agents causing renin release: ALTACE antihypertensive effect increased. Lithium: Lithium levels may be increased. Administer lithium with caution and monitor levels frequently. Antacids: The bioavailability of ALTACE and the pharmacokinetics of ramiprilat were not affected. Digoxin: No change in ramipril, ramiprilat or digoxin serum levels. Warfarin: The co-administration of ALTACE with warfarin did not alter the anticoagulant effects. Acenocoumarol: No significant changes. Non-steroidal anti-inflammatory agents (NSAID): The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs (*e.g. indomethacin*).

ADVERSE REACTIONS: *Essential Hypertension.* Serious adverse events occurring in North American placebo-controlled clinical trials with ramipril monotherapy in hypertension (*n*=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); syncope (0.1%). Among all North American ramipril patients (*n*=1,244), angioedema occurred in patients treated with ramipril and a diuretic (0.1%). The most frequent adverse events occurring in these trials with ALTACE monotherapy in hypertensive patients (*n*=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); dyspnea (1.1%). Discontinuation of therapy due to clinical adverse events was required in 5 patients (0.8%). In placebo-controlled trials, an excess of upper respiratory infection and flu syndrome was seen in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ALTACE patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ALTACE monotherapy in North American controlled clinical trials (*n*=972) have required discontinuation because of cough.

Treatment Following Acute Myocardial Infarction
Adverse events (except laboratory abnormalities) in a controlled clinical trial of post-AMI patients with clinical signs of heart failure considered possibly/probably related to ALTACE and occurring in more than 1% of stabilized patients (n=1,004) were: hypotension (10.7%); increased cough (7.6%); dizziness/vertigo (5.6%); nausea/vomiting (3.8%); angina pectoris (2.9%); postural hypotension (2.2%); syncope (2.1%); heart failure (2.0); severe/resistant heart failure (2.0%); myocardial infarction (1.7%); vomiting (1.6%); headache (1.2%); abnormal kidney function (1.2%); abnormal chest pain (1.1%); diarrhea (1.1%). Isolated cases of death have been reported with the use of ramipril that appear to be related to hypotension (including first dose effects), but many of these are difficult to differentiate from progression of underlying disease (see WARNINGS – Hypotension). Discontinuation of therapy due to adverse reactions was required in 368/1,004 post-AMI patients taking ramipril (36.7%), compared to 401/982 patients receiving placebo (40.8%).

Clinical Laboratory Test Findings: increased creatinine; increases in blood urea nitrogen (BUN); decreases in hemoglobin or hematocrit; hyponatraemia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; proteinuria and significant increases in serum potassium.

DOSAGE AND ADMINISTRATION

Essential Hypertension: Dosage of ALTACE (ramipril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ALTACE may need to be adjusted.

Monotherapy: The recommended initial dosage of ALTACE in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ALTACE.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ALTACE and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ALTACE to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg of ALTACE should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ALTACE should subsequently be titrated (as described above) to the optimal response.

Use in Renal Impairment: For patients with a creatinine clearance below 40 mL/min/1.73 m^2 (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg of ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance below 10 mL/min/1.73 m^2) the maximum total daily dose of 2.5 mg of ALTACE should not be exceeded.

Treatment Following Acute Myocardial Infarction:
Initiation of therapy requires consideration of concomitant medication and baseline blood pressure and should be instituted under close medical supervision, usually in a hospital, three to ten days following an acute myocardial infarction in haemodynamically stable patients with clinical signs of heart failure. The recommended initial dosage of ALTACE is 2.5 mg given twice a day (b.i.d.), one in the morning and one in the evening. If tolerated, and depending on the patient's response, dosage may be increased by doubling at intervals of one to three days. The maximum daily dose of ALTACE should not exceed 5 mg twice daily (b.i.d). After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If a patient becomes hypotensive at this dosage, it is recommended that the dosage be lowered to 1.25 mg b.i.d. following effective management of the hypotension. (see WARNINGS – Hypotension).

Patients who have been fluid or salt depleted, or treated with diuretics are at an increased risk of hypotension (see WARNINGS – Hypotension). An excessive fall in blood pressure may occur particularly in the following: after the initial dose of ALTACE; after every first increase of dose of ALTACE; after the first dose of a concomitant diuretic and/or when increasing the dose of the concomitant diuretic. If appropriate, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension (see PRECAUTIONS – Drug Interactions). Consideration should be given to reducing the initial dose to 1.25 mg of ALTACE in these patients.

Use in Renal Impairment: In patients with impaired renal function (creatinine clearance of 20-50 mL/min/1.73 m^2 body surface area), the initial recommended dosage is generally 1.25 mg of ALTACE once daily. This dosage may be increased with caution up to 1.25 mg of ALTACE twice daily, depending upon clinical response and tolerability.

Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and severe renal failure. (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Renal Impairment).

Use in Hepatic Impairment: Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and hepatic dysfunction. Dose reduction and careful monitoring of these patients is required (see ACTIONS AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Patients with Impaired Liver Function).

Management of Patients at Increased Risk of Cardiovascular Events:
Recommended initial dose: 2.5 mg of ALTACE once daily. Depending on the tolerability, the dose is gradually increased. It is recommended to double the dose after one week of treatment and – after another three weeks – to increase it to 10 mg. Usual maintenance dose: 10 mg of ALTACE daily (see ACTION AND CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS). Dosage recommendations for special risk groups such as patients with renal or hepatic impairment, or at an increased risk of hypotension (fluid or salt depletion, treated with diuretics) are to be followed as previously described (see WARNINGS and PRECAUTIONS).

DOSAGE FORM

a) Composition
ALTACE (ramipril) capsules 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg contain the medicinal ingredient ramipril in quantities of 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg respectively. The qualitative formulation for all potencies of ALTACE is: ramipril, pre-gelatinized starch NF (as filler, gliding agent and disintegration agent) and empty gelatin capsules. Empty gelatin capsules for all potencies of ALTACE are composed of gelatin NF and coloring agents specific to each potency (see below).

POTENCY	CAP	BODY
1.25 mg	Yellow iron oxide Titanium dioxide	Titanium dioxide
2.5 mg	Yellow iron oxide FD & C red no. 3 Titanium dioxide	Titanium dioxide
5.0 mg	FD & C blue no. 2 FD & C red no. 3 Titanium dioxide	Titanium dioxide
10.0 mg	FD & C blue no. 2 FD & C red no. 3 Black iron oxide Titanium dioxide	Titanium dioxide

b) Stability and storage recommendations
Store ALTACE (ramipril) in original container at room temperature, below 25°C and not beyond the date indicated on the container.

AVAILABILITY: No. 4 hard gelatin capsules:
- 1.25 mg (white/yellow);
- 2.5 mg (white/orange);
- 5.0 mg (white/red);
- 10.0 mg (white/blue).

ALTACE capsules 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg are packaged in cartons of 30 (2 x 15 blister-packed) capsules. Bottles of 100 capsules and 500 capsules also available.

Product monograph available upon request.

References:
1. ALTACE Product Monograph. **2**. The Heart Outcomes Prevention Evaluation Study Investigators (HOPE) Trial. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342(3):145-53.

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Pr Rebif® 44 mcg x 3.

Interferon beta-1a

22 mcg /0.5mL and 44 mcg /0.5mL liquid formulation for injection

THERAPEUTIC CLASSIFICATION:
Immunomodulator

INDICATIONS AND CLINICAL USE:
Multiple Sclerosis: Rebif® is indicated for the treatment of relapsing forms of multiple sclerosis, to reduce the number and severity of clinical exacerbations, slow the progression of physical disability, reduce the requirement for steroids, and reduce the number of hospitalizations for treatment of multiple sclerosis and reduction in T_1-Gd enhanced and T_2 (burden of disease) as seen on MRI. Relapsing forms of multiple sclerosis include the subgroups of MS in which patients still experience recurrent attacks of neurological dysfunction including traditional RRMS but also SPMS patients still experiencing relapses. Although Rebif® did not affect progression of disability in SPMS, the clinical trial has shown that secondary progressive MS patients who still experience relapses, had a statistically significant improvement on relapse rate and on MRI measures of disease activity as compared to patients on placebo. Rebif® has not yet been investigated in patients with primary progressive multiple sclerosis and should not be administered to such patients.

CONTRAINDICATIONS:
Rebif® (Interferon beta-1a) is contraindicated in patients with a known hypersensitivity to natural or recombinant interferon beta, albumin (human), or any other component of the formulation. Rebif® is contraindicated in pregnant patients (see WARNINGS).

WARNINGS:
Rebif® (Interferon beta-1a) should be used under the supervision of a physician. The first injection should be performed under the supervision of an appropriately qualified health care professional.
Relapsing forms of Multiple Sclerosis: Depression: Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use, including Rebif®. Some association of increased depression has been noted with interferon use. However, clinical trial data with Rebif® has not shown an increase in depression compared to placebo-treated patients. Patients treated with Rebif® should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Rebif® and treated appropriately. Cessation of therapy with Interferon beta-1a should be considered. **Hepatic Injury:** Isolated, life-threatening cases of acute hepatic failure have been reported with Rebif® therapy. Symptomatic hepatic dysfunction, primarily presenting as jaundice, has been reported as a rare complication of Rebif® use. Several possible mechanisms may explain the effect of Rebif® on the liver (including direct toxicity, indirect toxicity via release of cytokines and/or autoimmunity). Asymptomatic elevations of transaminases (particularly ALT) is common with interferon therapy (see ADVERSE REACTIONS). Dose reduction or discontinuation should be considered if ALT rises 5 times above the ULN. **Anaphylaxis:** Anaphylaxis has been reported as a rare complication of Rebif® use. Other allergic reactions have included skin rash, angioedema, and urticaria, and have ranged from mild to severe without a clear relationship to dose or duration of exposure. Several allergic reactions, some severe, have occurred after prolonged use. **Pregnancy and Lactation:** Rebif® should not be administered in case of pregnancy and lactation. There are no adequate and well-controlled studies of Rebif® in pregnant women. In the clinical trials there were 2 spontaneous abortions observed and 5 fetuses carried to term among 7 women in the Rebif® groups. There have been cases of spontaneous abortion in the post-marketing setting. In cynomolgous monkeys administered doses approximately 2 times the cumulative weekly human dose (based on either body weight or surface area), Rebif® treatment has been associated with significant increases in embryolethal or abortifacient effects either during the period of organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or other evidence of teratogenesis noted in these studies; however, it is not known if teratogenic effects exist in humans. These effects are consistent with the abortifacient effects of other type I interferons. Patients should be advised about the abortifacient potential of Rebif®. **Fertile women receiving Rebif® should be advised to take adequate contraceptive measures.** It is not known if interferons alter the efficacy of oral contraceptives. Patients planning for pregnancy and those becoming pregnant should be informed of the potential hazards of interferons to the foetus and Rebif® should be discontinued (see CONTRAINDICATIONS and also PRECAUTIONS: Information to be provided to the patient). It is not known whether Rebif® is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made either to discontinue nursing or to discontinue Rebif® therapy. **Cardiac Disease:** Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation and continued therapy with Rebif®. Symptoms of the flu-like syndrome associated with Rebif® may prove stressful to patients with cardiac conditions.

PRECAUTIONS:
General: Patients should be informed of the most common adverse reactions associated with interferon beta administration, including symptoms of the flu-like syndrome (see ADVERSE REACTIONS). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment. Caution should be exercised when administering Rebif® (Interferon beta-1a) to patients with pre-existing seizures disorder. For patients without a pre-existing seizure disorder who develop seizures during therapy, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to continuing treatment with Rebif®. The effect of Rebif® administration on the medical management of patients with seizure disorder is unknown. Serum neutralising antibodies against Rebif® may develop. The precise incidence and clinical significance of antibodies is as yet uncertain (see ADVERSE REACTIONS). **Pediatric use:** There is no controlled clinical experience with Rebif® in children under 16 years of age with multiple sclerosis and therefore Rebif® should not be used in this population. **Patients with Special Diseases and Conditions:** Caution should be used and close monitoring considered when administering Rebif® to patients with severe renal failure, patients with severe myelosuppression, and patients with cardiac disease (see WARNINGS). **Drug Interaction:** No formal drug interaction studies have been conducted with Rebif® in humans. Interferons have been reported to reduce the activity of hepatic cytochrome p_{450}-dependent enzymes in humans and animals. Caution should be exercised when administering Rebif® in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome p_{450} system for clearance, e.g. antiepileptics and some classes of antidepressants. The interaction of Rebif® with corticosteroids or ACTH has not been studied systematically. Clinical studies indicate that multiple sclerosis patients can receive Rebif® and corticosteroids or ACTH during relapses. Rebif® should not be mixed with other drugs in the same syringe. **Laboratory Tests: Relapsing forms of multiple sclerosis:** Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, liver enzymes should be monitored at baseline, every month for the first 6 months and every 6 months thereafter (see WARNINGS). Complete and differential white blood cell counts, platelet counts and blood chemistries are also recommended during Rebif® therapy. These tests should be performed at baseline, months 1, 3 and 6, and every 6 months thereafter. Patients being treated with interferon beta may occasionally develop new or worsening thyroid abnormalities. Thyroid testing should be performed at baseline and every 6 months. In case of abnormal results or in patients with a past history of thyroid dysfunction, any necessary treatment and more frequent testing should be performed as clinically indicated (see ADVERSE REACTIONS).

ADVERSE REACTIONS:
Multiple Sclerosis: As with other interferon preparations, flu-like symptoms are not uncommon. The use of interferon beta may cause flu-like syndrome, asthenia, pyrexia, chills, arthralgia, myalgia, headache, and injection site reactions. Less frequent adverse reactions include cold sores, stuffy nose, light headedness, mucosal irritation, haematological disorders (leukopenia, lymphopenia, granulocytopenia), and alterations in liver function tests such as elevated AST and ALT. These effects are usually mild and reversible. Fever and flu-like symptoms can be treated with acetaminophen or ibuprofen. Depending on the severity and persistence of the side-effects, the dose may be lowered or temporarily interrupted, at the discretion of the physician. Most injection site reactions are mild to moderate. Allergic reactions, such as pruritus, rash, erythematous rash and maculo-papular rash may occur. Cases of skin ulceration/necrosis at the site of injection have been reported with long term treatment. Anaphylaxis has also been observed with the use of Rebif® (see WARNINGS). Serious adverse hepatic reactions such as hepatitis, with or without jaundice, have been rarely reported and isolated cases of acute hepatic failure have been reported (see WARNINGS). Occasional thyroid dysfunction, generally transient and mild, may occur during the first year of treatment, particularly in patients with pre-existing thyroiditis (see PRECAUTIONS: Laboratory Tests). The adverse events experienced during the first two years of the PRISMS study are listed below, by WHOART System Organ Class. The most common amongst the injection site reactions was in the form of mild erythema. The majority of the other injection site reactions were also mild in the 2 Rebif® groups. Necrosis was reported in 8 patients treated with Rebif®. Two of these patients were in the 66 mcg weekly and six in the 132 mcg weekly groups. All patients completed the planned treatment period, with only 1 requiring temporary dose reductions and another patient stopping treatment for 2 weeks. Those that required treatment, received antibiotics.

Proportion of Patients Enrolled in the PRISMS study Reporting Adverse Events During Years 1 and 2 of Treatment

Body System	Preferred term	Placebo	Rebif® 66 mcg weekly	Rebif® 132 mcg weekly
Application site disorders	Injection site inflammation (a)(b)	15.0%	65.6%	65.8%
	Injection site reaction (a)(b)	13.4%	31.2%	34.8%
	Injection site pain (b)	14.4%	20.1%	22.8%
Body as a whole - general disorders	Influenza-like symptoms	51.3%	56.1%	58.7%
	Fatigue	35.8%	32.8%	41.3%
	Fever (a)(b)	15.5%	24.9%	27.7%
	Leg pain	14.4%	10.1%	13.0%
	Rigors(b)(c)	5.3%	6.3%	13.0%
Centr. & periph. nervous system disorders	Headache	62.6%	64.6%	70.1%
	Dizziness	17.6%	14.3%	16.3%
	Paraesthesia	18.7%	19.6%	16.3%
	Hypoaesthesia	12.8%	12.2%	7.6%
Respiratory system disorders	Rhinitis	59.9%	52.4%	50.5%
	Upper Resp Tract Infection	32.6%	36.0%	29.3%
	Pharyngitis (b)	38.5%	34.9%	28.3%
	Coughing	21.4%	14.8%	19.0%
	Bronchitis	9.6%	10.6%	9.2%
Gastro-intestinal system disorders	Nausea	23.0%	24.9%	24.5%
	Abdominal pain	17.1%	22.2%	19.6%
	Diarrhoea	18.7%	17.5%	19.0%
	Vomiting	12.3%	12.7%	12.0%
Musculo-skeletal system disorders	Back pain	19.8%	23.3%	24.5%
	Myalgia	19.8%	24.9%	25.0%
	Arthralgia	17.1%	15.3%	19.0%
	Skeletal pain	10.2%	14.8%	9.8%
Psychiatric disorders	Depression	27.8%	20.6%	23.9%
	Insomnia	21.4%	19.6%	23.4%
White cell & res. disorders	Lymphopenia (a)(b)	11.2%	20.1%	28.8%
	Leucopenia (a)(b)(c)	3.7%	12.7%	22.3%
	Granulocytopenia (a)(b)	3.7%	11.6%	15.2%
	Lymphadenopathy	8.0%	11.1%	12.0%
Skin & appendages disorders	Pruritus	11.8%	9.0%	12.5%
Liver & biliary system disorders	ALT increased (a)(b)	4.3%	19.6%	27.2%
	AST increased (a)(b)(c)	3.7%	10.1%	17.4%
Urinary system disorders	Urinary tract infection	18.7%	18.0%	16.8%
Vision disorders	Vision abnormal	7.0%	7.4%	13.0%
Secondary terms	Fall	16.0%	16.9%	15.8%

(a) Significant difference between placebo and Rebif® 66 mcg weekly groups ($p \leq 0.05$)
(b) Significant difference between placebo and Rebif® 132 mcg weekly groups ($p \leq 0.05$)
(c) Significant difference between Rebif® 66 mcg and Rebif® 132 mcg weekly groups ($p \leq 0.05$)

In addition to the above listed adverse events, the following events have been experienced less frequently, in one or both of the relapsing-remitting multiple sclerosis studies: asthenia, fluid retention, anorexia, gastroenteritis, heartburn, paradentium affections, dental abcess or extraction, stomatitis, glossitis, sleepiness, anxiety, irritability, confusion, lymphadenopathy, weight gain, bone fracture, dyspnoea, cold sores, fissure at the angle of the mouth, menstrual disorders, cystitis, vaginitis. After 2 years, the placebo patients were switched to Rebif®, and along with the patients for the Rebif® treatment groups, they were treated for an additional two years. Listed below by WHOART System Organ Class, are the proportion of patients reporting the most common adverse events during years 3 and 4 of treatment. The results are similar to those obtained in the original phase of the study. The findings indicate that the incidence of interferon-related adverse events diminishes somewhat with continued exposure to the medication. Cases of necrosis were rare and not a cause of drop-out. For Rebif® 66 mcg weekly, there was one episode of skin necrosis per 92 years of exposure or per 14,100 injections. The comparable figures for Rebif® 132 mcg weekly are 1 episode of necrosis per 61 years of exposure or per 9,300 injections.

Proportion of Patients Reporting the Most Common Adverse Events During Years 3 and 4 of Treatment

Body system	Preferred term	Placebo/66 (n=85)	Placebo/132 (n=87)	Rebif® 66 mcg weekly (n=167)	Rebif® 132 mcg weekly (n=167)
Application site disorders	Injection site inflammation	65.9%	65.5%	56.9%	66.5%
	Injection site reaction	28.2%	37.9%	29.9%	31.7%
	Injection site pain	18.8%	21.8%	15.0%	13.8%
Body as a whole - general disorders	Influenza-like symptoms	42.4%	60.9%	50.3%	42.5%
	Fatigue	34.1%	36.8%	24.6%	27.5%
	Fever	14.1%	14.9%	15.6%	12.0%
	Leg pain	8.2%	12.6%	6.6%	7.8%
	Trauma	15.3%	5.7%	14.4%	11.4%
	Hypertonia	14.1%	11.5%	10.8%	9.6%
	Pain	4.7%	14.9%	4.2%	4.2%
Centr. & periph. nervous system disorders	Headache	44.7%	55.2%	46.7%	46.7%
	Dizziness	4.7%	11.5%	13.2%	12.6%
	Paraesthesia	15.3%	13.8%	10.2%	7.8%
	Hypoaesthesia	7.1%	13.8%	7.2%	9.0%
Respiratory system disorders	*Rhinitis*	38.8%	29.9%	39.5%	33.5%
	Upper Resp Tract Infection	18.8%	14.9%	22.8%	20.4%
	Pharyngitis	23.5%	12.6%	19.8%	15.0%
	Coughing	5.9%	11.5%	8.4%	13.8%
	Sinusitis	8.2%	11.5%	5.4%	10.2%
Gastro-intestinal system disorders	Nausea	12.9%	19.5%	10.8%	11.4%
	Abdominal pain	8.2%	16.1%	13.2%	10.8%
	Diarrhoea	5.9%	8.0%	12.0%	9.0%
	Constipation	14.1%	9.2%	6.0%	7.2%
Musculo-skeletal system disorders	Back pain	14.1%	20.7%	20.4%	22.2%
	Myalgia	21.2%	23.0%	15.6%	14.4%
	Arthralgia	16.5%	18.4%	12.6%	18.0%
	Muscle weakness	12.9%	17.2%	7.2%	9.6%
	Skeletal pain	8.2%	11.5%	7.2%	6.6%
Psychiatric disorders	Depression	29.4%	27.6%	23.4%	25.1%
	Insomnia	22.4%	21.8%	16.2%	21.6%
White cell & res. disorders	Lymphopenia	22.4%	23.0%	19.8%	25.7%
	Leucopenia	16.5%	14.9%	12.0%	13.8%
	Granulocytopenia	9.4%	10.3%	7.8%	12.0%
	Lymphadenopathy	2.4%	14.9%	8.4%	10.2%
Liver & biliary system disorders	ALT increased	11.8%	14.9%	13.8%	12.6%
Urinary system disorders	Urinary tract infection	8.2%	14.9%	16.2%	13.8%
Gastro-intestinal system disorders	Nausea (b)	26.3%	23.9%	17.6%	
	Abdominal pain	18.0%	14.8%	15.2%	
	Diarrhoea	15.6%	18.7%	13.7%	
	Constipation	19.0%	14.8%	13.2%	
Musculo-skeletal system disorders	Myalgia	23.9%	24.9%	27.9%	
	Arthralgia	25.4%	24.4%	23.0%	
	Back pain	22.4%	21.5%	22.1%	
	Muscle weakness	18.0%	17.2%	16.7%	
Psychiatric disorders	Depression	28.8%	32.1%	34.8%	
	Insomnia	22.0%	20.6%	23.5%	
White cell & res. disorders	Lymphopenia (b)	15.1%	21.5%	26.0%	
	Leucopenia (a)(b)(c)	4.9%	11.0%	21.1%	
	Granulocytopenia (a)(b)	2.0%	9.1%	13.2%	
Liver & biliary system disorders	ALT increased (a)(b)	7.3%	21.1%	23.0%	
	AST increased (a)(b)	3.4%	11.5%	13.2%	
Urinary system disorders	Urinary tract infection	26.3%	34.4%	27.0%	
	Cystitis	12.7%	17.2%	10.8%	
Vision disorders	Vision abnormal (a)(b)	11.7%	10.5%	4.9%	
Secondary terms	Traumas Nos	28.3%	24.9%	23.0%	

(a) Significant difference between placebo and Rebif® 66 mcg weekly groups (p=0.05)
(b) Significant difference between placebo and Rebif® 132 mcg weekly groups (p=0.05)
(c) Significant difference between Rebif® 66 mcg and Rebif® 132 mcg weekly groups (p=0.05)

Asymptomatic laboratory abnormalities were reported frequently with interferon dosing over the 4 years. Of the abnormalities noted, the cytopenias and abnormalities of liver function showed dose-related differences. Lymphopenia occurred in 35% of high-dose patients and 27% of low-dose patients. Thrombocytopenia was seen in 2.6% of patients on low-dose, and 8.2% of patients on high dose. Differences in the frequency of abnormal liver enzymes were seen which included elevated ALT (24% for low dose vs. 30% for high dose, p=0.07) and elevated AST (11% vs. 20%, p=0.03). Severe elevations are uncommon and not different between dose groups. These data suggest that there is only minimal evidence of significant dose-dependent lab abnormalities with interferon therapy in MS patients. After 4 years of therapy, 23.7% of the low dose and 14.3% of the high-dose patients had developed persistent neutralising antibodies (p=0.024, 44 mcg vs. 22 mcg), the vast majority of which (91%) developed within 24 months. The lower incidence in the high dose group may be due to the phenomenon of high-zone tolerance. While continuing interferon treatment, 20.0% of low-dose Nab+ patients reverted, while 25.7% of high-dose Nab+ patients reverted. The neutralising antibodies were associated with reduced clinical efficacy during years 3 and 4 and reduced MRI efficacy over 4 years. The table below presents adverse events that were reported in at least 10% of the patients in any treatment group of the SPECTRIMS study; the AEs are listed by WHOART System Organ Class and preferred term (sorted by preferred term in order of frequency). The most frequently reported adverse event was injection site inflammation, which occurred in 67% of both treated groups compared to 16% for placebo. Lower frequencies of the closely associated but more symptomatic injection site reactions were reported in 3 to 4 times as many treated patients as placebo patients. Injection site necrosis was seen in 3.3% and 8.8% of patients in the 22 mcg and 44 mcg groups respectively, but almost always as a single event per patient. The rate of necrosis was 1/3800 injections for high-dose and 1/9600 for low-dose therapy. Liver function abnormalities were also reported 3 to 4 times more commonly with active therapy. The haematopoietic system was also affected, with increased reports of leucopenia, granulocytopenia and lymphopenia associated with active therapy and most prominently with the higher dose. These haematopoietic abnormalities are expected side-effects of interferon therapy. Increased reports of anaemia and thrombocytopenia were noted with treatment, but these events occurred in less than 10% of patients.

Adverse Events Experienced by Patients Enrolled in the SPECTRIMS Study

Body System	Preferred term	Placebo	Rebif® 66 mcg weekly	Rebif® 132 mcg weekly
Application site disorders	Injection site inflammation (a)(b)	15.6%	66.5%	67.2%
	Injection site reaction (a)(b)(c)	7.8%	21.1%	31.9%
	Injection site pain	18.0%	17.2%	22.5%
	Injection site bruising (a)	16.1%	8.1%	9.8%
Body as a whole - general disorders	Influenza-like symptoms	52.2%	50.7%	49.5%
	Headache (c)	56.6%	52.2%	63.2%
	Fatigue (b)(c)	32.2%	33.0%	43.1%
	Fever (c)	11.7%	14.4%	19.1%
	Leg pain	9.3%	11.5%	12.3%
	Asthenia (c)	9.8%	5.7%	12.3%
Centr. & periph. nervous system disorders	Hypertonia	26.8%	24.4%	30.4%
	Dizziness	18.0%	16.3%	17.2%
	Paraesthesia	13.2%	8.1%	9.3%
	Hypoaesthesia	9.3%	10.0%	8.3%
Respiratory system disorders	Rhinitis	41.5%	38.3%	33.3%
	Upper Resp Tract Infection	33.2%	31.1%	26.0%
	Pharyngitis	20.0%	19.6%	17.2%

The data indicate that Rebif® is safe when administered chronically even at high dose. Furthermore, studies with Rebif® have included patients with disability ranging from none to severe, age ranging from 18 to 55 at study start and in the forms of MS (SPMS, RRMS) that comprise over 80% of all MS patients. In the ETOMS study adverse events were reported more frequently in patients assigned Rebif® than in those assigned placebo. These events included injection-site inflammation (60% vs. 12%), fever (28% vs. 12%), myalgia (17% vs. 9%) and chills (11% vs. 5%). Serious adverse events were reported in five patients in the placebo group and six in the Interferon beta-1a group.

DOSAGE AND ADMINISTRATION:

Relapsing Forms of Multiple Sclerosis: Before initiating a patient on Rebif® therapy, please review completely the *CONTRAINDICATIONS section of this Product Monograph. The recommended dose is 44 mcg given 3 times per week* by subcutaneous injection. The dose can be reduced to 22 mcg tiw if the patient is not able to tolerate the higher dose. Treatment should be initiated under supervision of a physician experienced in the treatment of the disease. When first starting treatment with Rebif®, in order to allow tachyphylaxis to develop thus reducing adverse events, it is recommended that 20% of the total dose be administered during the initial 2 weeks of therapy, 50% of total dose be administered in weeks 3 and 4, and the full dose from the fifth week onwards. Please also review the WARNINGS and PRECAUTIONS sections and ensure appropriate monitoring of patients with depression, hepatic dysfunction, a history of seizures, cardiac disease, renal dysfunction, thyroid dysfunction, myelosuppression, and female patients of child-bearing potential. Patients should be advised of Rebif®'s side-effects and instructed on the use of aseptic technique when administering Rebif®. The Rebif® Patient Leaflet should be carefully reviewed with all patients, and patients should be educated on self-care and advised to keep the Leaflet for continued reference during Rebif® therapy. At the present time, it is not known for how long patients should be treated. Safety and efficacy with Rebif® have been demonstrated following 4 years of treatment. Therefore, it is recommended that patients should be evaluated after 4 years of treatment with Rebif® and a decision for longer-term treatment be made on an individual basis by the treating physician.

Preparation of Solution: Liquid formulation: The liquid formulation in a pre-filled syringe is ready for use. These syringes are graduated to facilitate therapy initiation. The pre-filled syringes contain 22 mcg and 44 mcg of Rebif® respectively. The pre-filled syringes are ready for subcutaneous use only.

STABILITY AND STORAGE RECOMMENDATIONS: Liquid formulation: Refer to the date indicated on the labels for the expiry date. Rebif® liquid in a pre-filled syringe should be stored at 2-8°C. Rebif® syringes may be stored for a limited period at room temperature (up to 25°C), but not more than 1 month. Do not freeze.

AVAILABILITY OF DOSAGE FORM:

Rebif® is available as a liquid formulation, in pre-filled syringes. Two package strengths are available: 22 mcg /0.5mL and 44 mcg /0.5mL. The pre-filled syringes are supplied as single units, 3-packs and 12-packs. The pre-filled syringes are ready for subcutaneous use only.

The route of administration for Relapsing forms of Multiple Sclerosis is subcutaneous.

The Product Monograph is available upon request.

Serono Canada Inc., Oakville, Ontario, Canada L6M 2G2

If you have any questions, call:
The Multiple Support Program at 1-888-MS-REBIF® (1-888-677-3243)

References:

1. Rebif® product monograph. Serono Canada. November 2003
2. The PRISMS Study Group and University of British Columbia MS/MRI Analysis Group. PRISMS 4: long-term efficacy of interferon-beta-1a in relapsing MS. *Neurology* 2001; 56: 1628-1636.

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IMITREX DF
SUMATRIPTAN SUCCINATE

25mg, 50mg and 100 mg Tablet

IMITREX®

(sumatriptan succinate)

6 mg Subcutaneous Injection and Autoinjector

IMITREX®

(sumatriptan)

5 mg and 20 mg Nasal Spray

THERAPEUTIC CLASSIFICATION
Migraine Therapy

PHARMACOLOGIC CLASSIFICATION
5-HT_1 Receptor Agonist

Pharmacokinetics
Pharmacokinetic parameters following subcutaneous, oral or intranasal administration are shown in Table 1. Sumatriptan is rapidly absorbed after oral, subcutaneous and intranasal administration. The low oral and intranasal bioavailability is primarily due to metabolism (hepatic and presystemic) and partly due to incomplete absorption. The oral absorption of sumatriptan is not significantly affected either during migraine attacks or by food. Inter-patient and intra-patient variability was noted in most pharmacokinetic parameters assessed.

Table 1: Summary of Pharmacokinetic Parameters

Parameter	Subcutaneous	Oral	Intranasal
Bioavailability	96%	14%	16%
C_{max} (ng/mL)	6mg: 72 ng/mL	100mg: 50-60ng/mL 25mg: 18ng/mL	5mg: 4.7ng/mL 10mg: 8.5ng/mL 20mg: 14.4ng/mL
T_{max}	6mg: 15min	100mg: 0.5-5hr*	1-1.5hr
$T_{1/2}$	2hr (1.7-2.3hr)	2hr (1.9-2.2hr)	2hr (1.3-5.4hr)
Protein Binding	14-21%		
Volume of Distribution	170L		
Total Plasma Clearance	1160mL/min		
Renal Plasma Clearance	260mL/min		

* 70% to 80% of C_{max} values were attained within 30-45 minutes of dosing.

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure.

Non-renal clearance of sumatriptan accounts for about 80% of the total clearance. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the urine where it is present as a free acid (35%) and the glucuronide conjugate (11%). It has no known 5-HT_1 or 5- HT_2 activity. Minor metabolites have not been identified.

No differences have been observed between the pharmacokinetic parameters in healthy elderly volunteers compared with younger volunteers (less than 65 years old). Significant relief begins about 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.

INDICATIONS AND CLINICAL USES
IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) is indicated for the acute treatment of migraine attacks with or without aura.

IMITREX DF™ and IMITREX® is not for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

CONTRAINDICATIONS
IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive IMITREX DF™ and IMITREX® . Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS).

Because IMITREX DF™ and IMITREX® may increase blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension.

Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY AND PRECAUTIONS: Drug Interactions). Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because IMITREX DF™ and IMITREX® may also cause coronary vasospasm and these effects may be additive, the use of IMITREX DF™ and IMITREX® within 24 hours before or after treatment with other 5-HT_1 receptor agonists, or ergotamine-containing drugs or their derivatives (eg. dihydroergotamine, methysergide) is contraindicated.

IMITREX DF™ and IMITREX® should not be administered to patients with severe hepatic impairment.

IMITREX DF™ and IMITREX® is contraindicated in patients with hemiplegic, basilar, or ophthalmoplegic migraine.

IMITREX DF™ and IMITREX® is contraindicated in patients with hypersensitivity to sumatriptan or any of the ingredients of the formulations.

IMITREX® Injection should not be given intravenously because of its potential to cause coronary vasospasm.

WARNINGS
IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) should only be used where a clear diagnosis of migraine has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: **IMITREX DF™ and IMITREX® has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of IMITREX DF™ and IMITREX® . IMITREX DF™ and IMITREX® should not be given to patients who have documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that IMITREX DF™ and IMITREX® not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, IMITREX DF™ and IMITREX® should not be administered (see CONTRAINDICATIONS).**

For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of IMITREX DF™ and IMITREX® should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following IMITREX DF™ and IMITREX® administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations. Intermittent long term users of IMITREX DF™ and IMITREX® who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluations over the course of treatment. If symptoms consistent with angina occur after the use of IMITREX DF™ and IMITREX®, ECG evaluation should be carried out to look for ischemic changes.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to IMITREX DF™ and IMITREX® .

Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: IMITREX DF™ and IMITREX® can cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. The fact that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to IMITREX DF™ and IMITREX® use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With IMITREX DF™ and IMITREX® : Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral IMITREX DF™ and IMITREX®, two experienced clinical adverse events shortly after receiving oral IMITREX DF™ and IMITREX® that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous IMITREX DF™ and IMITREX®, there were eight patients who sustained clinical events during or shortly after receiving IMITREX DF™ and IMITREX® that may have reflected coronary artery vasospasm. Six of these eight patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these eight patients, four had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of IMITREX® nasal spray, one patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Postmarketing Experience With IMITREX DF™ and IMITREX® : Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX® Injection or IMITREX DF™ and IMITREX® Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by IMITREX DF™ and IMITREX® or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX DF™ and IMITREX® and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX DF™ and IMITREX® .

Cardiac events that have been observed to have onset within 1 hour of IMITREX DF™ and IMITREX® administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among reports from the USA of serious cardiac events occurring within 1 hour of IMITREX DF™ and IMITREX® administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

Cerebrovascular Events and Fatalities with 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous IMITREX DF™ and IMITREX®, and some have resulted in fatalities. The relationship of IMITREX DF™ and IMITREX® to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, IMITREX DF™ and IMITREX® having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. IMITREX DF™ and IMITREX® should not be administered if the headache being experienced is atypical for the patient. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given.

Special Cardiovascular Pharmacology Studies: In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increase in coronary resistance (~20%), and decrease in hyperemic myocardial blood flow (~10%) were noted. The relevance of these finding to the use of the recommended oral doses of this 5-HT_1 agonist is not known.

Similar studies have not been done with IMITREX DF™ and IMITREX®. However, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as IMITREX DF™ and IMITREX®. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS). Owing to the possibility of cross-reactive hypersensitivity reactions, IMITREX DF™ and IMITREX® should not be used in patients having a history of hypersensitivity to chemically-related 5-HT_1 receptor agonists. There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of IMITREX DF™ and IMITREX®. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.

Other Vasospasm Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of IMITREX DF™ and IMITREX® to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. IMITREX DF™ and IMITREX® is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS). In patients with controlled hypertension, IMITREX DF™ and IMITREX® should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

PRECAUTIONS
Cluster Headache: There is insufficient information on the efficacy and safety of IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) in the treatment of cluster headache, which is present in an older, predominantly male population. The need for prolonged use and the demand for repeated medication in this condition renders the dosing information inapplicable for cluster headache.

Cardiovascular: Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of IMITREX DF™ and IMITREX®. Because 5-HT_1 agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following IMITREX DF™ and IMITREX® should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following IMITREX DF™ and IMITREX® should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS AND WARNINGS).

Neurological Conditions: Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of IMITREX DF™ and IMITREX® .

Seizures: Caution should be observed if IMITREX DF™ and IMITREX® is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold.

Psychomotor Impairment: Patients should be cautioned that drowsiness may occur as a result of treatment with IMITREX DF™ and IMITREX®. They should be advised not to perform skilled tasks (e.g. driving or operating machinery) if drowsiness occurs.

Renal Impairment: The effects of renal impairment on the efficacy and safety of IMITREX DF™ and IMITREX® have not been evaluated. Therefore IMITREX DF™ and IMITREX® is not recommended in this patient population.

Hepatic Impairment: The effect of hepatic impairment on the efficacy and safety of IMITREX DF™ and IMITREX® has not been evaluated, however, the pharmacokinetic profile of sumatriptan in patients with moderate[1] hepatic impairment shows that these patients, following an oral dose of 50mg, have much higher plasma sumatriptan concentrations than healthy subjects (Table 2). Therefore, an oral dose of 25 mg may be considered in patients with hepatic impairment.

[1] Assessed by aminopyrine breath test (>0.2-0.4 scaling units).

Table 2: Pharmacokinetic Parameters After Oral Administration of IMITREX® 50 mg to Healthy Volunteers and Moderately Hepatically Impaired Patients

Parameter	Mean Ratio (hepatic impaired/healthy) n=8	90% CI	p-value
AUC_∞	181%	130 to 252%	0.009*
C_{max}	176%	129 to 240%	0.007*

* Statistically significant

The pharmacokinetic parameters of 6 mg subcutaneous sumatriptan do not differ statistically between normal volunteers and moderately hepatically impaired subjects. However, sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).

Drug Interactions: Single dose pharmacokinetic drug interaction studies have not shown evidence of interactions with propranolol, flunarizine, pizotifen or alcohol. Multiple dose interaction studies have not been performed. The pharmacokinetics of sumatriptan nasal spray were unaltered when preceded by a single clinical dose of the nasal decongestant xylometazoline (Otrivin™[2]).

[2] Trademark Ciba Self Medication

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of IMITREX DF™ and IMITREX® administration (see CONTRAINDICATIONS).

MAO Inhibitors: In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of IMITREX DF™ and IMITREX® in patients receiving MAO inhibitors is contraindicated (see CONTRAINDICATIONS, AND CLINICAL PHARMACOLOGY).

Other Serotonergic Drugs: Rare postmarketing reports describe patients with weakness, hyperreflexia, and incoordination following the combined use of a selective serotonin reuptake inhibitor (SSRI) and 5-HT_1 agonists. If concomitant treatment with IMITREX DF™/ IMITREX® and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline), tricyclic antidepressant, or other drug with serotonergic activity is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.

Other 5-HT_1 agonists: The administration of IMITREX DF™ and IMITREX® with other 5-HT_1 agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with co-administration of 5-HT_1 agonists, use of these drugs within 24 hours of each other is contraindicated.

Drug/Laboratory Test Interactions: IMITREX DF™ and IMITREX® are not known to interfere with commonly employed clinical laboratory tests.

Use in Elderly (>65 years): Experience of the use of IMITREX DF™ and IMITREX® in patients aged over 65 years is limited. Therefore the use of IMITREX DF™ and IMITREX® in patients over 65 years is not recommended.

Use in Children (<18 years): The safety and efficacy of IMITREX DF™ and IMITREX® in children has not been established and its use in this age group is not recommended.

Use in Pregnancy: Reproduction studies, performed in rats, have not revealed any evidence of impaired fertility, teratogenicity, or post-natal development due to IMITREX DF™ and IMITREX® . Reproduction studies, performed in rabbits by the oral route, have shown increased incidence of variations in cervico-thoracic blood vessel configuration in the foetuses. These effects were only seen at the highest dose tested, which affected weight gain in the dams, and at which blood levels were in excess of 50 times those seen in humans after therapeutic doses. A direct association with IMITREX DF™ and IMITREX® treatment is considered unlikely but cannot be excluded. Therefore, the use of IMITREX DF™ and IMITREX® is not recommended in pregnancy. In a rat fertility study, oral doses of IMITREX DF™ and IMITREX® resulting in plasma levels approximately 150 times those seen in humans after a 6 mg subcutaneous dose and approximately 200 times those seen in humans after a 100 mg oral dose were associated with a reduction in the success of insemination. This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 100 times those in humans by the subcutaneous route and approximately 150 times those in humans by the oral route.

To monitor maternal-foetal outcomes of pregnant women exposed to sumatriptan, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-336-2176.

Lactation: Sumatriptan is excreted in human breast milk. Therefore, caution is advised when administering IMITREX DF™ and IMITREX® to nursing women. Infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.

Binding to Melanin Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Because there could be an accumulation in melanin rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long term ophthalmologic effects.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with IMITREX DF™ and IMITREX®.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Experience in Controlled Clinical Trials with IMITREX DF™ and IMITREX®

Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 agonists, IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.

Acute Safety: In placebo-controlled migraine trials, 7,668 patients received at least one dose of IMITREX DF™ and IMITREX® (3095 oral, 1432 subcutaneous, 3141 intranasal). The following tables (Tables 3-5) list adverse events occurring in these trials at an incidence of 1% or more in any of the IMITREX DF™ and IMITREX® dose groups and that occurred at a higher incidence than in the placebo groups.

Table 3: Treatment-Emergent Adverse Events in Oral Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	IMITREX® 25 mg	IMITREX® 50 mg	IMITREX® 100 mg
Number of Migraine Attacks Treated	1187	945	1889	14750
Symptoms of Potentially Cardiac Origin				
• Chest Sensations*	0.6%	2.3%	2.6%	3.2%
• Neck/Throat/Jaw Sensations*	1.4%	2.3%	3.5%	5.2%
• Upper Limb Sensations*	1.2%	1.4%	2.5%	3.6%
• Palpitations	0.6%	0.3%	1.0%	1.1%
Neurological				
• Head/Face Sensations*	1.3%	2.3%	2.5%	4.7%
• Dizziness	2.5%	3.1%	3.3%	6.2%
• Headache	3.3%	4.0%	2.2%	3.3%
• Vertigo	0.6%	1.1%	1.1%	1.0%
• Drowsiness	1.6%	1.1%	1.2%	2.1%
• Tremor	0.4%	0.9%	0.4%	1.1%
Gastrointestinal				
• Nausea	5.8%	2.8%	4.4%	11.0%
• Hyposalivation	1.2%	1.4%	1.1%	1.2%
• Vomiting	2.9%	4.3%	1.1%	4.4%
• Gastrointestinal Discomfort & Pain	1.4%	1.1%	0.8%	2.0%
• Abdominal Discomfort & Pain	0.3%	NR	0.4%	1.2%
• Diarrhea	0.9%	0.3%	0.6%	1.1%
Musculoskeletal				
• Musculoskeletal Pain	0.7%	2.3%	0.4%	1.4%
• Muscle Pain	0.3%	0.9%	0.1%	1.0%
• Muscle Atrophy Weakness & Tiredness	NR	0.6%	0.4%	1.4%
Ear, Nose & Throat				
• Infections	0.6%	0.6%	1.1%	1.4%
• Nasal Signs & Symptoms	0.7%	1.4%	0.8%	1.0%
• Throat & Tonsil Symptoms	0.6%	NR	0.4%	2.3%
Respiratory				
• Viral Infection	0.3%	1.1%	0.1%	1.0%
Non-Site Specific				
• Limb Sensations*	0.4%	1.1%	0.4%	1.5%
• Sensations* (body region unspecified)	4.5%	5.7%	8.0%	9.0%
• Malaise/Fatigue	5.1%	3.7%	2.6%	9.5%
• Sweating	0.4%	0.6%	0.6%	1.6%

* The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
** Includes patients receiving up to 3 doses of 100mg
NR = Not Reported

Table 4: Treatment-Emergent Adverse Events in Subcutaneous Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	IMITREX® 6 mg
Number of Patients	615	1432
Number of Migraine Attacks Treated	742	2540
Symptoms of Potentially Cardiac Origin		
• Chest Sensations*	1.6%	5.7%
• Neck/Throat/Jaw Sensations*	1.3%	12.0%
• Upper Limb Sensations*	2.0%	6.8%
Neurological		
• Head/Face Sensations*	3.7%	16.6%
• Dizziness	3.7%	7.9%
• Headache	0.7%	3.4%
• Drowsiness	1.8%	2.9%
Gastrointestinal		
• Nausea	5.9%	9.4%
• Hyposalivation	2.8%	3.3%
Musculoskeletal		
• Muscle Atrophy Weakness & Tiredness	NR	1.7%
Ear / Nose and Throat		
• Throat & Tonsil Symptoms	0.3%	1.0%
Respiratory		
• Breathing Disorders	0.8%	1.3%
Non-Site Specific		
• Sensations* (body region unspecified)	15.9%	39.0%
• Injection Site Reactions	10.4%	24.7%
• Limb Sensations*	1.5%	6.0%
• Malaise/Fatigue	2.3%	4.7%
• Sweating	1.1%	1.7%
• Trunk Symptoms*	0.5%	1.4%

* The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
NR = Not Reported

Table 5: Treatment-Emergent Adverse Events in Intranasal Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	IMITREX® 5 mg	IMITREX® 10 mg	IMITREX® 20 mg**
Number of Patients	741	496	1007	1638
Number of Migraine Attacks Treated	1047	933	1434	2070
Symptoms of Potentially Cardiac Origin				
• Chest Sensations*	0.3%	1.0%	0.7%	0.6%
• Neck/Throat/Jaw Sensations*	1.2%	0.6%	1.6%	2.3%
Neurological				
• Head/Face Sensations*	0.8%	1.4%	2.4%	2.4%
• Dizziness	1.2%	1.6%	1.5%	1.2%
• Headache	0.7%	1.4%	0.9%	0.8%
• Migraine	2.6%	3.2%	2.4%	1.8%
Gastrointestinal				
• Nausea	10.4%	14.3%	9.6%	8.3%
• Vomiting	7.6%	11.1%	9.6%	6.8%
Ear, Nose & Throat				
• Sensitivity to Noise	3.1%	4.4%	2.5%	1.5%
• Nasal Signs & Symptoms	1.3%	3.0%	1.6%	1.8%
• Infections	0.9%	1.8%	1.3%	0.5%
• Upper Respiratory Inflammation	0.5%	1.0%	0.6%	0.7%
• Throat & Tonsil Symptoms	0.8%	0.2%	1.0%	0.7%
Non-Site Specific				
• Sensations* (body region unspecified)	1.8%	2.4%	2.7%	2.4%
• Malaise/Fatigue	1.3%	1.8%	1.3%	0.8%
• Descriptions of odor or taste	1.8%	15.3%	20.2%	20.8%

* The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
** Includes patients receiving up to 3 doses of 20mg

IMITREX DF™ and IMITREX® is generally well tolerated. Most of the events were transient in nature and resolved within 45 minutes of subcutaneous administration and within 2 hours of oral or intranasal administration.

Of the 3630 patients treated with IMITREX® Nasal Spray in clinical trials, there was one report of a coronary vasospasm related to IMITREX® administration.

Minor disturbances of liver function tests have occasionally been observed with sumatriptan treatment. There is no evidence that clinically significant abnormalities occurred more frequently with sumatriptan than with placebo.

Patients treated with IMITREX DF™ and IMITREX® rarely exhibit visual disorders like flickering and diplopia. Additionally cases of nystagmus, scotoma and reduced vision have been observed. Very rarely a transient loss of vision has been reported. However, visual disorders may also occur during a migraine attack itself.

DOSAGE AND ADMINISTRATION

General:

IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) is indicated for the acute treatment of migraine headache with or without aura. Sumatriptan should not be used prophylactically. Sumatriptan may be given orally, subcutaneously or as a nasal spray. The safety of treating an average of more than four headaches in a 30 day period has not been established.

In selecting the appropriate formulation for individual patients, consideration should be given to the patient's preference for formulation and the patient's requirement for rapid onset of relief. Significant relief begins about 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.

In addition to relieving the pain of migraine, sumatriptan (all formulations) has also been shown to be effective in relieving associated symptoms of migraine (nausea, vomiting, phonophobia, photophobia). Sumatriptan is equally effective when administered at any stage of a migraine attack. Long term (12-24 months) clinical studies with maximum recommended doses of sumatriptan indicate that there is no evidence of the development of tachyphylaxis, or medication-induced (rebound) headache.

Tablets:

The minimal effective single adult dose of IMITREX DF™ Tablets is 25mg. The maximum recommended single dose is 100 mg.

The optimal dose is a single 50mg tablet. However, depending on individual patient's needs and response to treatment, some patients may require 100mg.

Clinical trials have shown that approximately 50 - 75% of patients have headache relief within two hours after oral dosing with 100mg, and that a further 15 - 25% have headache relief by 4 hours. Comparator studies have shown similar efficacy rates with the 50mg and 100mg tablets. There is evidence that doses of 50 and 100mg may provide greater effect than 25mg.

If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 200mg should be taken in any 24 hour period.

If a patient does not respond to the first dose of IMITREX DF™ Tablets, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX DF™ and IMITREX® may be taken to treat subsequent migraine attacks.

The tablet should be swallowed whole with water, not crushed, chewed or split.

Hepatic Impairment

In patients with mild or moderate hepatic impairment, plasma sumatriptan concentrations up to two times those seen in healthy subjects have been observed. Therefore, a 25 mg dose (single tablet) may be considered in these patients (see PRECAUTIONS). Sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).

Injection

IMITREX® Injection should be injected subcutaneously (on the outside of the thigh or in the upper arm) using an autoinjector.

The recommended adult dose of sumatriptan is a single 6 mg subcutaneous injection.

Clinical trials have shown that approximately 70-72% of patients have headache relief within one hour after a single subcutaneous injection. This number increases to 82% by 2 hours.

If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 1 hour. Not more than 12 mg (two 6 mg injections) should be taken in any 24 hour period.

If a patient does not respond to the first dose of IMITREX® Injection, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX® may be taken for subsequent attacks.

Administration during migraine aura prior to other symptoms occurring may not prevent the development of a headache.

Patients should be advised to read the patient instruction leaflet regarding the safe disposal of syringes and needles.

Nasal Spray

The minimal effective single adult dose of sumatriptan nasal spray is 5mg. The maximum recommended single dose is 20mg.

If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 40mg should be taken in any 24 hour period.

In clinical studies totalling 3693 patients, optimal rates of headache relief were seen with the 20mg dose. Single doses above 20mg should not be used due to limited safety data and lack of increased efficacy relative to the 20mg single dose. Within the range of 5-20 mg, an increase in dose was not associated with any significant increase in the incidence or severity of adverse events other than taste disturbance (See ADVERSE REACTIONS).

The nasal spray should be administered into one nostril **only**. The device is a ready to use single dose unit and **must not** be primed before administration. Patients should be advised to read the patient instruction leaflet regarding the use of the nasal spray device before administration.

COMPOSITION

IMITREX DF™ Tablets contain 100 mg, 50 mg or 25 mg sumatriptan (base) as the succinate salt. IMITREX DF™ Tablets also contain croscarmellose sodium, iron oxide red (100mg only), dibasic calcium phosphate anhydrous, sodium bicarbonate, magnesium stearate, methylhydroxypropyl cellulose, microcrystalline cellulose, titanium dioxide, and triacetin.

IMITREX® Injection contains 6 mg sumatriptan (base) as the succinate salt in an isotonic sodium chloride solution containing water for injection.

IMITREX® Nasal Spray contains 5 mg, or 20 mg of sumatriptan base (as the hemisulphate salt formed *in situ*) in an aqueous buffered solution containing anhydrous dibasic sodium phosphate, monobasic potassium phosphate, purified water, sodium hydroxide and sulphuric acid.

AVAILABILITY OF DOSAGE FORMS

IMITREX DF™ Tablets are available as pink 100mg, white 50mg, or white 25mg film-coated tablets in blister packs containing 6 tablets.

IMITREX® Injection (6mg; total volume = 0.5 mL) is available in prefilled syringes placed in a tamper-evident carrying/disposal case. Two pre-filled syringes plus an IMITREX STATdose Pen™ autoinjector are packed in an IMITREX STATdose System™ autoinjector kit. A refill pack is available containing 2 pre-filled syringes in a carton.

IMITREX® Injection is also available to physicians or hospitals in a single dose vial (6mg; total volume = 0.5 mL). There are 5 vials per carton.

IMITREX® Nasal Spray 5 mg and 20 mg are each supplied in boxes of 6 nasal spray devices (3 X 2 devices). Each unit dose spray supplies 5 and 20 mg, respectively.

Product Monograph available to physicians and pharmacists upon request.

Please contact GlaxoSmithKline Inc., 7333 Mississauga Road N., Mississauga, Ontario L5N 6L4.

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Date of preparation: January 17, 1992
Date of revision: May 07, 2004

References: 1. Walls C *et al.* Pharmacokinetic profile of a new form of sumatriptan tablets in healthy volunteers. *Current Medical Research and Opinion* 2004;20(6):803-809. **2.** Carpay J *et al.* Efficacy and tolerability of sumatriptan tablets in a fast-disintegrating, rapid-release formulation for the acute treatment of migraine: results of a multicenter, randomized, placebo-controlled study. *Clin Therapeutics* 2004;26(2):214-223. **3.** Product Monograph IMITREX DF™/IMITREX® (sumatriptan succinate/sumatriptan) GlaxoSmithKline Inc. May 2004.

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7333 Mississauga Road North
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See IBC

NEW Pr

Keppra® levetiracetam

CONNECTING EXCELLENT PROFILES IN EFFICACY AND TOLERABILITY

PRESCRIBING INFORMATION

Tablets of 250 mg, 500 mg, and 750 mg
Therapeutic classification: Antiepileptic

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Levetiracetam is a drug of the pyrrolidine class chemically unrelated to existing antiepileptic drugs (AEDs). Levetiracetam exhibits anti-seizure and antiepileptogenic activity in several models of chronic epilepsy in both mice and rats, while being devoid of anticonvulsant activity in the classical screening models of acute seizures.

The mechanism of action of levetiracetam has not yet been fully established, however, it appears to be unlike that of the commonly used AEDs. *In vitro* studies show that levetiracetam, at concentrations of up to 10 μM did not result in significant ligand displacement at known receptor sites such as benzodiazepine, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites or second messenger systems. Furthermore, levetiracetam does not modulate neuronal voltage-gated sodium and T-type calcium currents and does not induce conventional facilitation of the GABAergic system.

Pharmacokinetics

Summary: Single- and multiple-dose pharmacokinetics of levetiracetam have included healthy volunteers, adult and pediatric patients with epilepsy, elderly subjects, and subjects with renal and hepatic impairment. Results of these studies indicate that levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance

receptor sites such as benzodiazepine, GABA (gamma-
butyric acid), glycine, NMDA (N-methyl-D-aspartate), re-
sites or second messenger systems. Furthermore,
acetam does not modulate neuronal voltage-gated sodium
type calcium currents and does not induce conventional
tion of the GABAergic system.

acokinetics

ary: Single- and multiple-dose pharmacokinetics of levetiracetam have included healthy volunteers, adult and pediatric
ts with epilepsy, elderly subjects, and subjects with renal and
c impairment. Results of these studies indicate that
acetam is rapidly and almost completely absorbed after oral
stration. The pharmacokinetic profile is linear with low intra-
er-subject variability. There is no modification of the clearance
epeated administration. Food does not affect the extent of
tion of levetiracetam, although the rate is decreased.
acetam is not protein-bound (< 10% bound) and its volume of
ution is close to the volume of intracellular and extracellular
Sixty-six percent (66%) of the dose is renally excreted
nged. The major metabolic pathway of levetiracetam (24% of
se) is an enzymatic hydrolysis of the acetamide group. It is not
ytochrome P450 dependent. The metabolites have no known
acodynamic activity and are renally excreted. Plasma half-life
etiracetam across studies is 6-8 hours. Plasma half-life is
sed in subjects with renal impairment, and in the elderly
ly due to impaired renal clearance.

on its pharmacokinetic characteristics, levetiracetam is
y to produce or to be subject to metabolic interactions.
armacokinetic profile is comparable in healthy volunteers and
ents with epilepsy.
its complete and linear absorption, plasma levels can be
ed from the oral dose of levetiracetam expressed as mg/kg
eight. Therefore, there is no need for plasma level monitoring
iracetam.

n Pharmacology

acokinetics: The pharmacokinetics of levetiracetam have
haracterized in single and multiple dose PK studies, with doses
5000 mg; these studies included healthy volunteers (n = 98),
ts with epilepsy (n = 58 adult patients and n = 24 pediatric
ts), elderly subjects (n = 16) and subjects with renal and
impairment (n = 36 and 16, respectively).

otion and Distribution: Levetiracetam is rapidly and almost
etely absorbed after oral administration. The oral
ilability of levetiracetam tablets is 100%. Plasma peak
ntrations (C_{max}) are achieved at 1.3 hours after dosing. The
of absorption is independent of both dose and the presence
, but the latter delays T_{max} by 1.5 hours and decreases C_{max} by
The pharmacokinetics of levetiracetam are linear over the dose
f 500 – 5000 mg. Steady-state is achieved after two days of
e daily administration schedule. Mean peak concentrations
are 31 and 43 μg/mL, respectively, following a single 1000 mg
nd a repeated 1000 mg twice daily dose.

r levetiracetam nor its primary metabolite is significantly
to plasma proteins (< 10%). The volume of distribution of
acetam is approximately 0.5 to 0.7 L/kg, a value that is close
total body water volume. No tissue distribution data for
s are available.

olism: Levetiracetam is not extensively metabolized in
s. The major metabolic pathway is the enzymatic hydrolysis
acetamide group, which produces the pharmacologically
e carboxylic acid metabolite, ucb L057 (24% of dose). The
ction of this metabolite is not dependent on any liver
rome P450 isoenzymes and is mediated by serine esterase(s)
ous tissues, including blood cells. Two minor metabolites were
ied as the product of hydroxylation of the 2-oxo-pyrrolidine
% of dose) and opening of the 2-oxo-pyrrolidine ring in
n 5 (1% of dose). There is no evidence for enantiomeric
nversion of levetiracetam or its major metabolite.

ation: Levetiracetam plasma half-life in adults is 7 ± 1 hours
as unaffected by dose, route of administration or repeated
etiracetam plasma half-life in adults is 7 ± 1 hours
ed by dose, route of administration or repeated

Special Populations: *Elderly:* Pharmacokinetics of levetiracetam were evaluated in 16 elderly patients, ranging in age from 61-88 years, with 11 of the 16 patients aged 75 years of age or over with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of 500 mg bid for 10 days, total body clearance decreased by 38% and the half-life was increased about 40% (10 to 11 hours) when compared to healthy adults. This is most likely due to the decrease in renal function in these subjects. *Pediatrics (6 to 12 years):* Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after a single dose. The apparent clearance of levetiracetam adjusted to body weight was approximately 40% higher than in epileptic adults. *Gender:* Levetiracetam C_{max} and AUC were 20% higher in women (n = 11) compared to men (n = 12). However, clearances adjusted for body weight were comparable. *Race:* Formal pharmacokinetic studies of the effects of race have not been conducted. Because levetiracetam is primarily renally excreted and there are no known important racial differences in creatinine clearance, significant pharmacokinetic differences due to race are not expected.

Renal Impairment: Single dose pharmacokinetics were performed in 20 subjects with renal impairment (n = 7 mild/CL_{cr} of 50-79 mL/min; n = 8 moderate/CL_{cr} of 30-49 mL/min; n = 5 severe/CL_{cr} < 30 mL/min), and n = 11 matching healthy volunteers. Clearance of levetiracetam is correlated with creatinine clearance and levetiracetam pharmacokinetics following repeat administration were well predicted from single dose data. The apparent body clearance of the parent drug levetiracetam is reduced in patients with impaired renal function by approximately 40% in the mild group, 50% in the moderate group, and 60% in the severe renal impairment group. For the primary metabolite ucb L057, the decrease in clearance values from baseline was greater than that seen for the parent drug in all subject groups.

In anuric (end stage renal disease) patients, the apparent body clearance was approximately 30% compared to that of normal subjects. Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: A single-dose pharmacokinetic study was performed in 16 subjects with hepatic impairment (n = 5 mild/Child-Pugh Grade A; n = 6 moderate/Grade B; n = 5 severe/Grade C vs 5 healthy controls). For the mild and moderate subgroups neither mean nor individual pharmacokinetic values were clinically different from those of controls. In patients with severe hepatic impairment, mean apparent body clearance was 50% that of normal subjects, with decreased renal clearance accounting for most of the decrease. Patients with severe hepatic impairment thus require a reduced dosage of Keppra® (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Table 1:
Total Combined Incidence Rate for Each of the Three Categories of CNS Adverse Events in Placebo-controlled Add-on Clinical Trials.

Category of CNS adverse event	Keppra®* + AED therapy (n = 672)	Placebo + AED therapy (n = 351)
Somnolence and fatigue		
Somnolence	15%	10%
Asthenia	14%	10%
Behavioral/psychiatric symptoms		
Nonpsychotic[1]	14%	6%
Psychotic[2]	1%	0%
Coordination difficulties[3]	3%	2%

* Reflects Keppra® doses of 1000 mg, 2000 mg, 3000 mg, and 4000 mg per day.

[1] "Non-psychotic behavioral/psychiatric symptoms" encompasses the following terms: agitation, antisocial reaction, anxiety, apathy, depersonalization, depression, emotional lability, euphoria, hostility, nervousness, neurosis, personality disorder and suicide attempt.

[2] "Psychotic behavioral/psychiatric symptoms" encompasses the following terms: hallucinations, paranoid reaction, psychosis and psychotic depression.

[3] "Coordination difficulties" encompasses the following terms: ataxia, abnormal gait, incoordination.

See **ADVERSE EVENTS, Table 2,** for incidence rate of individual AEs contained within the categories.

Behavioral/psychiatric symptoms (including agitation, emotional lability, hostility, anxiety, etc.) have been reported approximately equally in patients with and without a psychiatric history.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. In a controlled study including a dose of 4000 mg, administered without titration, the incidence rate of somnolence during the first four weeks of treatment for patients receiving the high dose was 42%, compared to 21% for patients receiving 2000 mg/day.

Special Populations

Patients with Renal Impairment: Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, pharmacokinetic studies in renally-impaired patients indicate that apparent clearance is significantly

the primary metabolite ucb L057, the decrease in clearance values from baseline was greater than that seen for the parent drug in all subject groups.

In anuric (end stage renal disease) patients, the apparent body clearance was approximately 30% compared to that of normal subjects. Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: A single-dose pharmacokinetic study was performed in 16 subjects with hepatic impairment (n = 5 mild/Child-Pugh Grade A; n = 6 moderate/Grade B; n = 5 severe/Grade C vs 5 healthy controls). For the mild and moderate subgroups neither mean nor individual pharmacokinetic values were clinically different from those of controls. In patients with severe hepatic impairment, mean apparent body clearance was 50% that of normal subjects, with decreased renal clearance accounting for most of the decrease. Patients with severe hepatic impairment thus require a reduced dosage of Keppra® (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND CLINICAL USE

Keppra® (levetiracetam) is indicated as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra® (levetiracetam) tablets.

WARNINGS

Central Nervous System Adverse Events

Keppra® (levetiracetam) use is associated with the occurrence of central nervous system (CNS) adverse events; the most significant of these can be classified into the following categories: 1) somnolence and fatigue, 2) behavioral/psychiatric symptoms and 3) coordination difficulties.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. Somnolence/asthenia and coordination difficulties occurred most frequently within the first four weeks of treatment and usually resolved while patients remained on treatment. In the case of behavioral/psychiatric symptoms (including such adverse events as aggression, agitation, anger, anxiety, emotional lability, hostility, irritability), approximately half of the patients reported these events within the first four weeks, with the remaining events occurring throughout the duration of the trials. See also **PRECAUTIONS,** *Central Nervous System Adverse Events.*

Withdrawal of Anti-Epileptic Drugs

As with all antiepileptic drugs, Keppra® should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

General

Hematological Abnormalities: Minor but statistically significant decreases compared to placebo were seen in total mean RBC count, mean hemoglobin, and mean hematocrit in Keppra®-treated patients in controlled trials. For hemoglobin values, the percentage of Keppra® or placebo treated patients with possibly clinically significant abnormalities were less than 0.5% each. For hematocrit values, a total of 5.1% of Keppra® treated versus 3.2% of placebo patients had at least one possibly significant decrease in hematocrit (≤ 37% in males and 32% in females).

For white blood cells (WBC), 2.9% of treated versus 2.3% of placebo patients had at least one possibly clinically significant decrease in WBC count (≤ 2.8 x 10^9/L), while 2.6% of treated vs. 1.7% of placebo patients had at least one possibly significant decrease in neutrophil count (≤ 1.0 x 10^9/L). Of the Keppra®-treated patients

with a low neutrophil count, all but one experienced

neutrophil count (≤ 1.0 x 10^9/L). Of the Keppra®-treated patients

inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase

and w

Clinical Pharmacokinetic Data

Other Antiepileptic Drugs (AEDs): Potential drug interactions between Keppra® and other AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data suggest that levetiracetam may not significantly influence the plasma concentrations of these other AEDs, and that the other AEDs may not significantly influence the plasma concentrations of levetiracetam.

For two of these AEDs — phenytoin and valproate — formal pharmacokinetic interaction studies with Keppra® were performed. Keppra® was co-administered with either phenytoin or valproate at doses of 3000 mg/day and 1000 mg/day respectively. No clinically significant interactions were observed.

Other Drug Interactions

Oral Contraceptives: A pharmacokinetic clinical interaction study has been performed in healthy subjects between the oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgesterol, and the lowest therapeutic dose of Keppra® (500 mg bid). No clinically significant pharmacokinetic interactions were observed.

However, pharmacokinetic interaction studies using Keppra® as adjunctive therapy and covering the recommended dosage range, have not been conducted. Therefore, physicians should advise their female patients to be alert to any irregular vaginal bleeding or spotting, and to immediately report to them any occurrences.

Digoxin: Keppra® (1000 mg bid) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin: Keppra® (1000 mg bid) did not influence the pharmacokinetics of R and S warfarin (2.5 mg, 5 mg, or 7.5 mg daily). Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid: Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg bid. C_{ssmax} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid and the renal clearance of the metabolite ucb L057 was decreased by 60%; this alteration is likely related to competitive inhibition of tubular secretion of ucb L057. The effect of Keppra® on probenecid was not studied.

ADVERSE EVENTS

Commonly Observed

In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra® in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, dizziness and infection. Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first four weeks of treatment with Keppra®.

Incidence of AEs in Controlled Clinical Trials

Table 2:

Incidence (%) of Treatment-emergent Adverse Events in Placebo-controlled, Add-on Studies by Body System. (Adverse Events Occurred in at least 1% of Keppra®-treated Patients and Occurred More Frequently than Placebo-treated Patients.) (Studies N051, N052, N132 and N138)

Body system/ adverse event	Keppra®+ AED therapy (n = 672) (%)	Placebo + AED therapy (n = 351) (%)
Body as a whole		
Asthenia	14	10
Infection*	13	7
Digestive system		
Tooth disorders	2	1
Hemic and lymphatic system		
Ecchymosis	2	1
Nervous system		
Amnesia	2	0
Anxiety	2	1
Ataxia	3	1
Depression	4	2
Dizziness	9	4
Emotional lability	2	0
Hostility	2	1
Nervousness	4	2
Personality disorders	1	0
Somnolence	15	10
Thinking abnormal	2	1
Vertigo	3	1
Respiratory system		
Pharyngitis	6	4
Rhinitis	4	3
Sinusitis	2	1

* In levetiracetam-treated patients, the majority of "infection" events (93%) were coded to reported terms of "common cold" or "infection upper respiratory".

Additional Events Observed in Placebo Controlled Trials

Lack of Dose-related Incidence within Therapeutic Range: Based on the data from the controlled clinical trials, there was no evidence of dose relationship within the recommended dose range of 1000 to 3000 mg/day.

Discontinuation or Dose Reduction in Well-controlled Clinical Studies: In well-controlled clinical studies, 14.3% of patients receiving Keppra® and 11.7% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (>1%) with discontinuation or dose reduction in either treatment group are presented in **Table 3.**

Table 3:

Adverse Events Most Commonly Associated with Discontinuation or Dose Reduction in Placebo-controlled Studies in Patients with Epilepsy

	Keppra® (n = 672)	Placebo (n = 351)
Asthenia	9 (1.3%)	3 (0.9%)
Headache	8 (1.2%)	2 (0.6%)
Convulsion	16 (2.4%)	10 (2.8%)
Dizziness	11 (1.6%)	0
Somnolence	31 (4.6%)	6 (1.7%)
Rash	0	5 (1.4%)

The overall adverse experience profile of Keppra® was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race.

Post-marketing Experience

In post-marketing experience, nervous system and psychiatric disorders have most frequently been reported. In addition to adverse reactions during clinical studies, and listed above, the following adverse reactions have been reported in post-marketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

Blood and lymphatic disorders: leukopenia, neutropenia, pancytopenia, thrombocytopenia.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms

The highest reported Keppra® overdose is approximately 10 times the therapeutic dose. In the majority of overdose cases, multiple drugs were involved. Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression, and coma were observed with Keppra® overdoses. The minimal lethal oral dose in rodents is at least 233 times the maximum clinically studied dose.

Treatment

There is no antidote for overdose with Keppra®; treatment is symptomatic and may include hemodialysis. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Standard hemodialysis procedures result in significant removal of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

General

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, reduced doses are recommended for patients with renal impairment.

Keppra® is given orally with or without food.

Adults

Treatment should be initiated at a dose of 1000 mg/day, given as twice daily dosing (500 mg bid). Depending on clinical response and tolerability, the daily dose may be increased every two weeks by increments of 1000 mg, to a maximum recommended daily dose of 3000 mg.

In clinical trials, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice a day dosing, were shown to be effective. Although there was a tendency toward greater response rate with higher dose, a consistent statistically significant increase in response with increased dose has not been shown. There are limited safety data from controlled clinical trials at doses higher than 3000 mg/day (approximately 40 patients), therefore these doses are not recommended.

Patients with Impaired Renal Function

Keppra® dosage should be reduced in patients with impaired renal function (see **Table 4** below). Patients with end stage renal disease should receive supplemental doses following dialysis. To use this dosing table, an estimate of the patient's CL_{cr} in mL/min is needed. CL_{cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$CL_{cr} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Table 4:

Dosing Adjustment for Patients with Impaired Renal Function

Group	Creatinine clearance (mL/min)	Dosage and frequency
Normal	≥ 80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe*	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis[1]	—	500 to 1000 mg once daily

[1] Following dialysis, a 250 to 500 mg supplemental dose is recommended.
* or according to best clinical judgement

Patients with Impaired Hepatic Function

No dose adjustment is needed in patients with mild-to-moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 70 mL/min.

Elderly Patients

Dose selection and titration should proceed cautiously in elderly patients, as renal function decreases with age.

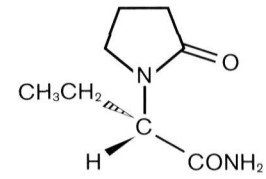
PHARMACEUTICAL INFORMATION

Drug Substance

U.S.A.N: levetiracetam

Chemical Name: (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide

Structural Formula:



Molecular Formula: $C_8H_{14}N_2O_2$

Molecular Weight: 170.21

Physical Form: A white to off-white crystalline powder with a faint odor and a bitter taste.

Solubility: It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane.

pKa and pH values: The pKa of levetiracetam is < -2 and cannot be determined with accuracy due to the chemical instability of the protonated form.

The protonation of ucb L059 starts at H_0 values between -1 and -2.

Partition Co-efficient: Δ log P ($\log P_{octanol} - \log P_{cyclohexane}$) was calculated at pH 7.4 using phosphate buffered saline and at pH 1.0 using KCl/HCl. The Δ log P at pH 7.4 is 3.65 and at pH 1.0 is 3.10.

Melting Range: 115-119°C

Composition: Keppra® tablets contain the labeled amount of levetiracetam. Inactive ingredients include colloidal silicon dioxide, corn starch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 4000, povidone, talc, titanium dioxide and coloring agents.

The individual tablets contain the following coloring agents:
250 mg tablets: FD&C Blue No. 2,
500 mg tablets: FD&C Blue No. 2 and yellow iron oxide,
750 mg tablets: FD&C Blue No. 2, FD&C Yellow No. 6 and red iron oxide.

Stability and Storage Recommendations

Store between 15-30°C (59-86°F).

AVAILABILITY OF DOSAGE FORMS

Keppra® (levetiracetam) tablets, 250 mg are blue, oblong-shaped, film-coated tablets debossed with "ucb" and "250" on one side. They are supplied in bottles of 120 tablets.

Keppra® (levetiracetam) tablets, 500 mg are yellow, oblong-shaped, film-coated tablets debossed with "ucb" and "500" on one side. They are supplied in bottles of 120 tablets.

Keppra® (levetiracetam) tablets, 750 mg are orange, oblong-shaped, film-coated tablets debossed with "ucb" and "750" on one side. They are supplied in bottles of 120 tablets.

For more information, please refer to the complete Keppra® Product Monograph.

References: 1. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000;55:236-4. **2.** Keppra Product Monograph. UCB Pharma, Inc.

See pages A-12, A-13

PrCOPAXONE®
(glatiramer acetate injection)

20 mg, single use vials and 20 mg/1.0 mL, pre-filled syringes for Subcutaneous Injection

THERAPEUTIC CLASSIFICATION Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

COPAXONE® [glatiramer acetate for injection (formerly known as copolymer-1)] is a sterile, lyophilized mixture of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine with an average molar fraction of 0.141, 0.427, 0.095 and 0.338, respectively.

The mechanism(s) by which glatiramer acetate exerts its effect on Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in animals that is generally accepted as an experimental model of MS.

Studies in animals and *in vitro* systems suggest that upon its administration glatiramer acetate specific suppressor T cells are induced and activated in the periphery.

Because the immunological profile of glatiramer acetate remains to be fully elucidated, concerns exist about its potential to alter naturally occurring immune responses (see **PRECAUTIONS**).

Pharmacokinetics: Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, larger fragments of glatiramer acetate can be recognized by glatiramer acetate reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some, may enter the systemic circulation intact.

Clinical Studies: The efficacy of COPAXONE® (glatiramer acetate for injection) was evaluated in two placebo-controlled trials in patients with Relapsing-Remitting MS (RR-MS). In a third placebo-controlled study the effects of glatiramer acetate on MRI parameters were assessed. In these studies, a dose of 20 mg/day was used. No other dose or dosing regimen has been studied in placebo-controlled trials of RR-MS.

The first trial was a pilot study Trial 1 (Trial BR-I) which was conducted at a single-center and was a double-blind, randomized, matched-pair, parallel group placebo-controlled trial. Fifty patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n=25) or placebo (n=25) subcutaneously. The protocol-specified primary outcome measure was the proportion of patients who were relapse free during the 2-year duration of the trial, but two additional relevant outcomes were also specified as endpoints: frequency of attacks during the trial, and the change in the number of attacks compared to the rate of attacks in the 2 years prior to study entry. Results from this study (see Table 1) show that there was a statistically significant effect of glatiramer acetate on number of relapses.

TABLE 1 – Trial BR-1: Efficacy Results

Outcome	Trial I[a]		
	Glatiramer acetate n=25	Placebo n=25	p-Value
% Relapse Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate compared to pre-study	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

[a] The primary efficacy measure for **Trial I** was the proportion of patients who were relapse free during the 2 year duration of the trial (% **Relapse Free**). Analyses were based on the intent-to-treat population.

* Progression defined as an increase of at least 1 point on the DSS that persists for at least 3 consecutive months.

Trial II (01-9001) was a multicenter double-blind, randomized, placebo-controlled trial. Two hundred and fifty-one patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n=125) or placebo (n=126) subcutaneously. Patients were diagnosed with RR-MS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients had a score of no more than 5 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 5 is defined as one at which a patient is still ambulatory but for whom full daily activities are impaired due to disability, a score of 6 is defined as one at which the patient is still ambulatory but requires assistance and a score of 7 on this scale means that the patient requires a wheelchair.

Patients were seen every 3 months for 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the lesion for at least 48 hours).

The protocol-specified primary outcome measure was the mean number of relapses during treatment. Table 2 shows results of the analysis of primary as well as several secondary outcome measures at two years based on the intent-to-treat population.

TABLE 2 – Core (24-month) Double-Blind Study: Effect on Relapse Rate

Outcome	Trial II[a]		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean No. of Relapses/2 years[b]	1.19	1.68	0.055
% Relapse Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Patients Progression Free[c]	98/125 (78%)	95/126 (75%)	0.48
Mean Change in EDSS	-0.05	+0.21	0.023

[a] The primary efficacy measure for **Trial II** was the number of relapses during treatment. Analyses were based on the intent-to-treat population.

[b] Baseline adjusted mean.

[c] Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months.

The effects of glatiramer acetate on relapse severity were not evaluated in either trial.

Both studies showed a beneficial effect of glatiramer acetate on relapse rate, and on this basis glatiramer acetate is considered effective.

The third study (9003) was a multi-national, multi-center, MRI-monitored study. A total of 239 patients with RR-MS (119 on glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in Trial II (Study 01-9001) with the additional criteria that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated initially in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over nine months. Other MRI parameters were assessed as secondary endpoints. Table 3 summarizes the results for the parameters monitored during the nine-month double-blind phase for the intent-to-treat cohort. Because the link between MRI findings and the clinical status of patients is contentious, the prognostic value of the following statistically significant findings is unknown.

TABLE 3 – Nine-Month Double-Blind Phase: MRI Endpoints – Results

No.	Outcome	Glatiramer acetate n=113	Placebo n=115	p-Value
Primary Endpoint				
1.	Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	12	17	0.0037
Secondary Endpoints				
2.	Medians of the Cumulative Number of New T1 Gd-Enhancing Lesions	9	14	0.0347
3.	Medians of the Cumulative Number of New T2 Lesions	5	8	0.01
4.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Gd-Enhancing Lesions	-0.309	0	0.0248
5.	Medians of the Cumulative Change from Baseline in volumes (mL) of T2 Lesions	8.852	13.566	0.0229
6.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Hypointense Lesions	1.642	1.829	0.7311
7.	Proportion of T1 Gd-Enhancing Lesion-Free Patients	46.4%	32.2%	0.0653

The mean number of relapses in this 9-month study was 0.50 for the COPAXONE® group and 0.77 for the placebo group (p=0.0077).

INDICATIONS AND CLINICAL USE

For use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis to reduce the frequency of relapses.

The safety and efficacy of COPAXONE® in chronic progressive MS have not been established.

CONTRAINDICATIONS

COPAXONE® (glatiramer acetate for injection) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS

The only recommended route of administration of COPAXONE® (glatiramer acetate for injection) injection is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

Symptoms of Potentially Cardiac Origin: Approximately 26% of COPAXONE® patients in the pre-marketing multicenter controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain (see **ADVERSE REACTIONS: Chest Pain**). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**), many did not. The pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with COPAXONE® treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

COPAXONE® has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**).

COPAXONE® has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE® in such patients.

Anaphylactoid reactions associated with the use of COPAXONE® have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

PRECAUTIONS

General: Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE® (glatiramer acetate for injection) (see **INFORMATION FOR THE PATIENT**). The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture-resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

Considerations Involving the Use of a Product Capable of Modifying Immune Responses: **COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE® may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.**

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled clinical trial of 125 RR-MS patients given glatiramer acetate 20 mg for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype – and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested. Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and, therefore, this risk cannot be excluded.

Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice (see **TOXICOLOGY: Carcinogenicity**). The relevance of these findings for humans is unknown (see **PRECAUTIONS: Considerations Involving the Use of a Product Capable of Modifying Immune Responses**).

Drug Interactions: Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical trial did not report any serious or unexpected adverse events thought to be related to treatment.

Use in Pregnancy: There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies (see **TOXICOLOGY: Reproduction and Teratology**). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During pre-marketing clinical trials with COPAXONE®, seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE® should only be considered after careful risk/benefit assessment and be used with caution.

Use in Children: The safety and effectiveness of COPAXONE® have not been established in individuals below 18 years of age.

Use in the Elderly: COPAXONE® has not been studied in the elderly (>65 years old).

Use in Patients with Impaired Renal Function: The pharmacokinetics of COPAXONE® in patients with impaired renal function have not been determined.

ADVERSE REACTIONS

In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate for injection) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), and to over 7 years (69 patients) at a daily dose of 20 mg.

In controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® which occurred at a higher frequency than in placebo treated patients were: injection site reactions, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia.

Of a total of 844 patients who could be evaluated for safety, approximately 8% discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness and tremor. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE® treatment included a case of life-threatening serum sickness.

Immediate Post-Injection Reaction: Approximately 10% of Multiple Sclerosis patients exposed to COPAXONE® in pre-marketing studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE®. Symptoms experienced could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria. These symptoms were invariably transient, self-limited, did not require specific treatment and in general, arose several months after initiation of treatment, although they may occur earlier in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE®. Whether these episodes are mediated by an immunologic or non-immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care (see **WARNINGS**).

Chest Pain: Approximately 26% of glatiramer acetate patients in the multicenter pre-marketing controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. There has been only one episode of chest pain during which a full ECG was performed; the ECG showed no evidence of ischemia. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown (see **WARNINGS: Symptoms of Potentially Cardiac Origin**).

Table 4 lists the adverse experiences after up to 35 months of treatment (>27-33 months: COPAXONE®, n=84; Placebo, n=75; >33 months: COPAXONE®, n=12; Placebo, n=24) in the pre-marketing multicenter placebo-controlled study (Trial II) in relapsing-remitting Multiple Sclerosis patients that occurred at an incidence of at least 2% among patients who received COPAXONE® and at an incidence that was at least 2% more than that observed in the same trial for placebo patients regardless of their causal relationship to treatment. No laboratory adverse experiences that met these criteria were reported.

It should be noted that the figures cited in Table 4 cannot be used to predict the incidence of side effects during the course of usual medical practice, where patient characteristics and other factors differ from those that prevailed in the clinical trials. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 4
Pre-marketing Controlled Trial in Patients with Multiple Sclerosis
Adverse Experiences ≥ 2% Incidence and ≥ 2% Above Placebo

	COPAXONE® n=125		Placebo n=126	
Adverse Experience	**n**	**%**	**n**	**%**
Body as a Whole				
Injection Site Pain	83	66.4	46	36.5
Asthenia	81	64.8	78	61.9
Injection Site Erythema	73	58.4	17	13.5
Injection Site Pruritus	48	38.4	5	4.0
Flu syndrome	38	30.4	34	27.0
Injection Site Inflammation	35	28.0	9	7.1
Back pain	33	26.4	28	22.2
Chest pain	33	26.4	13	10.3
Injection Site Mass	33	26.4	10	7.9
Injection Site Induration	25	20.0	1	0.8
Injection Site Welt	19	15.2	5	4.0
Neck pain	16	12.8	9	7.1
Face Edema	11	8.8	2	1.6
Injection Site Urticaria	9	7.2	0	0
Injection Site Hemorrhage	8	6.4	4	3.2
Chills	5	4.0	1	0.8
Cyst	5	4.0	1	0.8
Injection Site Reaction	4	3.2	1	0.8
Injection Site Atrophy	3	2.4	0	0
Abscess	3	2.4	0	0
Cardiovascular				
Vasodilatation	34	27.2	14	11.1
Palpitation	14	11.2	6	4.8
Migraine	9	7.2	5	4.0
Syncope	8	6.4	4	3.2
Digestive				
Nausea	29	23.2	22	17.5
Vomiting	13	10.4	7	5.6
Anorexia	6	4.8	3	2.4
Gastroenteritis	6	4.8	2	1.6
Oral Moniliasis	3	2.4	0	0
Tooth Caries	3	2.4	0	0
Hemic and Lymphatic				
Lymphadenopathy	23	18.4	12	9.5
Ecchymosis	15	12.0	12	9.5
Metabolic and Nutritional				
Peripheral Edema	14	11.2	7	5.6
Weight gain	7	5.6	0	0
Edema	5	4.0	1	0.8
Musculo-Skeletal				
Arthralgia	31	24.8	22	17.5
Nervous System				
Hypertonia	44	35.2	37	29.4
Tremor	14	11.2	7	5.6
Agitation	7	5.6	4	3.2
Confusion	5	4.0	1	0.8
Nystagmus	5	4.0	2	1.6
Respiratory				
Rhinitis	29	23.2	26	20.6
Dyspnea	23	18.4	8	6.4
Bronchitis	18	14.4	12	9.5
Skin and Appendages				
Sweating	15	12.0	10	7.9
Erythema	8	6.4	4	3.2
Skin Disorder	5	4.0	2	1.6
Skin Nodule	4	3.2	1	0.8
Wart	3	2.4	0	0
Special Senses				
Ear Pain	15	12.0	12	9.5
Eye Disorder	8	6.4	1	0.8
Urogenital System				
Urinary Urgency	20	16.0	17	13.5
Vaginal Moniliasis	16	12.8	9	7.1
Dysmenorrhea	12	9.6	9	7.1
Unintended Pregnancy	4	3.2	0	0
Impotence	3	2.4	0	0

Other events which occurred in at least 2% of patients but were present at equal or greater rates in the placebo group included: *Body as a whole:* Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis and malaise. *Digestive System:* Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth. *Musculo-Skeletal:* Myasthenia and myalgia. *Nervous System:* Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder. *Respiratory System:* Pharyngitis, sinusitis, increased cough and laryngitis. *Skin and Appendages:* Acne, alopecia, and nail disorder. *Special Senses:* Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness. *Urogenital System:* Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 92% of patients were Caucasian, which is representative of the population of patients with Multiple Sclerosis. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any trial due to abnormal laboratory findings.

Other Adverse Events Observed During All Clinical Trials

COPAXONE® has been administered to approximately 900 individuals during clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients. **Body as a whole:** *Frequent:* Injection site edema, injection site atrophy, abscess and injection site hypersensitivity. *Infrequent:* Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma and photosensitivity reaction. **Cardiovascular:** *Frequent:* Hypertension. *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension and varicose veins. **Digestive:** *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discolouration and duodenal ulcer. **Endocrine:** *Infrequent:* Goiter, hyperthyroidism, and hypothyroidism. **Gastrointestinal:** *Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis. **Hemic and Lymphatic:** *Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly. **Metabolic and Nutritional:** *Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma. **Musculoskeletal:** *Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis. **Nervous:** *Frequent:* Abnormal dreams, emotional lability, and stupor. *Infrequent:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression and transient stupor. **Respiratory:** *Frequent:* Hyperventilation, hay-fever. *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration. **Skin and Appendages:** *Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy and warts. *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash. **Special Senses:** *Frequent:* Visual field defect. *Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss. **Urogenital:** *Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, urinary frequency and vaginal hemorrhage. *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Adverse Events Reported Post-Marketing and Not Previously Noted in Clinical Trials

Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate for injection) not mentioned above, that have been received since market introduction and that may have or not have causal relationship to the drug include the following: **Body as a whole:** Sepsis, LE syndrome, hydrocephalus, enlarged abdomen, injection site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection. **Cardiovascular:** Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, coronary occlusion, congestive heart failure, cardiomyopathy cardiomegaly, arrhythmia, angina pectoris, tachycardia. **Digestive:** Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, eructation, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder. **Hemic and Lymphatic:** Thrombocytopenia, lymphoma-like reaction, acute leukemia. **Metabolic and Nutritional:** Hypercholesteremia. **Musculoskeletal:** Rheumatoid arthritis, generalized spasm. **Nervous:** Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo. **Respiratory:** Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus. **Skin and Appendages:** Herpes simplex, pruritis, rash, urticaria. **Special Senses:** Glaucoma, blindness, visual field defect. **Urogenital:** Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose with COPAXONE® has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE® at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE® at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow-up several hours later produced no report of adverse experiences from either patient.

DOSAGE AND ADMINISTRATION

COPAXONE® should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

The recommended dose of COPAXONE® (glatiramer acetate for injection or glatiramer acetate injection) for the treatment of relapsing-remitting MS is a daily injection of 20 mg given subcutaneously.

Instructions for Use: *To reconstitute lyophilized COPAXONE® for injection, use a sterile syringe and adapter to transfer 1.1 mL* of the diluent supplied, Sterile Water for Injection, into the COPAXONE® vial. Gently swirl the vial of COPAXONE® and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist before use if it contains particulate matter. Use within 8 hours after reconstitution. Withdraw 1.0 mL of the solution into a sterile syringe. Remove the adapter, connect a 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include arms, stomach (abdomen), buttocks, and thighs. A vial is suitable for single use only; unused portions should be discarded (see **INFORMATION FOR THE PATIENT: Reconstituted product**).

For the pre-filled syringe of COPAXONE®, please see the **INFORMATION FOR THE PATIENT: pre-filled syringe** for instructions on the preparation and injection of COPAXONE®.

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Glatiramer acetate

Chemical Name: Glatiramer acetate is the acetate salt of synthetic polypeptides.

Description: Glatiramer acetate is prepared by chemically reacting the activated derivatives of four amino acids: L-glutamic acid (L-Glu), L-alanine (L-Ala), L-tyrosine (L-Tyr), and L-lysine (L-Lys) in a specified ratio. The molar fraction of each amino acid residue ranges as follows: L-Glu 0.129-0.153, L-Ala 0.392-0.462, L-Tyr 0.086-0.100 and L-Lys 0.300-0.374.

Structural Formula: Poly[L-Glu$^{[1-7]}$, L-Ala$^{[39-46]}$, L-Tyr$^{[8-10]}$, L-Lys$^{[40-37]}$]•nCH$_3$CO$_2$H (n=15-24)

Molecular Weight: The average molecular weight of the polypeptide is between 4,700 and 11,000 daltons, with at least 68 percent of the material within the range of 2,500 to 22,500 daltons.

Physical Form: White to slightly yellowish lyophilized material.

Solubility: Sparingly soluble in water, insoluble in acetone.

pH: The pH of a 0.5% w/v solution of glatiramer acetate in water is in the range of 5.5-8.0.

Composition: COPAXONE® (glatiramer acetate for injection) is a sterile, lyophilized drug product, intended for subcutaneous injection following reconstitution with Sterile Water for Injection. Each vial of lyophilized drug product contains 20 mg glatiramer acetate, plus a 2 mg overage to allow for losses in reconstitution and transfer, and 40 mg mannitol. Each vial of Sterile Water for Injection contains 1.1 mL of Sterile Water for Injection plus a 0.35 mL overage to allow for losses in reconstitution and transfer.

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1.0 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e., 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection).

Stability and Storage Recommendations: Vials of lyophilized COPAXONE® should be stored under refrigeration (2° - 8°C). COPAXONE® may also be stored at room temperature (15° - 30°C) for up to 14 days. The vials of diluent (Sterile Water for Injection) should be stored at room temperature.

The pre-filled syringes of COPAXONE® should be refrigerated immediately upon receipt (between 2° - 8°C). DO NOT FREEZE. If you cannot have refrigerator storage, pre-filled syringes of COPAXONE® can be stored at room temperature (15° - 30°C) for up to one week. Do not store pre-filled syringes at room temperature for longer than one week. Note: this drug is light sensitive, do not expose to light when not injecting. Each pre-filled syringe is for single use only.

Reconstituted Solutions: To reconstitute lyophilized COPAXONE®, prior to injection, use a sterile syringe and adapter to transfer the diluent supplied, Sterile Water for Injection, into the COPAXONE® vial. Gently swirl the vial of COPAXONE® and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist if it contains particulate matter. Soon after the product is completely dissolved, withdraw 1.0 mL of the solution into a sterile syringe. Remove the adapter, connect a 27-gauge needle and inject the solution subcutaneously. A vial is suitable for single use only; unused portions should be discarded. The reconstituted solution should not be left longer than 8 hours at room temperature.

Parenteral Products: COPAXONE® should be reconstituted only with the provided diluent, Sterile Water for Injection.

Vial Size	Volume of Diluent to be Added	Volume to be Injected	Nominal Concentration per mL
2 mL	1.1 mL	1.0 mL	20 mg

AVAILABILITY OF DOSAGE FORMS

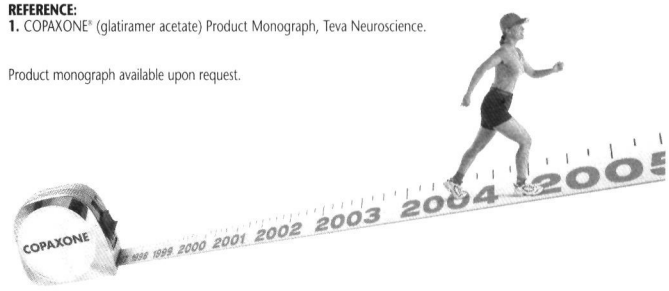
COPAXONE® (glatiramer acetate for injection) is supplied as a 20 mg dose of sterile lyophilized glatiramer acetate with mannitol, packaged in single use 2 mL amber vials. A separate vial, containing 1.1 mL of diluent (Sterile Water for Injection) plus 0.35 mL of overage of diluent is included in the Self Injection Administration Package for each vial of drug. COPAXONE® (glatiramer acetate for injection) is available in packs of 32 amber vials of sterile lyophilized material for subcutaneous injection. The diluent (Sterile Water for Injection) for COPAXONE® is supplied in packs of 32 clear vials and is located in the Self Injection Administration Package.

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1.0 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e., 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection). COPAXONE® (glatiramer acetate injection) is available in packs of 30 single-use 20 mg/1.0 mL pre-filled glass syringes with 33 alcohol preps (swabs).

REFERENCE:

1. COPAXONE® (glatiramer acetate) Product Monograph, Teva Neuroscience.

Product monograph available upon request.



TEVA NEUROSCIENCE
Teva Neuroscience
999 de Maisonneuve West, Suite 550
Montreal, Quebec H3A 3L4

PAAB

See page A-5

PrCOPAXONE®
(acétate de glatiramère injectable)

20 mg, flacons unidoses et 20 mg/1,0 mL, seringues préremplies pour injection sous-cutanée

CLASSIFICATION THÉRAPEUTIQUE Immunomodulateur

ACTION ET PHARMACOLOGIE CLINIQUE

COPAXONE® [acétate de glatiramère pour injection (connu auparavant sous le nom de copolymère1)] est un mélange lyophilisé stérile de polypeptides synthétiques renfermant quatre acides aminés naturels : l'acide L-glutamique, la L-alanine, la L-tyrosine et la L-lysine dans une fraction molaire moyenne de 0,141, de 0,427, de 0,095 et de 0,338, respectivement.

Le mode d'action de l'effet de l'acétate de glatiramère dans la sclérose en plaques (SEP) n'est pas encore complètement élucidé. On croit cependant que l'acétate de glatiramère exercerait un effet modulateur sur les processus immuns que l'on associe actuellement à la pathogenèse de la SEP. Cette hypothèse est étayée par les résultats des essais menés pour explorer la pathogenèse de l'encéphalomyélite allergique expérimentale (EAE), affection qui peut être déclenchée chez plusieurs espèces animales et qui est généralement acceptée comme modèle expérimental de la SEP.

Les études expérimentales sur animaux et les systèmes *in vitro* laissent supposer que l'administration de l'acétate de glatiramère induit et active des lymphocytes T suppresseurs spécifiques dans le sang périphérique.

Comme le profil immunologique de l'acétate de glatiramère n'est pas encore complètement élucidé, il est possible que le produit puisse avoir des effets sur les réactions immunitaires naturelles (voir **PRÉCAUTIONS**).

Pharmacocinétique : Les résultats obtenus au cours des essais pharmacocinétiques menés chez les humains (volontaires sains) et les animaux étayent l'hypothèse selon laquelle une fraction importante de la dose thérapeutique délivrée au patient par voie sous-cutanée est hydrolysée localement. Néanmoins, de grands fragments d'acétate de glatiramère peuvent être reconnus par les anticorps réactifs contre l'acétate de glatiramère. Une certaine proportion de la dose injectée, intacte ou partiellement hydrolysée, passerait dans la circulation lymphatique, ce qui permettrait au produit d'atteindre les ganglions lymphatiques régionaux ; de plus, il est possible qu'une partie du produit intact passe dans la circulation générale.

Essais cliniques : L'efficacité de COPAXONE® (acétate de glatiramère pour injection) a été évaluée dans le cadre de deux essais comparatifs (avec placebo) chez des patients atteints de SEP rémittente. Un troisième essai comparatif (avec placebo) a évalué les effets de l'acétate de glatiramère sur les paramètres IRM. Dans ces essais, on a eu recours à une dose de 20 mg/jour. Aucune autre dose ou schéma posologique n'ont été étudiés dans des essais comparatifs (avec placebo) sur la SEP rémittente.

Le premier essai Essai I (Essai BR-1) était un essai pilote comparatif (avec placebo) à répartition aléatoire en paires appariées, à groupes parallèles et à double insu qui a été mené dans un seul centre[15]. Cinquante patients atteints de SEP rémittente ont reçu, au hasard, 20 mg/jour d'acétate de glatiramère (n=25) ou un placebo (n=25) par voie sous-cutanée. Selon le protocole, le paramètre primaire de l'essai consistait en la proportion de patients exempts de poussée pendant les deux ans de l'essai. Deux autres résultats pertinents ont également servi de paramètres dans le cadre de cet essai : la fréquence des poussées pendant l'essai et la variation de la fréquence des poussées par comparaison à la fréquence des poussées pendant les deux années précédant l'entrée à l'essai. Les résultats de cet essai (tableau 1) démontrent que l'acétate de glatiramère exercait un effet statistiquement significatif sur le nombre de poussées.

TABLEAU 1 – Essai BR-1 : résultats quant à l'efficacité

Résultats	Essai I[a]		
	Acétate de glatiramère n=25	Placebo n=25	Valeur de *p*
% de patients exempts de poussée	14/25 (56 %)	7/25 (28 %)	0,085
Fréquence moyenne des poussées	0,6/2 ans	2,4/2 ans	0,005
Réduction de la fréquence des poussées comparativement aux données avant l'essai	3,2	1,6	0,025
Délai médian avant la première poussée (jours)	> 700	150	0,03
% de patients exempts de progression*	20/25 (80 %)	13/25 (52 %)	0,07

[a] Le paramètre primaire de l'efficacité de l'**Essai I** consistait en la proportion de patients exempts de poussée pendant les deux ans de l'essai (**% de patients exempts de poussée**). Les analyses portaient sur l'ensemble des sujets retenus au début de l'essai.

* La progression se définissait comme une augmentation d'au moins un point de la cote DSS persistant pendant au moins trois mois consécutifs.

L'Essai II (01-9001) était un essai comparatif (avec placebo), multicentrique, à double insu et à répartition aléatoire. Deux cent cinquante et un patients atteints de SEP rémittente ont reçu, au hasard, 20 mg/jour d'acétate de glatiramère (n=125) ou un placebo (n=126) par voie sous-cutanée[16]. Les patients avaient fait l'objet d'un diagnostic de SEP rémittente selon les critères standards et avaient subi au moins deux poussées pendant les deux années précédant immédiatement l'entrée à l'essai. Les patients devaient présenter une cote maximale de 5 sur l'échelle élargie de l'état d'invalidité de Kurtzke (EDSS, *Expanded Disability Status Scale*), échelle standard de 0 (état normal) à 10 (décès secondaire à la SEP). Une cote de 5 définit un patient ambulatoire qui a des difficultés à vaquer à toutes ses activités habituelles en raison d'une invalidité ; une cote de 6 définit un patient ambulatoire qui a besoin d'aide pour vaquer à ses occupations, tandis qu'une cote de 7 signifie que le sujet est confiné à un fauteuil roulant.

Les patients ont été examinés tous les trois mois pendant deux ans ainsi que dans les quelques jours suivant une poussée possible. Toute poussée devait être confirmée par un neurologue qui ignorait le traitement reçu et qui devait noter la présence de signes neurologiques objectifs ainsi que d'autres critères (p. ex., la persistance de la lésion pendant au moins 48 heures).

Le protocole précisait que le paramètre primaire de l'essai était le nombre moyen de poussées pendant le traitement.

Le tableau 2 présente les résultats de l'analyse du paramètre primaire et de plusieurs paramètres secondaires de l'Essai II à deux ans, analyse portant sur l'ensemble des sujets retenus au début de l'essai.

TABLEAU 2 – Essai de base (24 mois) à double insu: effet sur la fréquence des poussées

Résultats	Essai II[a]		
	Acétate de glatiramère n=125	Placebo n=126	Valeur de *p*
Nombre moyen de poussées (2 ans)[b]	1,19	1,68	0,055
% de patients exempts de poussée	42/125 (34 %)	34/126 (27 %)	0,25
Délai médian avant la première poussée (jours)	287	198	0,23
% de patients exempts de progression[c]	98/125 (78 %)	95/126 (75 %)	0,48
Variation moyenne de la cote EDSS	-0,05	+0,21	0,023

[a] Le paramètre primaire de l'efficacité de l'**Essai II** était le nombre de poussées pendant le traitement. Les analyses portaient sur l'ensemble des sujets retenus au début de l'essai.

[b] Moyenne ajustée de départ

[c] La progression se définissait comme une augmentation d'au moins un point de la cote EDSS persistant pendant au moins trois mois consécutifs.

Les effets de l'acétate de glatiramère sur la gravité des poussées n'ont pas été évalués dans ces deux essais.

Les deux essais ont révélé que l'acétate de glatiramère avait un effet bénéfique sur la fréquence des poussées ; on considère donc que l'acétate de glatiramère est un produit efficace à cet égard.

Le troisième essai (9003) était un essai multicentrique, multinational, avec surveillance IRM. Au total, 239 patients atteints de SEP rémittente (119 traités par l'acétate de glatiramère et 120 par un placebo) ont été répartis au hasard. Les critères d'inclusion étaient similaires à ceux de l'Essai II (Essai 01-9001) avec en plus le critère selon lequel les patients devaient présenter au moins une lésion rehaussée par le Gd à l'examen IRM de sélection. Les patients ont été d'abord traités à double insu pendant neuf mois, au cours desquels ils ont subi des examens IRM mensuels. Le paramètre primaire de la phase à double insu était le nombre cumulatif total de lésions rehaussées par le Gd en pondération T1 pendant les neuf mois. D'autres paramètres IRM ont été évalués à titre de paramètres secondaires. Le tableau 3 résume les résultats obtenus pour les paramètres surveillés pendant la phase à double insu de neuf mois pour l'ensemble des sujets retenus au début de l'essai. Compte tenu que le lien entre les résultats IRM et l'état clinique du patient fait l'objet d'une discussion, on ignore la valeur pronostique des résultats statistiquement significatifs suivants.

TABLEAU 3 – Phase à double insu de neuf mois : paramètres IRM - résultats

N°	Résultats	Acétate de glatiramère n=113	Placebo n=115	Valeur de *p*
Paramètre primaire				
1.	Médianes du nombre cumulatif de lésions rehaussées par le Gd en T1	12	17	0,0037
Paramètres secondaires				
2.	Médianes du nombre cumulatif de nouvelles lésions rehaussées par le Gd en T1	9	14	0,0347
3.	Médianes du nombre cumulatif de nouvelles lésions en T2	5	8	0,01
4.	Médianes de la variation cumulative par rapport aux valeurs de départ du volume (mL) des lésions rehaussées par le Gd en T1	-0,309	0	0,0248
5.	Médianes de la variation cumulative par rapport aux valeurs de départ du volume (mL) des lésions en T2	8,852	13,566	0,0229
6.	Médianes de la variation cumulative par rapport aux valeurs de départ du volume (mL) des lésions hypo-intenses en T1	1,642	1,829	0,7311
7.	Proportion de patients exempts de lésion rehaussée par le Gd en T1	46,4 %	32,2 %	0,0653

Le nombre moyen de poussées au cours de cet essai de neuf mois était de 0,50 pour le groupe COPAXONE® et de 0,77 pour le groupe placebo (p=0,0077).

INDICATIONS ET UTILISATION CLINIQUE Pour utilisation chez les patients ambulatoires atteints de sclérose en plaques rémittente en vue de réduire la fréquence des poussées.

L'innocuité et l'efficacité de COPAXONE® dans la sclérose en plaques chronique progressive n'ont pas été évaluées.

CONTRE-INDICATIONS COPAXONE® (acétate de glatiramère pour injection) est contre-indiqué chez les patients présentant une hypersensibilité avérée à l'acétate de glatiramère ou au mannitol.

MISES EN GARDE La seule voie d'administration recommandée de COPAXONE® (acétate de glatiramère pour injection) est la voie sous-cutanée. COPAXONE® ne doit pas être administré par voie intraveineuse. **Symptômes qui risquent d'avoir une origine cardiaque :** Environ 26 % des patients qui ont reçu COPAXONE® dans l'essai comparatif et multicentrique de précommercialisation (par comparaison à 10 % des patients ayant reçu un placebo) ont subi au moins un épisode de ce qui a été décrit comme une douleur thoracique transitoire (voir **EFFETS INDÉSIRABLES : Douleur thoracique**). Seulement certains de ces épisodes sont survenus dans le cadre de la réaction apparaissant immédiatement après l'injection (voir **EFFETS INDÉSIRABLES : Réaction suivant l'injection**). Aucune surveillance de l'ECG n'a été réalisée pendant l'un de ces épisodes, et la pathogenèse de ce symptôme demeure inconnue. Comme les patients des essais comparatifs ne présentaient pas de troubles cardiovasculaires significatifs (classe I ou II selon la *New York Heart Association*), on ignore les risques que courent les patients qui souffrent d'une atteinte cardiovasculaire et qui reçoivent COPAXONE® dans le traitement de la sclérose en plaques.

L'administration de COPAXONE® a été associée à une réaction suivant l'injection consistant en un ensemble de symptômes qui surviennent immédiatement après l'injection et qui peuvent comprendre les bouffées congestives, la douleur thoracique, les palpitations, l'anxiété, la dyspnée, la constriction de la gorge et l'urticaire (voir **EFFETS INDÉSIRABLES : Réaction suivant l'injection**).

COPAXONE® n'a pas été étudié chez des sujets présentant des antécédents de réactions anaphylactoïdes graves, de bronchopneumopathie chronique obstructive ou d'asthme ni chez des patients qui reçoivent des médicaments dans le traitement de l'une de ces deux dernières affections. Il convient donc de faire preuve de prudence pour ce qui est de l'utilisation de COPAXONE® chez ce type de patients.

De rares cas de réactions anaphylactoïdes (<1/1 000) ont été rapportés en association avec l'utilisation de COPAXONE® au cours de la période de postcommercialisation. Certains cas ont nécessité un traitement par l'épinéphrine et autre traitement médical approprié.

PRÉCAUTIONS Générales : Les patients doivent connaître les techniques de reconstitution et d'auto-injection respectant l'asepsie de sorte que COPAXONE® (acétate de glatiramère pour injection) soit administré de façon sûre (voir **INFORMATION À L'INTENTION DU PATIENT**). La première injection doit être effectuée sous la supervision d'un professionnel de la santé qualifié. Il convient de vérifier périodiquement si les patients comprennent et respectent les techniques d'auto-administration respectant l'asepsie. On doit avertir les patients de ne pas réutiliser les aiguilles et les seringues et leur expliquer les procédures de mise au rebut appropriées. Les patients doivent jeter les aiguilles et les seringues utilisées dans un contenant non perforable. On doit en outre expliquer aux patients comment mettre au rebut les contenants non perforables une fois remplis.

Considérations en matière d'utilisation d'un produit capable de modifier les réactions immunitaires : COPAXONE® étant une substance antigénique, son utilisation risque de déterminer des réactions délétères pour l'hôte. On ignore en outre si COPAXONE® peut modifier les réactions immunitaires normales de l'être humain, comme la reconnaissance des antigènes étrangers. Il est donc possible que le traitement par COPAXONE® puisse altérer les mécanismes de défense de l'organisme contre les infections ainsi que les mécanismes de surveillance des tumeurs. Aucune évaluation systématique de ces risques n'a encore été entreprise. L'altération continue de l'immunité cellulaire due au traitement chronique avec l'acétate de glatiramère pourrait entraîner des effets indésirables.

Des anticorps réactifs contre l'acétate de glatiramère sont formés chez presque tous les patients exposés au traitement quotidien avec la dose recommandée. Selon des essais menés chez le rat et le singe, des complexes immuns se déposent dans les glomérules rénaux. De plus, dans un essai comparatif portant sur 125 patients atteints de SEP rémittente qui ont reçu 20 mg d'acétate de glatiramère pendant deux ans, les taux sériques d'IgG ont atteint des taux au moins trois fois plus élevés que les taux de départ chez 80 % des patients trois mois après le début du traitement. Après 12 mois de traitement, cependant, 30 % des patients avaient toujours des taux d'IgG au moins trois fois plus élevés que les taux de départ et 90 % avaient des taux plus élevés que les taux de départ après 12 mois. Les anticorps sont uniquement de sous-type IgG, et surtout de sous-type IgG-1. Aucun anticorps de type IgE n'a été détecté chez aucun des 94 sérums testés. Néanmoins, compte tenu que l'anaphylaxie peut être associée à l'administration de presque toutes les substances étrangères, ce risque ne peut être exclu.

Des essais précliniques visant à évaluer le potentiel carcinogène de l'acétate de glatiramère chez la souris et le rat n'ont fait ressortir aucun signe de potentiel carcinogène associé à l'administration sous-cutanée de l'acétate de glatiramère à des doses allant jusqu'à 30 mg/kg/jour chez le rat et jusqu'à 60 mg/kg/jour chez la souris (voir **TOXICOLOGIE : Potentiel carcinogène**). On ignore si ces résultats sont extrapolables à l'humain (voir **PRÉCAUTIONS : Considérations en matière d'utilisation d'un produit capable de modifier les réactions immunitaires**).

Interactions médicamenteuses : Les interactions médicamenteuses entre COPAXONE® et d'autres produits n'ont pas fait l'objet d'une évaluation complète. Les résultats des essais cliniques à ce jour ne font pas ressortir d'interaction significative entre COPAXONE® et les traitements habituels de la SEP, y compris l'administration concomitante de corticostéroïdes pendant un maximum de 28 jours. COPAXONE® n'a pas été évalué de façon formelle en association à l'interféron bêta. En revanche, 246 patients chez lesquels le traitement par l'interféron bêta a échoué ou qui n'ont pas toléré le traitement et qui ont été par la suite traités avec COPAXONE® dans le cadre d'un essai clinique ouvert n'ont pas signalé l'apparition d'effets indésirables graves ou inattendus pouvant être liés au traitement.

Grossesse : Aucun essai comparatif rigoureux portant sur des femmes enceintes n'a été réalisé. Les essais précliniques n'ont pas fait ressortir de signe de toxicité liée à la reproduction (voir **TOXICOLOGIE : Reproduction et tératologie**). Étant donné que les essais de reproduction chez les animaux ne permettent pas toujours de prévoir les effets d'un produit chez l'être humain, ce médicament ne doit être administré pendant la grossesse que si son utilité a été clairement établie. Dans le cadre des essais cliniques de précommercialisation portant sur COPAXONE®, sept femmes sont devenues enceintes pendant le traitement par le produit actif. L'une de ces femmes a été perdue de vue pendant le suivi ; trois femmes ont choisi d'interrompre leur grossesse, et les trois autres ont cessé de prendre le produit un mois, un mois et demi et deux mois après avoir découvert qu'elles étaient enceintes. Ces trois femmes ont donné naissance à des enfants en bonne santé.

Allaitement : On ignore si le produit passe dans le lait maternel. Étant donné qu'un grand nombre de médicaments passent effectivement dans le lait maternel, l'administration de COPAXONE® à une femme qui allaite ne doit être envisagée qu'après une évaluation soigneuse du rapport risques-avantages, et le produit doit être utilisé avec prudence.

Enfants : L'innocuité et l'efficacité de COPAXONE® n'ont pas été établies chez les sujets de moins de 18 ans.

Patients âgés : COPAXONE® n'a fait l'objet d'aucune évaluation spécifique chez les personnes âgées (plus de 65 ans).

Insuffisants rénaux : Les paramètres pharmacocinétiques de COPAXONE® n'ont pas été déterminés chez les sujets souffrant d'un dysfonctionnement rénal.

EFFETS INDÉSIRABLES Au cours des essais cliniques de précommercialisation, environ 900 personnes ont reçu au moins une dose de COPAXONE® (acétate de glatiramère pour injection) dans le cadre d'essais cliniques comparatifs ou non. L'exposition totale des patients à COPAXONE® au cours d'essais cliniques s'échelonne de six mois (693 patients) à deux ans (306 patients), et à plus de sept ans (69 patients) à raison d'une dose quotidienne de 20 mg.

Au cours des essais comparatifs, les effets indésirables le plus fréquemment associés à l'utilisation de COPAXONE® et dont l'incidence était supérieure à celle qui a été observée chez les sujets qui recevaient le placebo étaient les suivants : réactions au point d'injection, vasodilatation, douleur thoracique, asthénie, infection, douleur, nausées,

arthralgie, anxiété et hypertonie.

Sur un total de 844 patients qui pouvaient faire l'objet d'une évaluation de l'innocuité du produit, environ 8 % des sujets ont abandonné le traitement en raison d'effets indésirables. Les effets indésirables le plus fréquemment associés à l'abandon du traitement étaient les suivants : réactions au point d'injection (6,5 %), vasodilatation, grossesse accidentelle, dépression, dyspnée, urticaire, tachycardie, étourdissements et tremblement. Au nombre des effets indésirables graves ayant entraîné l'abandon du traitement et que les chercheurs considéraient comme liés à l'administration de COPAXONE®, on compte un cas de maladie du sérum ayant menacé la survie du patient.

Réaction suivant l'injection : Environ 10 % des patients atteints de sclérose en plaques qui ont reçu COPAXONE® dans le cadre des essais précédant la commercialisation du produit ont signalé une réaction apparaissant immédiatement après l'injection sous-cutanée de COPAXONE®. Les symptômes ressentis pouvaient comprendre les bouffées congestives, la douleur thoracique, les palpitations, l'anxiété, la dyspnée, la constriction de la gorge et l'urticaire. Ces symptômes étaient toujours transitoires et spontanément résolutifs et n'exigeaient pas de traitement particulier. Ils survenaient en général plusieurs mois après l'établissement du traitement et parfois plus tôt. Un patient particulier pouvait subir un seul ou plusieurs de ces épisodes pendant son traitement par COPAXONE®. On ne sait pas si ces épisodes sont liés à des mécanismes immunologiques ou non, ni si plusieurs épisodes semblables survenant chez un même patient relèvent de mécanismes identiques. En fait, on ignore si cet ensemble de symptômes représente véritablement un syndrome spécifique. Au cours de la période de postcommercialisation, des patients ont signalé avoir subi des symptômes similaires et reçu des soins médicaux d'urgence (voir **MISES EN GARDE**).

Douleur thoracique : Environ 26 % des patients qui ont reçu de l'acétate de glatiramère dans l'essai comparatif multicentrique de précommercialisation (par comparaison à 10 % des patients ayant reçu un placebo) ont subi au moins un épisode de ce qui a été décrit comme une douleur thoracique transitoire. Seulement certains de ces épisodes sont survenus dans le cadre de la réaction apparaissant immédiatement après l'injection décrite dans le paragraphe précédent. Le lien temporel entre la douleur thoracique et l'injection d'acétate de glatiramère n'était pas toujours connu. La douleur était transitoire (elle ne durait habituellement que quelques minutes), apparaissait souvent seule et ne semblait pas laisser d'importantes séquelles cliniques. Aucune surveillance de l'ECG n'a été réalisée pendant l'un de ces épisodes. Certains patients ont subi plus d'un épisode de douleur thoracique, et ces épisodes commençaient à apparaître, en règle générale, au moins un mois après l'établissement du traitement. La pathogenèse de ce symptôme demeure inconnue. Il y a eu un seul épisode de douleur thoracique au cours duquel un ECG complet a été effectué; l'ECG n'a révélé aucun signe d'ischémie. Comme les patients des essais cliniques ne présentaient pas de troubles cardiovasculaires significatifs (classe I ou II selon la *New York Heart Association*), on ignore les risques que courent les patients qui souffrent d'une atteinte cardiovasculaire et qui reçoivent l'acétate de glatiramère dans le traitement de la sclérose en plaques (voir **MISES EN GARDE : Symptômes qui risquent d'avoir une origine cardiaque**).

Le tableau 4 dresse la liste des effets indésirables observés après un maximum de 35 mois de traitement (plus de 27 mois à 33 mois : COPAXONE®, n=84 ; placebo, n=75 ; plus de 33 mois : COPAXONE®, n=12 ; placebo, n=24) dans le cadre de l'Essai II (essai comparatif [avec placebo] multicentrique de précommercialisation portant sur des patients atteints de sclérose en plaques rémittente) et dont l'incidence était d'au moins 2 % parmi les sujets qui recevaient COPAXONE® et d'au moins 2 % de plus que l'incidence observée parmi les sujets du même essai qui recevaient le placebo, peu importe le lien de cause à effet entre la réaction et le traitement. Aucun résultat des épreuves de laboratoire répondant à ces critères n'a été signalé.

Il est à noter que les données du tableau 4 ne peuvent pas servir à prévoir l'incidence des effets indésirables du traitement dans le cadre de l'exercice normal de la médecine, étant donné que les caractéristiques des patients ainsi que d'autres facteurs risquent de ne pas être les mêmes que ceux des essais cliniques. Ces données fournissent tout de même au médecin traitant des points de repère lui permettant d'évaluer la contribution relative des facteurs liés au médicament et non liés au médicament en ce qui a trait à l'incidence des effets indésirables dans la population étudiée.

TABLEAU 4
Essai comparatif de précommercialisation chez des patients atteints de SEP
Effets indésirables dont l'incidence est ≥ 2 % et ≥ 2 % supérieure à celle du placebo

	COPAXONE® n=125		Placebo n=126	
Effets indésirables	**n**	**%**	**n**	**%**
Organisme dans son ensemble				
Douleur au point d'injection	83	66,4	46	36,5
Asthénie	81	64,8	78	61,9
Érythème au point d'injection	73	58,4	17	13,5
Prurit au point d'injection	48	38,4	5	4,0
Syndrome pseudo-grippal	38	30,4	34	27,0
Inflammation au point d'injection	35	28,0	9	7,1
Douleur dorsale	33	26,4	28	22,2
Douleur thoracique	33	26,4	13	10,3
Masse au point d'injection	33	26,4	10	7,9
Induration au point d'injection	25	20,0	1	0,8
Papule au point d'injection	19	15,2	5	4,0
Douleur au cou	16	12,8	9	7,1
Œdème du visage	11	8,8	2	1,6
Urticaire au point d'injection	9	7,2	0	0
Hémorragie au point d'injection	8	6,4	4	3,2
Frissons	5	4,0	1	0,8
Kyste	5	4,0	1	0,8
Réaction au point d'injection	4	3,2	1	0,8
Atrophie au point d'injection	3	2,4	0	0
Abcès	3	2,4	0	0
Appareil cardiovasculaire				
Vasodilatation	34	27,2	14	11,1
Palpitations	14	11,2	6	4,8
Migraine	9	7,2	5	4,0
Syncope	8	6,4	4	3,2
Appareil digestif				
Nausées	29	23,2	22	17,5
Vomissements	13	10,4	7	5,6
Anorexie	6	4,8	3	2,4
Gastro-entérite	6	4,8	2	1,6
Candidose orale	3	2,4	0	0
Carie dentaire	3	2,4	0	0
Systèmes hématopoïétique et lymphatique				
Adénopathie	23	18,4	12	9,5
Ecchymose	15	12,0	12	9,5
Troubles métaboliques et nutritionnels				
Œdème périphérique	14	11,2	7	5,6
Gain pondéral	7	5,6	0	0
Œdème	5	4,0	1	0,8
Appareil musculosquelettique				
Arthralgie	31	24,8	22	17,5
Système nerveux				
Hypertonie	44	35,2	37	29,4
Tremblement	14	11,2	7	5,6
Agitation	7	5,6	4	3,2
Confusion	5	4,0	1	0,8
Nystagmus	5	4,0	2	1,6
Appareil respiratoire				
Rhinite	29	23,2	26	20,6
Dyspnée	23	18,4	8	6,4
Bronchite	18	14,4	12	9,5
Peau et annexes cutanées				
Hypersudation	15	12,0	10	7,9
Érythème	8	6,4	4	3,2
Troubles dermatologiques	5	4,0	2	1,6
Nodule cutané	4	3,2	1	0,8
Verrue	3	2,4	0	0
Organes des sens				
Douleur auriculaire	15	12,0	12	9,5
Troubles oculaires	8	6,4	1	0,8
Voies urogénitales				
Miction impérieuse	20	16,0	17	13,5
Candidose vaginale	16	12,8	9	7,1
Dysménorrhée	12	9,6	9	7,1
Grossesse accidentelle	4	3,2	0	0
Impuissance	3	2,4	0	0

Voici les autres effets qui sont survenus chez au moins 2 % des patients mais dont l'incidence dans le groupe placebo était équivalente ou supérieure :

Organisme dans son ensemble : Céphalées, ecchymose au point d'injection, blessure accidentelle, douleur abdominale, rhinite allergique et malaise.

Appareil digestif : Dyspepsie, constipation, dysphagie, incontinence fécale, flatulence, nausées et vomissements, gastrite, gingivite, abcès périodontique et sécheresse de la bouche.

Appareil musculosquelettique : Myasthénie et myalgie.

Système nerveux : Étourdissements, hypoesthésie, paresthésie, insomnie, dépression, dysesthésie, troubles de la coordination, somnolence, troubles de la démarche, amnésie, instabilité émotionnelle, signe de Lhermitte, anomalies de la pensée, secousses musculaires, euphorie et troubles du sommeil.

Appareil respiratoire : Pharyngite, sinusite, aggravation de la toux et laryngite.

Peau et annexes cutanées : Acné, alopécie et troubles des ongles.

Organes des sens : Anomalies de la vision, diplopie, amblyopie, douleur oculaire, conjonctivite, acouphènes, dysgueusie et surdité.

Voies urogénitales : Infection des voies urinaires, augmentation de la fréquence des mictions, incontinence urinaire, rétention urinaire, dysurie, cystite, métrorragie, douleur mammaire et vaginite.

Les données portant sur les effets indésirables qui sont apparus au cours d'essais cliniques comparatifs ont été analysées dans l'optique d'évaluer les différences entre les sexes. Or, aucune différence cliniquement significative n'a été relevée. Dans ces essais cliniques, 92 % des patients étaient de race blanche, ce qui est représentatif de la population de patients atteints de sclérose en plaques. De plus, la vaste majorité des patients traités par COPAXONE® étaient âgés de 18 à 45 ans. Par conséquent, on disposait de trop peu de données pour effectuer une analyse de l'incidence des effets indésirables en fonction de groupes d'âge cliniquement pertinents.

Tous les patients ayant pris part aux essais cliniques sur COPAXONE® ont subi des analyses de laboratoire. Les variations des paramètres de laboratoire (hématologie, biochimie sanguine et analyse des urines) qui étaient significatives sur le plan clinique étaient comparables entre les patients du groupe COPAXONE® et ceux du groupe placebo, dans le cadre des essais cliniques à l'insu. Aucun patient ayant reçu COPAXONE® ne s'est retiré d'un essai en raison d'une anomalie des résultats des épreuves de laboratoire.

Autres effets indésirables observés durant tous les essais cliniques

COPAXONE® a été administré à environ 900 personnes dans l'ensemble des essais cliniques, dont seulement certains étaient comparatifs (avec placebo). Au cours de ces essais, tous les effets indésirables ont été enregistrés par les chercheurs cliniques à l'aide de leur propre terminologie. De façon à donner une estimation efficace de la proportion des patients qui ont subi des effets indésirables, les effets semblables ont été regroupés en un plus petit nombre de catégories normalisées faisant appel à la terminologie du dictionnaire COSTART II. Tous les effets signalés qui sont survenus à au moins deux reprises ainsi que les effets potentiellement graves qui sont survenus une seule fois sont inclus dans cette compilation, à l'exception des effets déjà inscrits au tableau précédent, les effets dont le caractère trop général ne procurait aucune information, les effets sans importance et les autres effets qui se sont manifestés chez au moins 2 % des patients traités et qui étaient présents à une fréquence égale ou plus grande que dans le groupe placebo.

Les effets indésirables ont été de plus classés en fonction des systèmes ou des appareils et énumérés en ordre décroissant de fréquence selon les définitions suivantes : les effets indésirables *fréquents* sont ceux qui sont survenus chez au moins un patient sur 100 (1/100), tandis que les effets indésirables *peu fréquents* sont ceux qui sont survenus dans une proportion de un patient sur 100 (1/100) à un patient sur 1 000 (1/1 000).

Organisme dans son ensemble : *Fréquents :* Œdème au point d'injection, atrophie au point d'injection, abcès et hypersensibilité au point d'injection.

Peu fréquents : Hématome au point d'injection, fibrose au point d'injection, faciès lunaire, cellulite, œdème généralisé, hernie, abcès au point d'injection, maladie du sérum, tentative de suicide, hypertrophie au point d'injection, mélanose au point d'injection, lipome et réaction de photosensibilité.

Appareil cardiovasculaire : *Frequent :* Hypertension. *Peu fréquents :* Hypotension, claquement systolique, souffle systolique, fibrillation auriculaire, bradycardie, apparition d'un quatrième bruit du cœur, hypotension orthostatique et varices.

Appareil digestif : *Peu fréquents :* Sécheresse de la bouche, stomatite, sensation de brûlure sur la langue, cholécystite, colite, ulcère de l'œsophage, œsophagite, cancer gastro-intestinal, hémorragie gingivale, hépatomégalie, augmentation de l'appétit, méléna, ulcération de la bouche, troubles du pancréas, pancréatite, hémorragie rectale, ténesme, coloration anormale de la langue et ulcère duodénal.

Système endocrinien : *Peu fréquents :* Goitre, hyperthyroïdie et hypothyroïdie.

Troubles gastro-intestinaux : *Fréquents :* Défécation impérieuse, candidose orale, hypertrophie des glandes salivaires, carie dentaire et stomatite ulcéreuse.

Systèmes hématopoïétique et lymphatique : *Peu fréquents :* Leucopénie, anémie, cyanose, éosinophilie, hématémèse, lymphœdème, pancytopénie et splénomégalie.

Troubles métaboliques et nutritionnels : *Peu fréquents :* Perte pondérale, intolérance à l'alcool, syndrome de Cushing, goutte, anomalies de la cicatrisation et xanthome.

Appareil musculosquelettique : *Peu fréquents :* Arthrite, atrophie musculaire, douleur osseuse, bursite, douleur rénale, troubles musculaires, myopathie, ostéomyélite, douleur tendineuse et ténosynovite.

Système nerveux : *Fréquents:* Rêves inhabituels, instabilité émotionnelle et stupeur. *Peu fréquents :* Aphasie, ataxie, convulsion, paresthésie péribuccale, dépersonnalisation, hallucinations, hostilité, hypocinésie, coma, troubles de la concentration, paralysie faciale, diminution de la libido, réaction maniaque, troubles de la mémoire, myoclonie, névralgie, réaction paranoïde, paraplégie, dépression psychotique et stupeur transitoire.

Appareil respiratoire : *Fréquent :* Hyperventilation, rhume des foins. *Peu fréquents :* Asthme, pneumonie, épistaxis, hypoventilation et modification de la voix.

Peau et annexes cutanées : *Fréquents :* Eczéma, zona, éruption pustuleuse, atrophie cutanée et verrues. *Peu fréquents :* Sécheresse cutanée, hypertrophie cutanée, dermatite, furonculose, psoriasis, angio-œdème, eczéma de contact, érythème noueux, dermatite fongique, éruption maculopapuleuse, pigmentation, tumeur cutanée bénigne, cancer de la peau, vergetures et éruption vésiculobulleuse.

Organes des sens : *Fréquents :* Atteinte du champ visuel. *Peu fréquents :* Sécheresse oculaire, otite externe, ptose, cataractes, ulcère de la cornée, mydriase, névrite optique, photophobie et agueusie.

Voies urogénitales : *Fréquents :* Aménorrhée, hématurie, impuissance, ménorragie, anomalies des résultats du test de Papanicolaou, pollakiurie et hémorragie vaginale. *Peu fréquents :* Vaginite, douleur au flanc (rein), avortement, engorgement mammaire, hypertrophie mammaire, douleur mammaire, cancer *in situ* du col de l'utérus, mastose sclérokystique, calcul rénal, nycturie, kyste ovarien, priapisme, pyélonéphrite, anomalies de la fonction sexuelle et urétrite.

Effets indésirables rapportés après la commercialisation et qui n'avaient pas déjà été notés lors des essais cliniques

L'expérience de postcommercialisation a dégagé un profil d'effets indésirables similaire à celui présenté ci-dessus. Après la mise sur le marché, on a signalé des effets indésirables, autres que celles indiquées ci-dessus, qui sont survenues pendant le traitement par COPAXONE® (acétate de glatiramère pour injection). Ces réactions, qui peuvent avoir ou non un lien de causalité avec le médicament, comprennent :

Organisme dans son ensemble : Septicémie, syndrome lupoïde, hydrocéphalie, distension de l'abdomen, hypersensibilité au point d'injection, réaction allergique, réaction anaphylactoïde, infection bactérienne, fièvre et infection.

Appareil cardiovasculaire : Thrombose, maladie vasculaire périphérique, épanchement péricardique, infarctus du myocarde, thrombophlébite extensive, occlusion coronarienne, insuffisance cardiaque congestive, cardiomyopathie, cardiomégalie, arrythmie, angine de poitrine et tachycardie.

Appareil digestif : Œdème de la langue, hémorragie gastrique d'origine ulcéreuse, altération de la fonction hépatique, atteinte hépatique, hépatite, éructation, cirrhose du foie, calculs biliaires, diarrhée et troubles gastro-intestinaux.

Systèmes hématopoïétique et lymphatique : Thrombocytopénie, réaction de type lymphome et leucémie aiguë.

Troubles métaboliques et nutritionnels : Hypercholestérolémie.

Appareil musculosquelettique : Polyarthrite rhumatoïde et spasme généralisé.

Système nerveux : Myélite, méningite, néoplasme du SNC, accident vasculaire cérébral, œdème cérébral, rêves inhabituels, aphasie, convulsion, névralgie, anxiété, pied tombant, nervosité, trouble de l'élocution et vertige.

Appareil respiratoire : Embolie pulmonaire, épanchement pleural, cancer du poumon, rhume des foins et laryngisme.

Peau et annexes cutanées : Herpès, prurit, éruption cutanée et urticaire.

Organes des sens : Glaucome, cécité et atteinte du champ visuel.

Voies urogénitales : Néoplasme des voies urogénitales, anomalie urinaire, cancer des ovaires, néphrose, insuffisance rénale, cancer du sein, cancer de la vessie et pollakiurie.

SURDOSAGE : SYMPTÔMES ET TRAITEMENT

Des surdosages de COPAXONE® ont été signalés chez trois patients. Un patient s'est injecté quatre doses (soit un total de 80 mg) de COPAXONE® à la fois. Aucune séquelle n'a été notée. Deux autres patients, un homme de 28 ans et une femme de 37 ans, ont reçu, par erreur, trois injections de 20 mg of COPAXONE® à des intervalles de une demi-heure. Aucun patient n'a manifesté de variation de sa pression artérielle, de sa fréquence cardiaque ni de sa température. Le suivi téléphonique effectué plusieurs heures plus tard n'a pas révélé d'effets indésirables dans un cas comme dans l'autre.

POSOLOGIE ET MODE D'ADMINISTRATION

La prescription de COPAXONE® doit être réservée aux médecins (ou après une consultation avec un médecin) qui connaissent à fond le diagnostic et la prise en charge de la sclérose en plaques.

La dose recommandée de COPAXONE® (acétate de glatiramère pour injection ou acétate de glatiramère injectable) dans le traitement de la SEP rémittente est de une injection quotidienne de 20 mg par voie sous-cutanée.

Directives d'administration : Pour reconstituer le lyophilisat de COPAXONE® avant l'injection, utiliser une

continué sur page A-40

LIPITOR*
atorvastatin calcium
tablets

power** you can **trust™

®LIPITOR*
(atorvastatin calcium)
10 mg, 20 mg, 40 mg and 80 mg tablets

THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

LIPITOR (atorvastatin calcium) is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake and catabolism of Low Density Lipoprotein (LDL).

LIPITOR reduces LDL-Cholesterol (LDL-C) and the number of LDL particles. LIPITOR also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Low serum concentration of HDL-C is also an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Epidemiologic, clinical and experimental studies have established that high LDL-C, low HDL-C and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. Some studies have also shown that the ratio of total cholesterol (total-C) to HDL-C (total-C/HDL-C) is the best predictor of coronary artery disease. In contrast, increased levels of HDL-C are associated with decreased cardiovascular risk. Drug therapies that reduce levels of LDL-C or decrease TG while simultaneously increasing HDL-C have demonstrated reductions in rates of cardiovascular mortality and morbidity.

Pharmacokinetics

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to lifestyle changes, including diet, (at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet), for the reduction of elevated total cholesterol, (total-C), LDL-C, TG and apolipoprotein B (apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa);
- Combined (mixed) hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern;
- Dysbetalipoproteinemia (Type III);
- Hypertriglyceridemia (Type IV);
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if such treatments are not available.

LIPITOR also raises HDL-cholesterol and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia (Fredrickson Type IIa and IIb dyslipidemia). In pooled data from 24 controlled clinical trials, LIPITOR raised HDL-C levels 5%-7% in primary hypercholesterolemic (type IIa) patients and 10%-15% in mixed (type IIb) dyslipidemic patients.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25 - 56%) and LDL-C levels (23 - 40%). LIPITOR has not been studied in conditions where the major abnormality is elevation of chylomicrons (TG levels > 11 mmol/L), i.e. types I and V.

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open label study in patients with homozygous familial hypercholesterolemia (FH) LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor negative patients (see PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

$$\text{LDL-C (mmol/L)} = \text{total-C} - [(0.37 \times \text{TG}) + \text{HDL-C})]$$

$$\text{LDL-C (mg/dL)} = \text{total-C} - [(0.2 \times \text{TG}) + \text{HDL-C})]$$

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

Patients with high or very high triglyceride levels, i.e. > 2.2 mmol/L (200 mg/dL) or > 5.6 mmol/L (500 mg/dL), respectively, may require triglyceride-lowering therapy (fenofibrate, bezafibrate or nicotinic acid) alone or in combination with LIPITOR.

In general, combination therapy with fibrates must be undertaken cautiously and only after risk-benefit analysis (see WARNINGS, Muscle Effects, PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions).

Elevated serum triglycerides are most often observed in patients with the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, small dense LDL particles and low HDL-cholesterol), insulin resistance with or without glucose intolerance, raised blood pressure and prothrombic and proinflammatory states).

(For the treatment of specific dyslipidemias refer to the Report of the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias or to the US NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III], under SELECTED BIBLIOGRAPHY).

When drugs are prescribed attention to therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, weight reduction, increased physical activity, ingestion of soluble fibers) should always be maintained and reinforced.

The Atorvastatin Versus Revascularization Treatments (AVERT) study examined the effect of intensive lipid-lowering in patients with stable coronary artery disease and LDL-C at least 3.0 mmol/L in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Patients were randomised for 18 months to LIPITOR 80 mg daily or to PTCA with usual medical care which could include lipid metabolism regulators. The results of the AVERT study should be considered as exploratory since several limitations may affect its design and conduct. In the medical-treated group with LIPITOR there was a trend for a reduced incidence of ischemic events and a delayed time to first ischemic event. The results also suggest that intensive treatment to target LDL-C levels with LIPITOR is **additive and complementary** to angioplasty and would benefit patients referred for this procedure (see SELECTED BIBLIOGRAPHY).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme. (See WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated Interactions).

Hepatic Effects

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR; if such a condition should develop during therapy, the drug should be discontinued.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatinine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic studies conducted in healthy subjects with erythromycin and clarithromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions).

Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors. LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ_{10}) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; SELECTED BIBLIOGRAPHY).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions).

Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

1. Friedewald WT, *et al. Clin Chem* 1972;18(6):489-502.

Pharmacokinetic Interaction Studies and Potential Drug Interactions

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also Geriatric Use; Renal Insufficiency; Patients with Severe Hypercholesterolemia).

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is limited experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class, including atorvastatin, is increased with concurrent administration (see WARNINGS, Muscle Effects and SELECTED BIBLIOGRAPHY).

Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).

Digoxin: In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily (see Human Pharmacokinetics). Patients taking digoxin should be monitored appropriately.

Antihypertensive agents (amlodipine): In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state (see Human Pharmacokinetics).

(quinapril): In a randomized, open-label study in healthy subjects, steady-state quinapril dosing (80 mg QD) did not significantly affect the pharmacokinetic profile of atorvastatin tablets (10 mg QD) (see Human Pharmacokinetics).

Oral Contraceptives and Hormone Replacement Therapy: Coadministration of LIPITOR with an oral contraceptive, containing 1 mg norethindrone and 35 µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox, TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR, however, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e. erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), protease inhibitors, or the antidepressant, nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; SELECTED BIBLIOGRAPHY).

In healthy subjects, coadministration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg), a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. preexisting prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a non-specific model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin): In healthy adults, coadministration of LIPITOR (10 mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg QD) with erythromycin (500 mg QID) or clarithromycin (500 mg BID), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin approximately 40% and 80%, respectively (see WARNINGS, Muscle Effects; Human Pharmacokinetics).

Protease Inhibitors (nelfinavir mesylate): In healthy adults, coadministration of nelfinavir mesylate (1250 mg BID), a known CYP 3A4 inhibitor, and atorvastatin (10 mg QD) resulted in increased plasma concentrations of atorvastatin. AUC and Cmax of atorvastatin were increased by 74% and 122% respectively.

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia (including familial hypercholesterolemia) are associated with increased plasma levels of atorvastatin. **Caution should be exercised in such patients who are also severely renally impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions; DOSAGE AND ADMINISTRATION).**

Drug/Laboratory Test Interactions

LIPITOR may elevate serum transaminase and creatinine phosphokinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid lowering agents) involving 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 for 1 year or more.

Adverse experiences occurring at an incidence ≥1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below:

TABLE 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials

	Placebo % (n=270)	LIPITOR % (n=1122)
GASTROINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVOUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports: severe myopathy with or without rhabdomyolysis (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated reports: thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis)]. These may have no causal relationship to atorvastatin.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Primary Hypercholesterolemia and Combined (Mixed) Dyslipidemia, Including Familial Combined Hyperlipidemia

The recommended starting dose of LIPITOR is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. Doses should be individualized according to the level of risk; the baseline LDL-C and/or TG levels; the LDL-C, TG and/or total-C/HDL-C targets (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Dyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP Adult Treatment Panel III]); the goal of therapy; and the patient's response. A significant therapeutic response is evident within two weeks, and the maximum response is usually achieved within two to four weeks. The response is maintained during chronic therapy. Adjustments of dosage, if necessary, should be made at intervals of two to four weeks. The maximum dose is 80 mg/day.

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

The following reductions in total cholesterol and LDL-C levels have been observed in 2 dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia
(Mean Percent Change from Baseline)[a]

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L[b] (273 mg/dL)[b]	-29	-33	-37	-45
LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b]	-39	-43	-50	-60

a. Results are pooled from 2 dose-response studies.
b. Mean baseline values.

Severe Dyslipidemias

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions).

Concomitant Therapy

See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency

See PRECAUTIONS.

PHARMACEUTICAL INFORMATION

Drug Substance

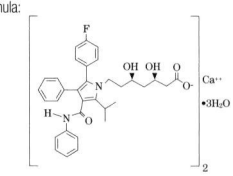
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$

Molecular Weight: 1209.42

Structural Formula:



Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition:

Each tablet contains either 10 mg, 20 mg, 40 mg or 80 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations:

Store at controlled room temperature 15 to 30°C.

AVAILABILITY OF DOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg atorvastatin per tablet.

10 mg: White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

20 mg: White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other. Available in bottles of 90 tablets.

40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PD 157" on the other. Available in bottles of 90 tablets.

80 mg: White, elliptical, film-coated tablet, coded "80" on one side and "PD 158" on the other. Available in blisters of 30 tablets (3 strips X 10).

References:

1. LIPITOR (atorvastatin calcium) Product Monograph, Pfizer Canada Inc., August 2003. **2.** IMS Health MIDAS; March 1997-March 2003. **3.** Pitt B, Waters D, Brown WV *et al.* Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. *N Engl J Med* 1999;341:70-76. **4.** Data on File, Pfizer Canada Inc. **5.** Simon Day. Dictionary for Clinical Trials, 1999, John Wiley & Sons Ltd. Pages 137-38.

For a copy of the Product Monograph or full Prescribing Information, please contact:

See page A-11

Pr Ebixa®
memantine

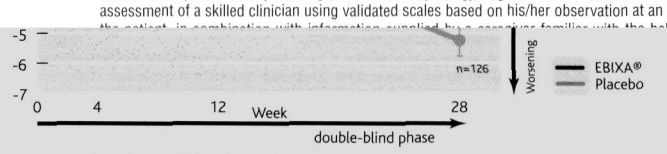
Memantine Hydrochloride Tablets 10 mg
THERAPEUTIC CLASSIFICATION:
N-methyl-D-aspartate (NMDA)
receptor antagonist

EBIXA®, indicated for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type, has been issued marketing authorization with conditions, to reflect the promising nature of the clinical evidence and the need for a confirmatory study to verify the clinical benefit. Patients should be advised of the nature of the authorization assessment.

ACTION AND CLINICAL PHARMACOLOGY: Persistent activation of the central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open channel) NMDA receptor antagonist, which binds preferentially to the NMDA receptor-operated cation channels. It blocks the effects of pathologically elevated sustained levels of glutamate that may lead to neuronal dysfunction. There is no clinical evidence that memantine prevents or slows neurodegeneration or alters the course of the underlying dementing process in patients with Alzheimer's disease. Memantine exhibits low to negligible affinity for other receptors (GABA, benzodiazepine, dopamine, adrenergic, noradrenergic, histamine and glycine) or voltage-dependent Ca^{2+}, Na^{+} or K^{+} channels. In addition, it does not directly affect the acetylcholine receptor or cholinergic transmission, which have been implicated in the cholinomimetic side effects (e.g., increased gastric acid secretion, nausea and vomiting) seen with acetylcholinesterase inhibitors. Memantine showed antagonist effects at the $5HT_3$ receptor with a potency similar to that for the NMDA receptor. In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil or galantamine.

PHARMACOKINETICS: ABSORPTION: Orally administered memantine is completely absorbed. Oral bioavailability is almost 100%. Time to maximum plasma concentration (t_{max}) following single oral doses of 10 to 40 mg memantine ranged between 3 to 8 hours. It has a terminal elimination half-life of about 60-80 hours, with the majority of the dose excreted unchanged in urine. There is no indication that food influences the absorption of memantine. Studies in volunteers have demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg. Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5-1 μ*M*) with large inter-individual variations. **DISTRIBUTION:** The apparent volume of distribution of memantine is approximately 9-11 L/kg and the plasma protein binding is approximately 45%. Memantine rapidly crosses the blood-brain barrier with a CSF/serum ratio of about 0.5. **METABOLISM AND ELIMINATION:** In a study using orally administered ^{14}C-memantine, a mean of 84% of the dose was recovered within 20 days, more than 99% being excreted renally. Memantine undergoes little metabolism being in majority excreted unchanged in urine (75-90%). The remaining dose is converted primarily to three polar metabolites: the N-gludantan conjugate, 6-hydroxy memantine and 1-nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. The hepatic microsome CYP450 enzyme system does not play a significant role in the metabolism of memantine. In volunteers with normal kidney function, total clearance (Cl_{tot}) amounts to 170 ml/min/1.73 m^2 and part of total renal clearance is achieved by tubular secretion. Renal handling also involves tubular reabsorption, probably mediated by cation transport proteins. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9 resulting in increased plasma levels of memantine (see WARNINGS, Genitourinary Conditions). Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalising gastric buffers. **SPECIAL POPULATIONS: ELDERLY PATIENTS:** The pharmacokinetics of memantine in young and elderly subjects is similar. No adjustment of dosage on the basis of age is recommended. **REDUCED HEPATIC FUNCTION:** The pharmacokinetics of memantine in patients with hepatic impairment has not been investigated. As memantine is metabolized to a minor extent into metabolites with no NMDA-antagonistic activity, changes in the pharmacokinetics are not expected to result in clinically relevant effects in patients with mild to moderate liver impairment. **REDUCED RENAL FUNCTION:** In elderly volunteers with normal and reduced renal function (creatinine clearance of 50 to ≤80 ml/min/1.73 m^2), a significant correlation was observed between creatinine clearance and total renal clearance of memantine. Following a single 20 mg oral dose of memantine, systemic exposure in geriatric subjects with mild and moderate renal impairment was 14% and 39% greater, respectively, compared to geriatric subjects with normal renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

NOC/c – CLINICAL TRIALS: The potential efficacy of EBIXA® (memantine hydrochloride) as a treatment for the symptomatic management of moderate to severe Alzheimer's disease was demonstrated by the results of 2 randomized, double-blind, placebo-controlled 6-month clinical studies. Both studies were conducted in patients with Alzheimer's disease. The mean age of patients participating in the EBIXA® trials was 76 with a range of 50 to 93 years. Approximately 66% of patients were women. Female patients participating in the clinical trials were required to be at least 50 years of age and at least 2 years postmenopausal or surgically sterile. The racial distribution was approximately 91% Caucasian. Study Outcome Measures: In each study, the effectiveness of EBIXA® was determined from instruments evaluating activities of daily living through caregiver-related evaluation, a measure of cognition, and a clinician's global assessment of change. The ability of EBIXA® to improve day-to-day function was assessed in both studies (Study 1 and Study 2) using the modified Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL_{sev}). The ADCS-ADL_{sev} consists of a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The inventory is performed by interviewing a caregiver familiar with the behaviour of the patient. The modified ADCS-ADL_{sev} consists of a subset of 19 items including ratings of the patients' ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores, and has been validated for the assessment of patients with moderate to severe dementia. The modified ADCS-ADL_{sev} scoring range is from 0 to 54, with lower scores indicating greater functional impairment. The ability of EBIXA® to improve cognitive performance was assessed in both studies (Study 1 and Study 2) with the Severe Impairment Battery (SIB), a multi-item instrument that has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. Unlike the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) the sensitivity of the SIB is not limited by floor effects in patients with advanced dementia. The SIB examines selected aspects of cognitive performance including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment. The SIB has been shown to be a valid and reliable instrument sensitive to longitudinal changes in patients with moderate to severe dementia. The ability of EBIXA® to produce an overall clinical effect was assessed in both studies (Study 1 and Study 2) using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus used in both trials was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of four domains: general (overall clinical status), functional (including activities of daily living), cognitive, and behavioural. It represents the assessment of a skilled clinician using validated scales based on his/her observation at an interview with the patient, in combination with information supplied by a caregiver familiar with the behaviour of the

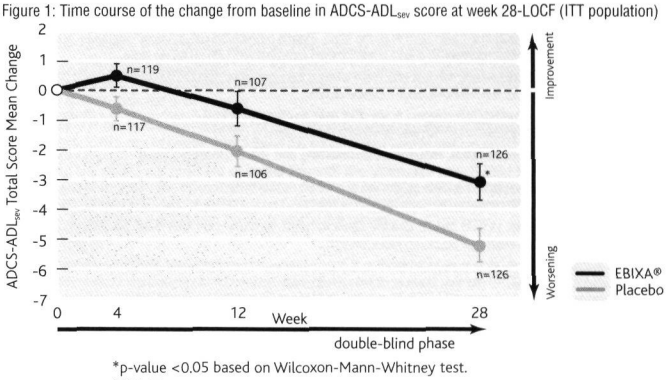


*p-value <0.05 based on Wilcoxon-Mann-Whitney test.
**LOCF

ects on the CIBIC-Plus: Figure 2 is a histogram of the percentage distribution of CIBIC-Plus scores ained by patients assigned to each of the treatment groups. The EBIXA®-placebo difference for these oups of patients in the mean rating was 0.25 units (p=0.06). EBIXA® treatment was numerically perior but not statistically significantly superior to placebo.

patients randomized to EBIXA®, treatment was initiated at 5 mg/day and increased weekly by 5 mg/day to a dose of 20 mg/day (10 mg twice a day). The percentages of randomized patients who completed the study were: placebo 67% and EBIXA® 77%. Results are presented for analyses based on all patients (ITT, Intent-to treat population) and carrying their last study observation forward (LOCF analysis). Primary efficacy endpoints were the ADCS-ADL_{sev} and CIBIC-Plus. **Effects on the ADCS-ADL_{sev}:** Figure 1 illustrates the time course for the change from baseline in the ADCS-ADL_{sev} score for the two treatment groups over the 28 weeks of the study. At endpoint, the mean difference in the ADCS-ADL_{sev} change scores for the EBIXA® -treated patients compared to the patients on placebo was 2.1 units (p=0.022). EBIXA® treatment was statistically significantly superior to placebo.

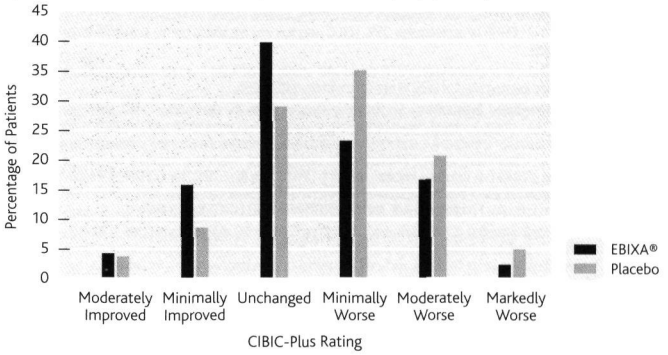
Figure 1: Time course of the change from baseline in ADCS-ADL_{sev} score at week 28-LOCF (ITT population)



*p-value <0.05 based on Wilcoxon-Mann-Whitney test.
**LOCF

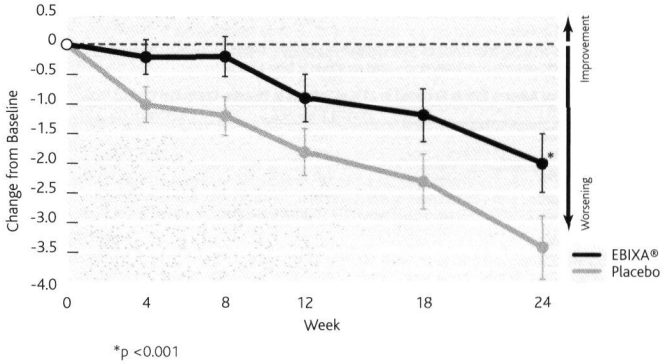
Effects on the CIBIC-Plus: Figure 2 is a histogram of the percentage distribution of CIBIC-Plus scores attained by patients assigned to each of the treatment groups. The EBIXA®-placebo difference for these groups of patients in the mean rating was 0.25 units (p=0.06). EBIXA® treatment was numerically superior but not statistically significantly superior to placebo.

Figure 2: Distribution of CIBIC-Plus ratings at week 28-LOCF (ITT population)



Effects on the SIB: The Severe Impairment Battery was used as a secondary efficacy measure. At study endpoint, the mean difference in the SIB change scores from baseline for the EBIXA®-treated patients compared to the patients on placebo was 5.9 units (p<0.001). EBIXA® treatment was statistically significantly superior to placebo. **Study 2 (Twenty-Four-Week Study)**: In a study of 24 weeks duration, 404 patients with moderate to severe Alzheimer's disease (diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥5 and ≤14) who had been treated with donepezil for at least 6 months and who had been on a stable dose of donepezil for 3 months prior to randomization were then randomized to EBIXA® or placebo, while still receiving donepezil. For patients randomized to EBIXA®, treatment was initiated at 5 mg/day and increased weekly by 5 mg/day to a dose of 20 mg/day (10 mg twice a day). The percentages of randomized patients who completed the study were: placebo/donepezil 75% and EBIXA®/donepezil 85%. The primary endpoints were the ADCS-ADL_{sev} and SIB. **Effects on the ADCS-ADL_{sev}:** Figure 3 illustrates the time course for the change from baseline in the ADCS-ADL_{sev} score for the two treatment groups over the 24 weeks of the study. The mean difference in the ADCS-ADL_{sev} change scores for the EBIXA®/donepezil treated patients compared to the patients on placebo/donepezil was 1.4 units (p=0.028). EBIXA®/donepezil treatment was statistically significantly superior to placebo/donepezil.

Figure 3: Time course of the change from baseline in ADCS-ADL_{sev} score at 24 weeks-LOCF (ITT Population)

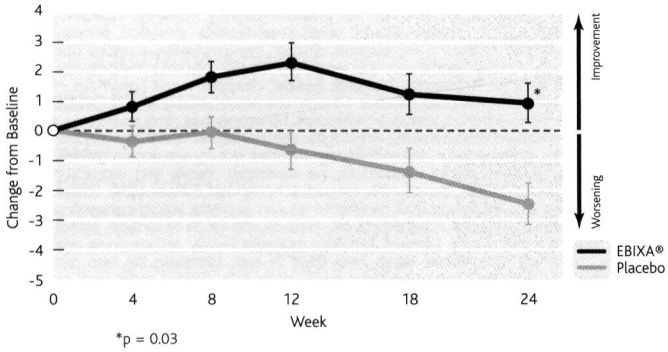


*p <0.001

Effects on the SIB: Memantine will typically ... voltage-dependent K^{+} channels. In addition, it does not direc affect the acetylcholine receptor or cholinergic transmission, which have been implicated in t cholinomimetic side effects (e.g., increased gastric acid secretion, nausea and vomiting) seen wi acetylcholinesterase inhibitors. Memantine showed antagonist effects at the $5HT_3$ receptor with a poten similar to that for the NMDA receptor. In vitro studies have shown that memantine does not affect t reversible inhibition of acetylcholinesterase by donepezil or galantamine.

PHARMACOKINETICS: ABSORPTION: Orally administered memantine is completely absorbed. O bioavailability is almost 100%. Time to maximum plasma concentration (t_{max}) following single oral dos of 10 to 40 mg memantine ranged between 3 to 8 hours. It has a terminal elimination half-life of abo 60-80 hours, with the majority of the dose excreted unchanged in urine. There is no indication that fo influences the absorption of memantine. Studies in volunteers have demonstrated line pharmacokinetics in the dose range of 10 to 40 mg. Daily doses of 20 mg lead to steady-state plasm concentrations of memantine ranging from 70 to 150 ng/ml (0.5-1 μ*M*) with large inter-individu variations. **DISTRIBUTION:** The apparent volume of distribution of memantine is approximately 9-11 L/

Figure 4: Time course of the change from baseline in SIB score at 24 weeks-LOCF (ITT Population)



*p = 0.03

Effects on the CIBIC-Plus: The CIBIC-Plus was used as a secondary efficacy measure. The EBIXA® - placebo difference of CIBIC-Plus mean rating was 0.25 units (p=0.027). EBIXA® /donepezil treatment was statistically significantly superior to placebo/donepezil.

NOC/c INDICATION AND CLINICAL USE: EBIXA® (memantine hydrochloride) may be useful as monotherapy or as adjunctive therapy with cholinesterase inhibitors[1] for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type. EBIXA® tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. In a 28-week placebo controlled monotherapy trial, patients with moderate to severe Alzheimer's disease showed stabilization or less worsening of functional and cognitive symptoms and of global assessment when treated with EBIXA® compared to placebo. In a 24 week "add-on" placebo controlled trial in which patients were treated with either EBIXA® or placebo as add-on to ongoing donepezil therapy, stabilization or less worsening of functional and cognitive symptoms and of global assessment was observed in patients with moderate to severe Alzheimer's disease when treated with EBIXA® compared to placebo. EBIXA® has not been studied in controlled clinical trials for the symptomatic treatment of moderate to severe Alzheimer's disease for more than 6 months.

[1] Cholinesterase inhibitors refers to only those which are approved in Canada for the symptomatic treatment of Alzheimers disease.

CONTRAINDICATIONS: EBIXA® (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

WARNINGS: NEUROLOGICAL CONDITIONS: Seizures: EBIXA® (memantine hydrochloride) has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the premarketing testing of EBIXA®. In clinical trials, seizures occurred in 0.3% of patients treated with EBIXA® and 0.4% of patients treated with placebo. Seizure activity may be a manifestation of Alzheimer's disease. The risk/benefit of memantine treatment for patients with a history of seizure disorder must therefore be carefully evaluated. **GENITOURINARY CONDITIONS:** Conditions that raise urine pH may reduce the urinary elimination of memantine by a factor of 7 to 9, resulting in increased plasma levels of memantine (see ACTIONS AND CLINICAL PHARMACOLOGY). These conditions include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalising gastric buffers (see Drugs Which Make Urine Alkaline, PRECAUTIONS). Also, urine pH may be elevated by states of renal tubulary acidosis (RTA) or severe infections of the urinary tract with *Proteus bacteria*. **CARDIOVASCULAR CONDITIONS:** In most clinical trials, patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), and uncontrolled hypertension were excluded. However, patients such as those with controlled hypertension (DBP <105 mm/Hg), right bundle branch blockage and pacemaker were included. Although cardiovascular adverse events occurred at low frequencies in the two placebo-controlled clinical trials involving patients with moderate to severe Alzheimer's disease, there were increased frequencies of hypertension, chest pain, bradycardia and cardiac failure adverse events in patients who were treated with EBIXA® compared to placebo in these trials. Consequently, caution should be observed when memantine is initiated in patients with cardiovascular conditions.

PRECAUTIONS: OPTHALMIC CONDITIONS: In an open label study where EBIXA® was administered to 10 elderly patients at a dose of 20 mg/day for approximately 48 months, memantine concentrations in lacrimal fluid were about 3 fold higher than in plasma and did not show ophthalmologic effects. In another 6-month placebo-controlled trial, no major treatment differences were reported for ocular effects but worsening of the corneal condition was reported for slightly more patients treated with EBIXA® than placebo (5.4% memantine vs. 3.3% placebo). Repeat-dose toxicology studies demonstrated corneal and lens histopathological changes in rodents treated with EBIXA®. Therefore, periodic monitoring of the patient's ophthalmic condition is recommended. **CONCOMITANT USE WITH OTHER DRUGS:** *Use with compounds chemically related to N-methyl-D-aspartate (NMDA) antagonists:* As these compounds act at the same receptor system as memantine, adverse drug reactions (mainly CNS-related) may be more frequent or pronounced. Pharmacotoxic psychosis has been reported in the literature in two Parkinson's disease patients who were treated concomitantly with memantine, amantadine, L-dopa and terguride (see PRECAUTIONS, Drug Interactions, Other agents). The combined use of EBIXA® with other compounds chemically related to NMDA antagonists such as amantadine, ketamine or dextromethorphan has not been systematically evaluated and is therefore not recommended. **DRUGS THAT MAKE URINE ALKALINE:** The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions. (see ACTION AND CLINICAL PHARMACOLOGY and WARNINGS). **SPECIAL POPULATIONS: HEPATIC IMPAIRMENT:** The pharmacokinetics or pharmacodynamic effects of EBIXA® have not been studied in patients with hepatic impairment. As EBIXA® undergoes minimal hepatic metabolism and is excreted primarily in its unchanged form by the kidneys, the pharmacokinetics of memantine would be expected to be only modestly affected. No adjustment in dosage is therefore recommended in hepatically impaired patients. **RENAL IMPAIRMENT:** There are limited data available from clinical trials for patients with mild to moderate renal impairment. In patients with normal to mildly impaired renal function (creatinine clearance >60 ml/min/1.73 m^2) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40-60 ml/min/1.73 m^2) daily dose should be reduced to 10 mg/day. (see PHARMACOKINETICS). There are no data available in patients with severe renal impairment (creatinine clearance less than 9 ml/min/1.73 m^2), and the use of EBIXA® in these patients is not recommended. (see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). **USE IN PATIENTS ≥ 85 YEARS OLD:** In placebo-controlled clinical studies, the number of patients aged 85 years or older who received memantine at the therapeutic dose of 20 mg/day was 40. There is limited safety information for EBIXA® in this patient population. **USE IN PATIENTS WITH SERIOUS CO-MORBID CONDITIONS:** There is limited information on the safety of memantine treatment in patients with moderate to severe Alzheimer's disease with serious co-morbidities, as these patients were excluded from clinical trials. The use of EBIXA® in Alzheimer's disease patients with chronic illnesses common among the geriatric population should be considered only after a proper risk/benefit assessment. Dose escalation in this patient population should proceed with caution. **PREGNANCY:** Oral treatment of female rats with memantine once daily during organogenesis produced mild maternal toxicity at doses of 6-18 mg/kg/day (3-9 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis); however, memantine was not teratogenic at doses up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis), the highest dose tested. In a rat reproduction and fertility study, reduced growth and a developmental delay were observed at 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). Memantine doses of 0, 3, 10 and 30 mg/kg/day were orally administered to pregnant rabbits during the period of organogenesis. At 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis) maternal toxicity and a slight increase in post-implantation loss were observed. No teratogenic effects were observed in rabbits administered memantine 30 mg/kg/day (30 times the MRHD on a mg/m^2 basis). The maternal and fetal no observed effect level (NOEL) was 10 mg/kg/day (10 times the MRHD on a mg/m^2 basis). In a peri and postnatal study, memantine was orally administered in rats at up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis). At 18 mg/kg/day pups showed reduced mean body weights but there was no effect on their development or behaviour. Animal studies showed no indication of an adverse effect of memantine on labor and delivery. There are no adequate and well-controlled studies of memantine in pregnant women to establish the safe use of EBIXA® for this population. Therefore, EBIXA® should not be used in women of childbearing potential, unless, in the opinion of the physician, the expected benefits to the patient markedly outweigh the possible hazards to the foetus. **NURSING MOTHERS:** It is not known whether memantine is excreted in human breast milk. Therefore EBIXA® should not be used in nursing mothers. **PEDIATRIC USE:** The safety and effectiveness of EBIXA® in any illness occurring in pediatric patients has not been established. Therefore, EBIXA® is not recommended for use in children. **DRUG INTERACTIONS:** *Effects of EBIXA® on substrates of microsomal enzymes:* In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) revealed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected. *Effects of inhibitors and/or substrates of microsomal enzymes on EBIXA®:* Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine. *Acetylcholinesterase (AChE) inhibitors: In vitro* studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil or galantamine. In healthy adult volunteers, under steady-state conditions of the AChE inhibitor donepezil HCl, coadministration of a single dose of EBIXA® did not affect the pharmacokinetics of either compound and did not affect donepezil-mediated AChE inhibition. In a 24-week study of patients with moderate to severe Alzheimer's disease the adverse event profiles were similar for patients treated with a combination of memantine and donepezil or placebo and donepezil. The mechanism of action and pharmacokinetics of other AChE inhibitors (e.g. galantamine and rivastigmine) differ from donepezil and the safety of co-administration of these drugs with EBIXA® has not been evaluated in clinical studies. *Drugs eliminated via renal mechanisms:* Co-administration of drugs that use the same renal cationic transport system as memantine, such as cimetidine, ranitidine, quinidine, hydrochlorothiazide (HCTZ), triamterene (TA), and nicotine could potentially alter the plasma levels of both agents. Coadministration of EBIXA® and hydrochlorothiazide/triamterene (HCTZ/TA) did not affect the bioavailability of either memantine or triamterene, and the bioavailability of HCTZ decreased by 20%. The pharmacokinetics of memantine is similar in smokers and non-smokers, suggesting that nicotine may not affect the disposition of memantine. *Drugs highly bound to plasma proteins:* Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely. Other agents: Since the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with EBIXA®, dosage adjustment of these other agents may be necessary. **CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY:** There was no evidence of carcinogenicity in a 113-week oral study in mice for either sex at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (19 and 10 times the MRHD on a mg/m^2 basis, respectively) through 128 weeks. Memantine did not show any genotoxic potential in assays for gene mutation (bacterial and mammalian cells in vitro) or in clastogenicity assays (human lymphocytes in vitro and mouse bone marrow in vivo). No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males. **ADVERSE EVENTS:** A total of 738 patients were treated with memantine in double-blind, placebo-controlled dementia studies. Of these patients, 592 (80%) completed the studies. Patients were treated with memantine for a mean of 150.3 days. Approximately 60% of patients received memantine for at least 24 weeks. **Adverse Events Leading to Discontinuation of Treatment:** In placebo-controlled trials in which dementia patients received doses of EBIXA® up to 20 mg/day, 10.8 % (80/738) of the EBIXA®-treated patients discontinued treatment due to an adverse event. The discontinuation rate in the placebo-treated patients was 11.2% (81/721). The most frequent adverse event leading to discontinuation was agitation with an observed frequency among patients who discontinued treatment of 1.2% in patients receiving memantine vs. 2.1% in patients administered placebo. None of the other adverse events leading to discontinuation met the criteria for most common adverse events, defined as those occurring at a frequency of at least 2% and at twice the incidence seen in placebo patients. **Adverse Events Reported in Placebo-Controlled Dementia Trials:** Table 1 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with EBIXA® than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving EBIXA® and at a Higher Frequency than Placebo-treated Patients

Body System	%	
Adverse Event	**Placebo (N=721)**	**EBIXA® (N=738)**
Body as a Whole		
Fatigue	0.7	2.3
Pain	1.0	2.4
Cardiovascular System		
Hypertension	2.4	3.3
Central and Peripheral Nervous System		
Dizziness	4.6	6.9
Headache	3.6	5.6
Gastrointestinal System		
Constipation	3.5	6.1
Nausea	2.4	2.8
Vomiting	2.1	3.0
Musculoskeletal System		
Back pain	2.5	2.7
Psychiatric Disorders		
Anorexia	1.2	2.2
Anxiety	0.8	2.6
Confusion	5.5	5.7
Hallucinations	1.2	2.6
Somnolence	2.2	2.8
Respiratory System		
Dyspnea	1.2	2.3

Other adverse events occurring with an incidence of at least 2% in EBIXA® -treated patients but at an equal or lower rate than placebo were agitation, arthralgia, bronchitis, cataract, coughing, depression, diarrhea, fall, gait abnormal, inflicted injury, influenza-like symptoms, insomnia, urinary incontinence and urinary tract infection. **Vital Sign Changes:** EBIXA® and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with EBIXA® treatment. **Laboratory Changes:** EBIXA® and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with EBIXA® treatment. **ECG Changes:** EBIXA® and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with EBIXA® treatment. **Adverse Events Observed in Placebo-Controlled Trial in Patients Previously Treated with Donepezil:** In an additional double-blind, placebo-controlled study, 202 patients who had been treated with donepezil for at least 6 months and who had been on stable doses of donepezil for 3 months prior to randomization were treated with memantine for a period of 24 weeks while still receiving donepezil. Of these patients, 172 (85%) completed the study. In this clinical trial, a total of 14.9% (30/202) of the memantine/donepezil patients discontinued the study compared to 25.4% (51/201) of the placebo/donepezil patients. The most frequent reason for discontinuation was adverse events and included 12% of placebo/donepezil patients and 7% of memantine/donepezil patients. Overall, the safety profile of the memantine/donepezil treated patients was similar to the one observed for the placebo-controlled dementia trials. The adverse events leading to discontinuation of the treatment, and for which the incidence was greater in the memantine/donepezil than in the placebo/donepezil group were: asthenia (memantine 1.0%; placebo 0%) dehydration (memantine 1.5%; placebo 0%) and confusion (memantine 2.0 %; placebo 1.5%). Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with EBIXA®/donepezil than for those treated with placebo/donepezil.

Table 2: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving EBIXA®/donepezil and at a Higher Frequency than Placebo/donepezil-treated Patients

Body System	**%**	
Adverse Event	**Placebo/donepezil (N=201)**	**EBIXA®/donepezil (N=202)**
Body as a Whole		
Chest pain	0.0	2.5
Fall	7.0	7.4
Fever	0.5	2.0
Oedema peripheral	4.0	5.0
Pain	0.5	3.0
Cardiovascular System		
Hypertension	1.5	4.5
Central and Peripheral Nervous System		
Gait abnormal	1.0	3.0
Headache	2.5	6.4
Gastrointestinal System		
Constipation	1.5	3.0
Vomiting	3.0	3.5
Metabolic and Nutritional Disorders		
Weight increase	0.0	2.5
Musculoskeletal System		
Arthralgia	1.5	2.5
Psychiatric Disorders		
Confusion	2.0	7.9
Depression	3.0	4.0
Red Blood Cell Disorder		
Anemia	0.5	2.0
Reproductive Disorders, Male		
Prostatic disorder	0.0	4.1
Respiratory System		
Coughing	1.0	3.0
Influenza-like symptoms	6.5	7.4
Skin and Appendages Disorders		
Rash	1.5	2.5
Urinary System Disorders		
Urinary tract infection	5.0	5.9
Urinary incontinence	3.0	5.4
Micturition frequency	0.5	2.0

Treatment emergent signs and symptoms that were reported in at least 2% of EBIXA®/donepezil treated patients (but less than 9%) were abdominal pain, agitation, anorexy, anxiety, asthenia, back pain, bronchitis, dehydration, diarrhea, dizziness, fatigue, fecal incontinence, hallucinations, inflicted injury, insomnia, personality disorder, somnolence, syncope, tremor, upper respiratory tract infection. **Other Adverse Events Observed During Clinical Trials:** EBIXA® has been administered to approximately 1150 patients with dementia, of whom more than 1000 received the maximum recommended dose of 20 mg/day. Approximately 739 patients received EBIXA® for at least 6 months of treatment and 387 patients were treated for approximately a year or more. All adverse events occurring in at least two patients are included, except for those already listed in Tables 1 and 2, WHO terms too general to be informative, or events unlikely to be caused by the drug. Also included are the adverse events observed in the placebo-controlled trial in patients who had been previously treated with donepezil prior to EBIXA® treatment. Events are classified by body system and listed using the following definitions: *frequent* – those occurring on one or more occasions in at least 1/100 patients; *infrequent* – those occurring in less than 1/100 patients but at least in 1/1000 patients. These adverse events are not necessarily related to EBIXA® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. **Autonomic Nervous System:** *Infrequent:* sweating increased, mouth dry. **Body as a Whole:** *Frequent:* asthenia, oedema, leg pain, malaise, sepsis, syncope. *Infrequent:* abscess, allergic reaction, allergy, chest pain precordial, choking, condition aggravated, ESR increased, flushing, hernia NOS, hot flushes, hypothermia, infection, infection fungal, infection viral, moniliasis, oedema peripheral, pallor, rigors, sudden death. **Cardiovascular System:** *Frequent:* angina pectoris, bradycardia, cardiac failure, cardiac failure left, heart murmur, oedema dependent. *Infrequent:* aneurysm, arrhythmia, cardiac arrest, embolism pulmonary, fibrillation atrial, heart block, heart disorder, hypertension aggravated, hypotension, hypotension postural, myocardial infarction, palpitation, phlebitis, pulmonary oedema, tachychardia, thrombophlebitis, thrombophlebitis deep, vascular disorder. **Central and Peripheral Nervous System:** *Frequent:* aphasia, ataxia, cerebrovascular disorder, hypokinesia, transient ischemic attack, vertigo. *Infrequent:* absences, cerebral hemorrhage, coma, convulsions, coordination abnormal, extrapyramidal disorder, hemiparesis, hemiplegia, hyperkinesia, hypertonia, hypoesthesia, muscle contractions involuntary, neuralgia, neuropathy, paralysis, paresthesia, ptosis, speech disorder, stupor, tremor. **Gastrointestinal System:** *Frequent:* abdominal pain, dyspepsia, fecal incontinence, hemorrhoids, tooth disorder. *Infrequent:* diverticulitis, dysphagia, esophageal ulceration, esophagitis, flatulence, gastroenteritis, gastroesophageal reflux, gastrointestinal disorder NOS, GI hemorrhage, gingivitis, hemorrhage rectum, melena, mucositis NOS, oesophagitis, saliva altered, saliva increased, stomatitis ulcerative, tooth ache, tooth caries. **Hemic and Lymphatic Disorders:** *Frequent:* purpura. *Infrequent:* epistaxis, hematoma, leukocytosis, leukopenia, polycythemia. **Metabolic and Nutritional Disorders:** *Frequent:* hyperglycemia, hypernatremia, hypokalemia, phosphatase alkaline increased, weight decrease. *Infrequent:* bilirubinemia, BUN increased, dehydration, diabetes mellitus, diabetes mellitus aggravated, gamma-GT increased, gout, hepatic enzymes increased, hepatic function abnormal, hypercholesterolemia, hyperkalemia, hyperuricemia, hyponatremia, NPN increased, polydipsia, AST increased, ALT increased, thirst. **Musculoskeletal System:** *Frequent:* arthritis, arthrosis, muscle weakness, myalgia. *Infrequent:* arthritis aggravated, arthritis rheumatoid, bursitis, skeletal pain. **Neoplasms:** *Infrequent:* basal cell carcinoma, breast neoplasm benign (female), breast neoplasm malignant (female), carcinoma, neoplasm NOS, skin neoplasm malignant. **Psychiatric Disorders:** *Frequent:* aggressive reaction, apathy, cognitive disorder, delusion, nervousness. *Infrequent:* amnesia, appetite increased, concentration impaired, crying abnormal, delirium, depersonalization, emotional lability, libido increased, neurosis, paranoid reaction, paroniria, personality disorder, psychosis, sleep disorder, suicide attempt, thinking abnormal. **Reproductive Disorders, Female:** *Infrequent:* vaginal hemorrhage, moniliasis; **Male:** *Frequent:* moniliasis. **Respiratory System:** *Frequent:* pharyngitis, pneumonia, upper respiratory tract infection, rhinitis. *Infrequent:* apnea, asthma, bronchospasm, hemoptysis, respiratory disorder, sinusitis. **Skin and Appendages:** *Frequent:* bullous eruption, herpes zoster, skin disorder, skin ulceration. *Infrequent:* alopecia, cellulitis, dermatitis, eczema, pruritus, rash erythematous, seborrhea, skin dry, skin reaction localized, urticaria. **Special Senses:** *Frequent:* cataract, conjunctivitis, eye abnormality, macula lutea degeneration, vision abnormal. *Infrequent:* blepharitis, blurred vision, conjunctival hemorrhage, corneal opacity, decreased visual acuity, diplopia, ear ache, ear disorder NOS, eye infection, eye pain, glaucoma, hearing decreased, lacrimation abnormal, myopia, xerophthalmia, retinal detachment, retinal disorder, retinal hemorrhage, tinnitus. **Urinary System:** *Frequent:* cystitis, dysuria. *Infrequent:* hematuria, micturition disorder, polyuria, pyuria, renal function abnormal, urinary retention. **Adverse Events From Other Sources:** Memantine has been commercially available in Europe since 1982, and has been evaluated in clinical trials including patients with neuropathic pain, Parkinson's disease, organic brain syndrome, and spasticity. Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment in more than one patient and are not described elsewhere in labeling: acne, bone fracture, carpal tunnel syndrome, claudication, hyperlipidemia, impotence, otitis media, thrombocytopenia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: SYMPTOMS: In a documented case of an overdosage with up to 400 mg memantine, the patient experienced restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae. **TREATMENT OF OVERDOSAGE:** Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric lavage and use of activated charcoal should be considered. Cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive measures. There are no specific antidotes for EBIXA®. Elimination of memantine can be enhanced by acidification of urine.

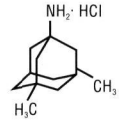
DOSAGE AND ADMINISTRATION: EBIXA® (memantine hydrochloride) should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. Therapy should only be started if a caregiver is available who will regularly monitor drug intake by the patient. Diagnosis should be made according to current guidelines. *Adults:* The recommended maintenance dose for memantine is 20 mg/day. In order to reduce the risk of side effects the maintenance dose is achieved by upward titration as follows: the usual starting dose is 5 mg/day. The dose should then be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (10 mg and 5 mg as separate doses), and 20 mg/day (10 mg twice a day), depending on the patient's response and tolerability. The minimum recommended interval between dose increases is one week. The recommended dose titration is summarized in the following table.

10 mg Tablets		
	AM	**PM**
Week 1	1/2 tablet	None
Week 2	1/2 tablet	1/2 tablet
Week 3	1 tablet	1/2 tablet
Week 4 and beyond	1 tablet	1 tablet

The tablets can be taken with or without food.

DOSES IN SPECIAL POPULATIONS: *Elderly:* On the basis of the clinical studies the recommended dose for patients over the age of 65 years is 20 mg/day (10 mg twice a day) as described above (see PHARAMCOKINETICS). *Renal impairment:* In patients with normal to mildly impaired renal function (creatinine clearance >60 ml/min/1.73 m^2) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40-60 ml/min/1.73 m^2) daily dose should be reduced to 10 mg/day. In patients with severe renal impairment the use of EBIXA® has not been systematically evaluated and is therefore not recommended in these patients (See PHARMACOKINETICS and PRECAUTIONS). *Hepatic impairment:* There are no data on the use of memantine in patients with hepatic impairment (see PHARMACOKINETICS and PRECAUTIONS). No adjustment in dosage is recommended in hepatically impaired patients.

PHARMACEUTICAL INFORMATION:
DRUG SUBSTANCE:
Common Name: Memantine hydrochloride.
Code Name: MEM3; D145; MRZ 2/145
Chemical Name: 1-amino-3,5-dimethyladamantane hydrochloride.
Structural Formula:



Molecular Formula: $C_{12}H_{22}Cl\,N$
Molecular Weight: 215.77 (hydrochloride) 179.31 (base)
Description: White, crystalline, practically odourless powder
pH: 5.5 – 6.0
pKa: 10.27
Solubility: water, hydrochloridic acid, methanol, n-hexane (soluble), methylene chloride, chloroform (freely soluble), ethylacetate (practically insoluble)
Partition Coefficient: Log P (n-octanol/water): 3.28
Composition: EBIXA® tablets contain 10 mg of memantine hydrochloride and the following non-medicinal ingredients: lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, talc, magnesium stearate, methacrylic acid-ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, triacetin, simethicone emulsion.
Stability and Storage Recommendations: EBIXA® tablets should be stored in a dry place at room temperature between 15° and 30°C.
AVAILABILITY OF DOSAGE FORMS: EBIXA® (memantine hydrochloride) is available as white to off-white tablets.
10 mg tablets: White to off-white, centrally tapered oblong, biconvex, film-coated tablet with a single break line on both sides. Blister packages of 30 tablets.

Product Monograph available to Healthcare professionals upon request.

Lundbeck Canada Inc.
413 St-Jacques Street West, Suite FB-230
Montreal (Quebec), Canada H2Y 1N9

Lundbeck

EBX-011-05 E

Member R&D PAAB

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ONCE-A-WEEK

AVONEX®

(Interferon beta-1a)

IM Injection

PRESCRIBING INFORMATION

THERAPEUTIC CLASSIFICATION

Immunomodulator

INDICATIONS AND CLINICAL USE

Relapsing Forms of Multiple Sclerosis:

AVONEX® (Interferon beta-1a) is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to slow the progression of disability, decrease the frequency of clinical exacerbations, and reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.

Single Demyelinating Event:

AVONEX® is also indicated for the treatment of people who have experienced a single demyelinating event, accompanied by abnormal Magnetic Resonance Imaging (MRI) scans with lesions typical of MS, to delay the onset of clinically definite multiple sclerosis (as determined by a second demyelinating event), and to decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans). Before initiating treatment with AVONEX, alternate diagnoses should first be excluded.

Safety and efficacy have not been evaluated in patients with chronic progressive multiple sclerosis.

CONTRAINDICATIONS

AVONEX® (Interferon beta-1a) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

WARNINGS

AVONEX® should be used under the supervision of a physician. The first injection should be performed under the supervision of an appropriately qualified health care professional (see **DOSAGE AND ADMINISTRATION**).

Depression and Suicide

AVONEX® (Interferon beta-1a) should be used with caution in patients with depression. Depression and suicide have been reported to occur in patients receiving other interferon compounds. Depression and suicidal ideation are known to occur at an increased frequency in the MS population. A relationship between the occurrence of depression and/or suicidal ideation and the use of AVONEX® has not been established. An equal incidence of depression was seen in the placebo-treated and the AVONEX®-treated patients in the placebo controlled study of relapsing MS patients. In the study of patients with a single demyelinating event AVONEX®-treated patients were more likely to experience depression than placebo-treated patients ($p = 0.05$). Suicidal tendency occurred in one subject treated with placebo, and there were no reports of suicide attempts. Patients treated with AVONEX® should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, antidepressant therapy or cessation of AVONEX® therapy should be considered.

Anaphylaxis

Anaphylaxis has been reported as a rare complication of AVONEX® use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria (see **ADVERSE EVENTS**).

Decreased Peripheral Blood Counts

Decreased peripheral blood counts in all cell lines, including very rare pancytopenia and thrombocytopenia have been reported from post-marketing experience (see **ADVERSE EVENTS**). Some cases of thrombocytopenia have had nadirs below 10,000/μL. Some cases reoccur with re-challenge. Patients should be monitored for signs of these disorders (see **PRECAUTIONS**: Laboratory Tests).

Pregnancy and Lactation

AVONEX® should not be administered in case of pregnancy and lactation. There are no adequate and well-controlled studies of AVONEX® in pregnant women. Patients should be advised of the abortifacient potential of AVONEX®. Fertile women receiving AVONEX® should be advised to take adequate contraceptive measures. It is not known if interferons alter the efficacy of oral contraceptives (see **PRECAUTIONS**: Information to Patients).

If a woman becomes pregnant or plans to become pregnant while taking AVONEX®, she should be informed of the potential hazards to the fetus, and it should be recommended that the woman discontinue therapy. The reproductive toxicity of AVONEX® has not been studied in animals or humans. In pregnant monkeys given interferon beta at 100 times the recommended weekly human dose (based upon a body surface area comparison), no teratogenic or other adverse effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses at this level. No abortifacient effects were observed in monkeys treated at 2 times the recommended weekly human dose (based upon a body surface area comparison). Although no teratogenic effects were seen in these studies, it is not known if teratogenic effects would be observed in humans. There are no adequate and well-controlled studies with interferons in pregnant women.

Nursing Mothers

It is not known whether AVONEX® is excreted in human milk. Because of the potential of serious adverse reactions in nursing infants, a decision should be made to either discontinue nursing or to discontinue AVONEX®.

PRECAUTIONS

General

Patients should be informed of the most common adverse events associated with interferon beta administration, including symptoms of the flu-like syndrome (see **ADVERSE EVENTS**). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment (see **PRECAUTIONS**: Information to Patients).

Seizures

Caution should be exercised when administering AVONEX® (Interferon beta-1a) to patients with pre-existing seizure disorder. In the two placebo-controlled studies of MS, 4 patients receiving AVONEX® experienced seizures, while no seizures occurred in the placebo group. Of these 4 patients, 3 had no prior history of seizure. It is not known whether these events were related to the effects of MS alone, to AVONEX®, or to a combination of both. For patients with no prior history of seizure who developed seizures during therapy with AVONEX®, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to considering resumption of AVONEX® treatment. The effect of AVONEX® administration on the medical management of patients with seizure disorder is unknown.

Cardiac Disease

Patients with cardiac disease, such as angina, congestive heart failure, or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation and continued treatment with AVONEX®. While AVONEX® does not have any known direct-acting cardiac toxicity, during the post-marketing period infrequent cases of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure have been reported in patients without known predisposition to these events or other known etiologies. In rare cases, these events have been temporally related to the administration of AVONEX® and have recurred upon re-challenge in patients with known predisposition.

Autoimmune Disorders

As with other interferon treatment, autoimmune disorders of multiple target organs have been reported post marketing including idiopathic thrombocytopenia, hyper and hypothyroidism, and rare cases of autoimmune hepatitis have also been reported. Patients should be monitored for signs of these disorders (see **PRECAUTIONS**: Laboratory Tests) and appropriate treatment implemented when observed.

Hepatic Injury

AVONEX®, like other interferon beta products, has the potential for causing severe liver injury (see **ADVERSE EVENTS**). Hepatic injury including elevated serum hepatic enzyme levels and hepatitis, some of which have been severe, has been reported post-marketing. In some patients a recurrence of elevated serum levels of hepatic enzymes have occurred upon AVONEX® re-challenge. In some cases, these events have occurred in the presence of other drugs that have been associated with hepatic injury. The potential of additive effects from multiple drugs or other hepatotoxic agents (e.g., alcohol) has not been determined. Patients should be monitored for signs of hepatic injury (see **PRECAUTIONS**: Laboratory Tests) and caution exercised when AVONEX® is used concomitantly with other drugs associated with hepatic injury.

Laboratory Tests

Laboratory abnormalities are associated with the use of interferons. During the placebo-controlled trials in multiple sclerosis, liver function tests were performed at least every 6 months. Liver function tests including serum ALT are recommended during AVONEX® therapy and should be performed at baseline, monthly at months 1 through 6, and every 6 months thereafter. AVONEX® should be initiated with caution in patients with a history of significant liver disease, clinical evidence of active liver disease, alcohol abuse, increased serum ALT (>2.5 times ULN), and in patients receiving concomitant medications associated with hepatic injury. These patients may require more frequent monitoring of serum hepatic enzymes. Discontinuation or interruption of AVONEX® should be considered if ALT rises above 5 times the ULN. Treatment with AVONEX® should be stopped if jaundice or other clinical symptoms of liver dysfunction appear. In addition to those laboratory tests normally required for monitoring patients with MS, and in addition to liver enzyme monitoring (see **PRECAUTIONS**: Hepatic Injury) complete blood cell counts and white blood cell differential, platelet counts, and blood chemistries, including thyroid function tests, are recommended during AVONEX® therapy (see **WARNINGS**: Decreased Peripheral Blood Counts and **ADVERSE EVENTS**). These tests should be performed at baseline, months 1, 3, 6, and every 6 months thereafter. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Immunogenicity

Serum neutralizing antibodies were reported to develop in only 2% to 6% of AVONEX®-treated patients. Although the exact clinical significance of antibodies has not been fully established, there are multiple literature reports indicating that the occurrence of neutralizing antibodies with beta interferon treatment impacts clinical efficacy, MRI measures and the induction of biological markers.

Drug Interactions

No formal drug interaction studies have been conducted with AVONEX®. In the placebo-controlled study, corticosteroids or ACTH were administered for treatment of exacerbations in some patients concurrently receiving AVONEX®. In addition, some patients receiving AVONEX® were also treated with anti-depressant therapy and/or oral contraceptive therapy. No unexpected adverse events were associated with these concomitant therapies.

Other interferons have been noted to reduce cytochrome P-450 oxidase-mediated drug metabolism. Formal hepatic drug metabolism studies with AVONEX® in humans have not been conducted. Hepatic microsomes isolated from AVONEX®-treated rhesus monkeys showed no influence of AVONEX® on hepatic P-450 enzyme metabolism activity.

As with all interferon products, proper monitoring of patients is required if AVONEX® is given in combination with myelosuppressive agents.

Carcinogenesis and Mutagenesis

Carcinogenesis: No carcinogenicity data for Interferon beta-1a are available in animals or humans.

Mutagenesis: Interferon beta-1a was not mutagenic when tested in the Ames bacterial test and in an in vitro cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation. These assays are designed to detect agents that interact directly with and cause damage to cellular DNA. Interferon beta-1a is a glycosylated protein that does not directly bind to DNA.

Impairment of Fertility

No studies were conducted to evaluate the effects of interferon beta on fertility in normal women or women with MS. It is not known whether AVONEX® can affect human reproductive capacity. Menstrual irregularities were observed in monkeys administered interferon beta at a dose 100 times the recommended weekly human dose (based upon a body surface area comparison). Anovulation and decreased serum progesterone levels were also noted transiently in some animals. These effects were reversible after discontinuation of drug.

Treatment of monkeys with interferon beta at 2 times the recommended weekly human dose (based upon a body surface area comparison) had no effects on cycle duration or ovulation.

The accuracy of extrapolating animal doses to human doses is not known. In the placebo-controlled study, 6% of patients receiving placebo and 5% of patients receiving AVONEX® experienced menstrual disorder. If menstrual irregularities occur in humans, it is not known how long they will persist following treatment.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients below the age of 18 years.

Information to Patients

Patients should be informed of the most common adverse events associated with AVONEX® administration, including symptoms associated with flu syndrome (see **ADVERSE EVENTS**).

Symptoms of flu syndrome are most prominent at the initiation of therapy and decrease in frequency with continued treatment. In the placebo-controlled study, patients were instructed to take 650 mg acetaminophen immediately prior to injection and for an additional 24 hours after each injection to modulate acute symptoms associated with AVONEX® administration.

Patients should be advised not to stop or modify their treatment unless instructed by their physician.

Patients should be cautioned to report depression or suicidal ideation (see **WARNINGS**).

Patients should be informed about the risk of decreased blood counts including white blood cells and platelet counts and of the requirement for periodic laboratory testing (see **WARNINGS**). Patients should be advised to report immediately any clinical symptoms associated with blood count abnormalities and laboratory testing should be performed according to standard medical practice (see **WARNINGS**). Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Patients should be informed of the potential risk of liver injury with AVONEX® therapy, and of the requirement for frequent laboratory testing (see **PRECAUTIONS**). Patients should be informed of the symptoms suggesting liver dysfunction, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, and jaundice, and advised to consult with their physician immediately should such symptoms arise.

Patients should be instructed to report any symptoms of thyroid dysfunction (hypo or hyperthyroidism) and thyroid function tests should be performed according to standard medical practice (see **PRECAUTIONS**).

Female patients should be advised about the abortifacient potential of AVONEX® and instructed to take adequate contraceptive measures (see **PRECAUTIONS**).

When a physician determines that AVONEX® can be used outside of the physician's office, persons who will be administering AVONEX® should receive instruction in reconstitution and injection, including the review of the injection procedures. If a patient is to self-administer, the physical ability of that patient to self-inject intramuscularly should be assessed. If home use is chosen, the first injection should be performed under the supervision of a qualified health care professional. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of injection site reactions. A puncture-resistant container for disposal of needles and syringes should be used. Patients should be instructed in the technique and importance of proper syringe and needle disposal and be cautioned against reuse of these items.

ADVERSE EVENTS

Relapsing Multiple Sclerosis

The safety data describing the use of AVONEX® (Interferon beta-1a) in MS patients are based on the placebo-controlled trial in which 158 patients with relapsing multiple sclerosis randomized to AVONEX® were treated for up to 2 years.

The 5 most common adverse events associated (at $p < 0.075$) with AVONEX® treatment were flu-like symptoms (otherwise unspecified), muscle ache, fever, chills, and asthenia. The incidence of all 5 adverse events diminished with continued treatment.

One patient in the placebo group attempted suicide; no AVONEX®-treated patients attempted suicide. The incidence of depression was equal in the 2 treatment groups. However, since depression and suicide have been reported with other interferon products, AVONEX® should be used with caution in patients with depression (see **WARNINGS**).

In the placebo-controlled study, 4 patients receiving AVONEX® experienced seizures, while no seizures occurred in the placebo group. Of these 4 patients, 3 had no prior history of seizure. It is not known whether these events were related to the effects of MS alone, to AVONEX®, or to a combination of both (see **PRECAUTIONS**).

Table 1 enumerates adverse events and selected laboratory abnormalities that occurred at an incidence of 2% or more among the 158 patients with relapsing MS treated with 30 mcg of AVONEX® once weekly by IM injection. Reported adverse events have been classified using standard COSTART terms. Terms so general as to be uninformative or more common in the placebo-treated patients have been excluded.

Table 1

Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study of Relapsing MS

Adverse Event	Placebo (N = 143)	AVONEX® (N = 158)
Body as a Whole		
Headache	57%	67%
Flu-like symptoms (otherwise unspecified)*	40%	61%
Pain	20%	24%
Fever*	13%	23%
Asthenia	13%	21%
Chills*	7%	21%
Infection	6%	11%

Continued on page 39

PRESCRIBING INFORMATION

PrReminyl*

Galantamine hydrobromide tablets

PrREMINYL*

galantamine hydrobromide tablets

4 mg, 8 mg, 12 mg galantamine base

Cholinesterase Inhibitor

CLINICAL PHARMACOLOGY

Although the etiology of cognitive impairment in Alzheimer's Disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's Disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's Disease).

REMINYL (galantamine hydrobromide), a tertiary alkaloid, is a competitive and reversible cholinesterase inhibitor. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible cholinesterase inhibition. It has also been postulated, based on *in vitro* data, that galantamine enhances the action of acetylcholine through binding to an allosteric site on the nicotinic receptors (see PRECAUTIONS). The clinical relevance to humans of these *in vitro* findings is unknown.

If these mechanisms are correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

Pharmacokinetics

Absorption

The summary of related pharmacokinetic parameters in healthy subjects is presented in Table 1. After oral intake of a single 8 mg galantamine solution in 12 healthy males, absorption is rapid, with a peak plasma concentration (C_{max}) of 43 ± 13 ng/mL, which is reached after 1.2 hours (T_{max}), and a mean AUC_{∞} of 427 ± 102 ng.h/mL.

The absolute oral bioavailability of galantamine is 88.5%. Bioavailability of the tablet was the same as the bioavailability of an oral solution in 27 healthy males. Food did not affect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours after repeated oral dosing of 12 mg galantamine b.i.d. in 24 healthy elderly subjects.

The maximum inhibition of anticholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Table 1. Pharmacokinetic parameters of galantamine after single or multiple dose administration

	C_{max} (ng/mL)	t_{max} (h)	$C_{ss,av}$ (ng/mL)	C_{min} (ng/mL)	AUC† (ng.h/mL)	$T_{1/2}$ (h)
Single dose, 12 healthy males						
8 mg, solution p.o.	42.6 ± 13.1	1.2 ± 0.6	-	-	427 ± 102	7.3 ± 1.7
8 mg, 1 hr i.v. infusion	-	-	-	-	482 ± 112	7.4 ± 1.7
Food effect, single dose, 24 healthy elderly						
Fasted, 8 mg p.o.	57.5 ± 15.8	1.1 ± 0.5	-	-	562 ± 180	9.7 ± 3.1
Non-fasted, 8 mg p.o.	42.5 ± 7.5	2.6 ± 1.4	-	-	543 ± 176	9.7 ± 3.3
Multiple oral dose, 27 healthy males						
12 mg b.i.d. tablet	89.4 ± 18.3	1.0 ± 0.6	51.9 ± 12.2	30.7 ± 10.3	623 ± 147	-
12 mg b.i.d. solution	87.6 ± 20.5	1.1 ± 0.5	50.5 ± 13.0	29.8 ± 10.2	606 ± 156	-
Dose-proportionality, multiple oral dose, 18 healthy subjects						
4 mg b.i.d. tablet	30.7 ± 6.2	1.9 ± 0.8	17.7 ± 4.6	10.6 ± 4.0	212 ± 56	-
8 mg b.i.d. tablet	63.8 ± 14.2	1.7 ± 0.8	36.6 ± 9.8	20.6 ± 6.8	439 ± 117	-
12 mg b.i.d. tablet	97.4 ± 31.4	1.9 ± 1.1	53.1 ± 12.7	29.1 ± 9.3	637 ± 152	-
16 mg b.i.d. tablet	137 ± 36	1.7 ± 0.9	76.5 ± 20.3	41.5 ± 14.2	918 ± 244	7.9 ± 0.8

† AUC = AUC_{∞} after single dose and AUC = AUC_{τ} after multiple dose

Distribution

Galantamine is a low-clearance drug (plasma clearance of approximately 300 mL/min) with a moderate volume of distribution (average Vd_{SS} of 175 L) after a one-hour i.v. infusion of 8 mg galantamine in 12 healthy males.

The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%) and plasma water (39.0%), whereas the fraction of galantamine bound to plasma proteins is only 8.4%. The blood-to-plasma concentration ratio of galantamine is 1.2.

Metabolism

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 are the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see PRECAUTIONS, Drug-Drug Interactions). O-demethylation, mediated by CYP2D6 is greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

Elimination

The elimination of galantamine is bi-phasic, with a terminal half-life in the order of 7-8 hours in young healthy subjects (n=4 males). Two studies in healthy elderly subjects indicated that the terminal half-life of galantamine is 8.5 hours (n=13 males and 16 females) and 9.7 hours (n=10 males and 14 females) after administering a single oral dose of 10 mg galantamine. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide accounted for 14-24%. Seven days after a single oral dose of 4 mg ^{3}H-galantamine, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose, and that of galantamine glucuronide for another 12% on average.

After i.v. and oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, with a renal clearance of about 65 mL/min, which represents 20-25% of the total plasma clearance of about 300 mL/min.

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of the CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar C_{max} and about 35% AUC_{∞} increase of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two Phase III studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability due to observed inter-patient variability.

Hepatic Impairment

Following a single 4 mg dose of galantamine, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child-Pugh score of 7-9), AUC and half-life of galantamine were increased by about 30% compared to normal subjects (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment

In patients with renal insufficiency, elimination of galantamine decreases with decreasing creatinine clearance. Following a single 8 mg dose of galantamine, AUC increased by 37% and 67% in moderately (n=8; creatinine clearance of 30 to 60 mL/min/1.73 m^2) and severely (n=9; creatinine clearance of 5 to 29 mL/min/1.73 m^2) renal-impaired patients compared to normal volunteers (n=8) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Patients with Alzheimer's Disease

Data from clinical trials in patients indicate that there is a difference in total clearance after oral administration between patients with Alzheimer's Disease and healthy subjects (13.2 L/h versus 19.4 L/h) based on pooled population analysis. Therefore, the plasma concentrations of galantamine in elderly patients (median age 75) with Alzheimer's Disease are 30-40% higher than in healthy young subjects (median age 28).

Gender and Race

No specific pharmacokinetic study was performed to investigate the gender differences. A population pharmacokinetic analysis (n=539 males and 550 females) suggests that galantamine clearance is about 20% lower in females than in males, which is explained by lower body weight in females.

Pharmacokinetic differences due to race have not been identified in a population pharmacokinetic analysis (n=1029 White, 24 Black, 13 Asian and 23 other).

Clinical Trials

Efficacy data for REMINYL (galantamine hydrobromide) in the symptomatic treatment of patients with Alzheimer's Disease were derived from 4 randomized, double-blind, placebo-controlled clinical trials in patients with probable Alzheimer's Disease [diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination Scores that were ≥10 and ≤24]. Doses studied were 8-32 mg/day given as twice daily doses. In 3 of the 4 studies, patients were started on a low dose of 8 mg, then titrated weekly by 8 mg/day to 24 or 32 mg as assigned (GAL-USA-1, GAL-INT-1, GAL-INT-2). In the fourth study (U.S. 4-week Dose-Escalation Fixed-Dose Study, GAL-USA-10) dose escalation of 8 mg/day occurred over 4 week intervals. The mean age of patients participating in the 4 REMINYL trials was 75 years with a range of 41 to 100. Approximately 62% of patients were women and 38% were men. The racial distribution was White 94%, Black 3% and other races 3%. Two other studies examined a three times daily dosing regimen; these also showed or suggested benefit but did not suggest an advantage over twice daily dosing.

Results for 2 of these studies are presented in this section. The data shown below were obtained from the Intent-To-Treat population (ITT analysis, i.e. all patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete the study, their last observation while on treatment was carried forward and used at endpoint).

Study Outcome Measures: In each study, the primary efficacy of REMINYL was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-plus).

The ability of REMINYL to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance, including elements of memory, orientation, attention, reasoning, language and praxis.

The patients recruited as participants in each study had mean scores on the ADAS-cog of approximately 27 units, with a range from 5 to 69. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in REMINYL trials was approximately 4.5 units per year.

The ability of REMINYL to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus used in the trials was a semi-structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 4 major areas of patient function: general, cognitive, behavioural and activities of daily living. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-plus evaluations from other clinical trials.

Among the secondary measures of efficacy, the Alzheimer's Disease Cooperative Study, Activities of Daily Living Inventory (ADCS/ADL) was used. The ADCS/ADL is a caregiver-rated evaluation which yields a compound score derived from a categorical scale of 23 items concerning participation in activities of daily living.

U.S. Twenty-One-Week Fixed-Dose Study (GAL-USA-10)

In a study of twenty-one weeks' duration, 978 patients were randomized to doses of 8, 16, or 24 mg of REMINYL per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to REMINYL, and increased by 8 mg/day every 4 weeks. Therefore, the maximum dose-escalation phase was 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day of REMINYL).

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 0.8, 2.9 and 2.9 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups.

Figure 1: Time-course of the Changes from Baseline in ADAS-cog Score (ITT Population)

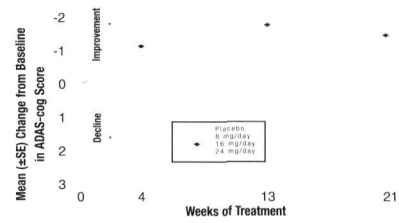
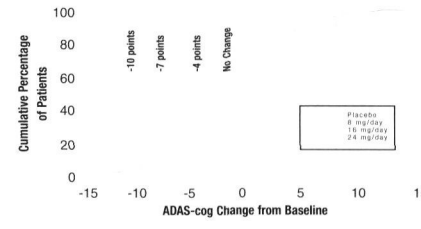


Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percentage of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements.

Figure 2: Cumulative Percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	3.7%	7.8%	19.0%	43.9%
8 mg/day	4.5%	11.4%	22.7%	47.7%
16 mg/day	6.4%	15.0%	33.1%	67.3%
24 mg/day	8.8%	19.8%	32.4%	62.6%

Effects on the CIBIC-plus: Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups. The REMINYL-placebo differences for these groups of patients in the mean rating were 0.10, 0.32 and 0.38 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.22 and 0.28, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

Figure 3: Distribution of CIBIC-plus Ratings at Week 21 (ITT Population)

of 24 mg or 32 mg of REMINYL per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose-escalation phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog score for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean difference in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 3.2 and 2.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not statistically significantly different from each other.

Figure 4: Time-course of the Changes from Baseline in ADAS-cog Score (ITT Population)

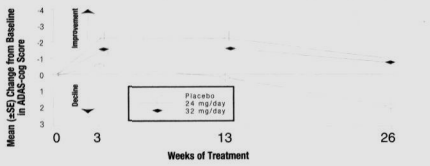
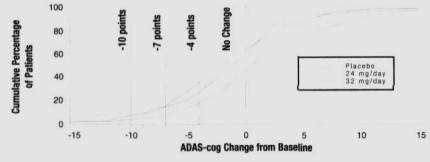


Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements. Curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

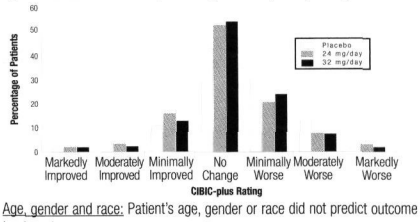
Figure 5: Cumulative Percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	2.3%	5.6%	16.4%	45.5%
24 mg/day	5.8%	14.0%	34.3%	63.8%
32 mg/day	7.7%	13.4%	25.8%	61.2%

Effects on the CIBIC-plus: Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups. The mean REMINYL-placebo differences for these groups of patients in the mean rating were 0.22 and 0.17 units for 24 and 32 mg/day of REMINYL, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 6: Distribution of CIBIC-plus Ratings Week 26 (ITT Population)



Age, gender and race: Patient's age, gender or race did not predict outcome of treatment.

INDICATIONS AND CLINICAL USE

REMINYL (galantamine hydrobromide) is indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL has not been studied in controlled clinical trials for longer than 6 months.

REMINYL should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease and of severe Alzheimer's Disease, non-Alzheimer dementias or individuals with Parkinson's Disease features. The efficacy and safety of REMINYL in these patient populations is unknown.

Pulmonary Conditions

Like other cholinomimetic drugs, REMINYL should be prescribed with care for patients with a history of asthma or obstructive pulmonary disease.

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and heart block. These actions may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction disorders, or to patients taking other drugs concomitantly which significantly slow heart rate. In clinical trials, patients with serious cardiovascular disease were excluded. Caution should be exercised in treating patients with active coronary artery disease or congestive heart failure. It is recommended that REMINYL not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes.

In randomized controlled trials, bradycardia was reported at 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo, and it rarely led to treatment discontinuation. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day at the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo, 0.7% [2/286]; 4 mg b.i.d., 0.4% [3/692]; 8 mg b.i.d., 1.3% [7/552]; 12 mg b.i.d., 2.2% [6/273]).

A 6-week cardiovascular safety clinical trial (GAL-USA-16; n=139) was performed to investigate the effect of galantamine at doses up to 32 mg/day. This dosing regimen was: 8 mg/day in Week 1, 16 mg/day in Week 2, 24 mg/day in Weeks 3 and 4, and 32 mg/day in Weeks 5 and 6. Heart block/pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients. It should be noted that a forced 1-week dose escalation was used in this study, which is not recommended. Whether these cardiac effects are attenuated by slower titration rates is not known. Particular caution is warranted during titration where the majority of pauses occurred in the above study.

Gastrointestinal Conditions

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g. those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). In controlled clinical studies with REMINYL, patients with symptomatic peptic ulceration were excluded. Clinical studies of REMINYL have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see ADVERSE REACTIONS).

REMINYL, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting and diarrhea, anorexia and weight loss. These effects appeared more frequently at higher doses (see ADVERSE REACTIONS), with nausea and vomiting being more prevalent in women and patients with lower body weight and correspondingly higher plasma drug concentrations. Females are more sensitive to the cholinergic adverse effects associated with cholinesterase inhibitors and in general are more likely to experience nausea and vomiting than are males. In most cases, these effects were of mild to moderate intensity and transient and have resolved during continued REMINYL treatment or upon treatment discontinuation.

Weight Loss

Cholinesterase inhibitors as well as Alzheimer's Disease can be associated with significant weight loss. In controlled clinical trials, the use of REMINYL was associated with weight loss. Weight decrease occurred early during treatment and was related to dose. Weight loss of ≥7% occurred more frequently in patients treated with REMINYL and in female patients than in patients receiving placebo. Where weight loss may be of clinical concern, body weight should be monitored.

Genitourinary

Although not observed in clinical trials of REMINYL, cholinomimetics may cause bladder outflow obstruction.

PRECAUTIONS

Concomitant Use with Other Drugs

Use with Anticholinergics

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use in Elderly Patients with Serious Comorbid Disease

There is limited information on the safety of REMINYL treatment in patients with mild to moderate Alzheimer's Disease and serious/significant comorbidity. The use of REMINYL in Alzheimer's Disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Dose escalation in this patient population should proceed with caution.

Renally and Hepatically Impaired Patients

There is limited information on the pharmacokinetics of REMINYL in renally and hepatically impaired patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics). It is therefore recommended that dose escalation with REMINYL in Alzheimer's Disease patients with renal impairment (creatinine clearance of 9 to 60 mL/min) or hepatic impairment be undertaken with caution and under conditions of close monitoring for adverse effects (see DOSAGE AND ADMINISTRATION, Special Populations). Since no data are available on the use of REMINYL in patients with a creatinine clearance of less than 9 mL/min and in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL is not recommended for these populations.

Drug-Drug Interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide.

Effect of Other Drugs on the Metabolism of REMINYL

Pharmacokinetic studies to assess the potential of REMINYL for interaction with cimetidine, ranitidine, ketoconazole, erythromycin, paroxetine, warfarin and digoxin were limited to short-term, mostly single-dose studies in young healthy volunteers. Similar studies in elderly patients were not done.

In vitro

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide, whereas CYP2D6 is involved in the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged in urine, no single pathway appears predominant.

In vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on Day 2 of a 3-day treatment with either cimetidine (800 mg daily; n=6 males and 6 females) or ranitidine (300 mg daily; n=6 males and 6 females). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the pharmacokinetics of galantamine.

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg b.i.d. for 4 days, increased the AUC of galantamine by 30% when subjects were treated with galantamine 4 mg b.i.d. for 8 days (n=8 males and 8 females).

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg q.i.d. for 4 days increased the AUC of galantamine by 10% when subjects received galantamine 4 mg b.i.d. for 6 days (n=8 males and 8 females).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, increased the AUC of 4 mg b.i.d., 8 mg b.i.d. and 12 mg b.i.d. galantamine by 40%, 45% and 48%, respectively, in 16 healthy volunteers (8 males and 8 females) who received galantamine together with 20 mg/day paroxetine.

Effect of Galantamine on the Metabolism of Other Drugs

In vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In vivo

Warfarin: Galantamine at 12 mg b.i.d. had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time (n=16 males). The protein binding of warfarin was unaffected by galantamine.

Digoxin: Galantamine at 12 mg b.i.d. had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were co-administered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia (n=8 males and 8 females).

Nicotinic Receptor Modulation

Single *in vitro* applications of galantamine dose-dependently modulate the effect on nicotinic receptors, having a positive allosteric (sensitizing) effect at concentrations below 0.28 µg/mL (1 µM) and an inhibitory effect at higher concentrations. Chronic *in vitro* or *in vivo* studies on nicotinic receptor modulation have not been conducted.

It is unknown whether galantamine has an effect on the pharmacodynamic action of other drugs that act on cholinergic nicotinic receptors (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis), and 30 mg/kg/day (12 times the MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

In a teratology study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the MRHD on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through Day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis.

The safety of REMINYL in pregnant women has not been established. REMINYL should not be used in women of childbearing potential unless, in the opinion of the physician, the potential benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether REMINYL is excreted in human breast milk and therefore REMINYL should not be used in nursing mothers.

Pediatric Use

The safety and effectiveness of REMINYL in any illness occurring in pediatric patients have not been established.

ADVERSE REACTIONS

A total of 2287 patients with mild to moderate Alzheimer's Disease were treated with REMINYL (galantamine hydrobromide) in Phase III controlled clinical studies using either a 1-week or 4-week dose-escalation period, and 761 patients received REMINYL 24 mg/day, the maximum recommended maintenance dose. The number of patients who completed the studies was 1686 (72%). The mean duration of treatment for all REMINYL groups was 130 days (range 1-214 days).

Adverse Events Leading to Discontinuation

Overall, 19% (441/2287) of patients treated with REMINYL discontinued from Phase III controlled clinical trials due to adverse events compared to 8% (98/1159) in the placebo group. For patients treated with REMINYL, the rate of discontinuation due to adverse events was 14% for males and 22% for females.

In the 4-week dose-escalation fixed-dose study (GAL-USA-10), 8% (55/692) of patients treated with REMINYL withdrew due to adverse events compared to 7% (20/286) in the placebo group. During the dose-escalation phase of this study the incidence of discontinuations due to adverse events was 4% for placebo, 5% for REMINYL 16 mg/day and 6% for REMINYL 24 mg/day. During the maintenance phase, 4% of patients who received placebo, 3% of patients who received REMINYL 16 mg/day and 4% of patients who received REMINYL 24 mg/day withdrew from this study due to adverse events.

Table 1 shows the most frequent adverse events leading to discontinuation for study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used.

Table 1: Most frequent adverse events leading to discontinuation in a placebo-controlled, double-blind trial with a 4-week dose-escalation schedule (GAL-USA-10)

Adverse Events	Recommended 4-week dose escalation		
	Placebo n=286	16 mg/day n=279	24 mg/day n=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate of placebo in study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used are shown in Table 2. These events were primarily gastrointestinal and tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose.

Table 2: Most frequent adverse events in a randomized placebo-controlled clinical trial with a 4-week dose increment during dose-escalation and maintenance phases (GAL-USA-10)

Adverse Events	Week 1-12†			Week 13-21		
	Placebo n=286	16 mg/day n=279	24 mg/day n=273	Placebo n=259	16 mg/day n=243	24 mg/day n=241
Nausea	5%	11%	13%	<1%	4%	6%
Vomiting	<1%	5%	6%	<1%	2%	6%
Diarrhea	5%	9%	4%	2%	5%	2%
Anorexia	2%	5%	5%	1%	2%	5%

† Dose escalation occurred with 4 weeks per dose increment.

The majority of these adverse events occurred during the dose-escalation period. Nausea and vomiting, the most frequent adverse events, occurred more frequently at higher doses, lasted 5-7 days in most cases, and the majority of patients had one episode. The incidence of weight loss in this study was, during dose escalation (Weeks 1-12): placebo, 1%; 16 mg/day, 3%; 24 mg/day, 2%; and during the maintenance phase (Weeks 13-21): placebo, <1%; 16 mg/day, 3%; 24 mg/day, 3%.

Dose escalation should be cautious and maintenance dosing should remain flexible and be adjusted according to individual needs.

Adverse Events Reported in Controlled Trials

The reported adverse events in REMINYL trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour and the types of patients treated may differ.

Table 3 lists the most common adverse events (adverse events occurring with an incidence of 2% with REMINYL treatment and in which the incidence was greater than with placebo treatment) for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL. The combined values presented in Table 3 were derived from trials using a 1-week or the recommended 4-week dose-escalation period.

Table 3: Adverse events reported in at least 2% of patients with Alzheimer's Disease administered REMINYL and at a frequency greater than with placebo (combined 1- and 4-week dose-escalation data)

Body System / Adverse Events	Placebo (n=801)	REMINYL† (n=1040)
Body as a whole - general disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & peripheral nervous system disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastro-intestinal system disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart rate and rhythm disorders		
Bradycardia	1%	2%
Metabolic and nutritional disorders		
Weight decrease	2%	7%
Psychiatric disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red blood cell disorders		
Anemia	2%	3%
Respiratory system disorders		
Rhinitis	3%	4%
Urinary system disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

† Adverse events in patients treated with 16 or 24 mg/day of REMINYL in three placebo-controlled trials with a 1-week dose-escalation period and a 26-week fixed-dose REMINYL treatment, and one placebo-controlled trial with the recommended 4-week dose-escalation period and a 21-week fixed-dose REMINYL treatment are included.

No clinically relevant abnormalities in laboratory values were observed. In a cardiovascular safety clinical trial (GAL-USA-16), pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients during the dose-escalation period (see WARNINGS).

Other Adverse Events Observed During Clinical Trials

REMINYL has been administered to 3055 patients with Alzheimer's Disease during clinical trials worldwide.

A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's Disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years. To establish the rate of adverse events, data from all patients for any dose of REMINYL in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All events occurring in approximately 0.1% of patients are included, except for those already listed elsewhere in labelling, WHO terms too general to be informative, or relatively minor events. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occurring in at least 1/100 patients; *infrequent adverse events* - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to REMINYL treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole - General Disorders: *Frequent:* chest pain.

Cardiovascular System Disorders: *Frequent:* hypertension; *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure.

Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia.

Gastrointestinal System Disorders: *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare:* esophageal perforation.

Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T-wave inversion, ventricular tachycardia.

Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased, NPN increased.

Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia.

Psychiatric Disorders: *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium.

Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

In a postmarketing report, one patient who had been taking 4 mg of galantamine daily inadvertently ingested eight 4 mg tablets (32 mg total) on the tenth day of treatment. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. ECG obtained just prior to initiation of galantamine treatment was normal.

Treatment

REMINYL (galantamine hydrobromide) has a plasma half-life of approximately 7-8 hours. It is recommended that, in case of asymptomatic overdose, no further dose of REMINYL should be administered and the patient should be monitored.

As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Tertiary anticholinergics such as atropine may be used as an antidote for REMINYL overdosage. Intravenous atropine sulphate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v., with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics. It is not known whether REMINYL and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

Continued on page 39

Pr REQUIP® ropinirole

Ropinirole (as ropinirole hydrochloride)

TABLETS: 0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

THERAPEUTIC CLASSIFICATION: AntiParkinsonian Agent / Dopamine Agonist

INDICATIONS AND CLINICAL USE: REQUIP® (ropinirole hydrochloride) is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease. REQUIP® can be used both as early therapy, without concomitant levodopa and as an adjunct to levodopa. Three year and five year active-comparator controlled clinical trials have been conducted.

CONTRAINDICATIONS: REQUIP® (ropinirole hydrochloride) is contraindicated in patients with a known hypersensitivity to ropinirole hydrochloride or the excipients of the drug product.

WARNINGS: Sudden Onset of Sleep – Patients receiving treatment with REQUIP® (ropinirole hydrochloride), and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including operating a motor vehicle, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on REQUIP®, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs. If drowsiness or sudden onset of sleep should occur, patients should immediately contact their physician. Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e.g., operating machines). Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products. Presently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness. There is insufficient information to determine whether this event is associated with REQUIP®, all dopaminergic agents or Parkinson's disease itself. **Orthostatic Symptoms** – Dopamine agonists appear to impair the systemic regulation of blood pressure with resulting orthostatic symptoms of dizziness or lightheadedness, with or without documented hypotension. These symptoms appear to occur especially during dose escalation. Therefore, patients treated with dopamine agonists should be carefully monitored for signs and symptoms of orthostatic hypotension, especially during dose escalation (see DOSAGE and ADMINISTRATION) and should be informed of this risk. **Hallucinations – *Early Therapy*:** In placebo- controlled trials, REQUIP® (ropinirole hydrochloride) caused hallucination in 5.1% of patients during early therapy (1.4% in the placebo group). Hallucination was of sufficient severity that it led to discontinuation in 1.3% of patients. The incidence of hallucination was dose-dependent. In a 5-year study comparing REQUIP® with levodopa in early Parkinson's patients, the overall incidence of hallucinations was 17.3% (31/179) for patients treated with REQUIP® and 5.6% (5/89) for levodopa patients. Hallucinations led to discontinuation of the study treatment in 5.0% of REQUIP® and 2.2% of levodopa patients. In a 3-year study comparing REQUIP® with another dopamine agonist, the overall incidence of hallucinations was 9.5% (16/168) for patients treated with REQUIP® and 9.0% (15/167) for patients receiving active comparator. Hallucinations led to discontinuation of the study treatment in 2.4% of REQUIP® patients and 3.0% of comparator patients. Concomitant Selegiline: In a 5-year study, REQUIP® patients receiving concomitant selegiline reported a higher incidence of hallucinations (23.5%) than did those without (12.2%); this subpopulation effect was not seen in the L-dopa arm (hallucinations with concomitant selegiline = 2.0% vs hallucinations without selegiline = 8.0%). ***Adjunct Therapy***: Hallucinations were experienced by 10.1% of patients receiving REQUIP® and levodopa, compared to 4.2% receiving placebo and levodopa. Hallucinations were of sufficient severity that it led to discontinuation in 1.9% of patients. The incidence of hallucinations was dose dependent.

PRECAUTIONS: Cardiovascular – Since REQUIP® (ropinirole hydrochloride) has not been studied in patients with a history or evidence of significant cardiovascular disease including myocardial infarction, unstable angina, cardiac decompensation, cardiac arrhythmias, vaso-occlusive disease (including cerebral) or cardiomyopathy, it should be used with caution in such patients. There is limited experience with REQUIP® in patients treated with antihypertensive and antiarrhythmic agents. Consequently, in such patients, the dose of REQUIP® should be titrated with caution. **Orthostatic Symptoms** - Orthostatic symptoms of dizziness or lightheadedness as well as somnolence may occur during REQUIP® therapy. **Neuroleptic Malignant Syndrome** – A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. A single spontaneous report of a symptom complex resembling the neuroleptic malignant syndrome has been observed in a 66 year old diabetic male patient with Parkinson's disease, who developed fever, muscle stiffness, and drowsiness 8 days after beginning REQUIP® treatment. The patient also experienced acute bronchitis, which did not respond to antibiotic treatment. REQUIP® was discontinued three days before the patient died. The reporting physician considered these events to be possibly related to REQUIP® treatment. (see DOSAGE AND ADMINISTRATION). A single spontaneous report of severe muscle pain has been reported in a 66 year old male patient around his thigh. The reporting physician considered the event to be probably related to REQUIP® treatment. **Retinal Pathology in Rats** – In a two year carcinogenicity study in albino Sprague-Dawley rats, retinal atrophy was observed at incidences of 0%, 1.4%, 1.4% and 10% of male rats and 0%, 4.4%, 2.9% and 12.9% of female rats dosed at 0, 1.5, 15 and 50 mg/kg/day respectively. The incidence was significantly higher in both male and female animals dosed at 50 mg/kg/day. The 50 mg/kg/day dose represents a 2.8 fold greater exposure (AUC) and a 13.1 fold greater exposure (C_{max}) to ropinirole in rats than the exposure would be in humans at the maximum recommended dose of 24 mg/day. The relevance of this finding to humans is not known. **Pregnancy** – The use of REQUIP® during pregnancy is not recommended. REQUIP® given to pregnant rats during organogenesis (gestation days 8 through 15) resulted in decreased fetal body weight at 60 mg/kg/day (approximately 3–4 times the AUC at the maximal human dose of 8 mg t.i.d.), increased fetal death at 90 mg/kg/day (approximately 5 times the AUC at the maximal human dose of 8 mg t.i.d.) and digital malformations at 150 mg/kg/day (approximately 8–9 times the AUC at the maximal human dose of 8 mg t.i.d.). These effects occurred at maternally toxic doses. There was no indication of an effect on development of the conceptus at a maternally toxic dose of 20 mg/kg/day in the rabbit. In a perinatal-postnatal study in rats, 10 mg/kg/day of REQUIP® (approximately 0.5 – 0.6 times the AUC at the maximal human dose of 8 mg t.i.d.) impaired growth and development of nursing offspring and altered neurological development of female offspring. **Nursing Mothers** – Since REQUIP® suppresses lactation, it should not be administered to mothers who wish to breast-feed infants. Studies in rats have shown that REQUIP® and/or its metabolites cross the placenta and are excreted in breast milk. Consequently, the human fetus and/or neonate may be exposed to dopamine agonist activity. **Use in Women Receiving Estrogen Replacement Therapy–** In female patients on long-term treatment with conjugated estrogens, oral clearance was reduced and elimination half-life prolonged compared to patients not receiving estrogens. In patients, already receiving estrogen replacement therapy, REQUIP® may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or introduced during treatment with REQUIP®, adjustment of the REQUIP® dosage may be required. **Pediatric Use** – Safety and effectiveness in the pediatric population have not been established. **Renal and Hepatic Impairment** – No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance of 30 to 50 mL/min). Because the use of REQUIP® in patients with severe renal impairment or hepatic impairment has not been studied, administration of REQUIP® to such patients is not recommended. **Drug Interactions** – ***Psychotropic Drugs:*** Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of REQUIP®. Therefore, concomitant use of these products is not recommended. Based on population pharmacokinetic assessment, no interaction was seen between REQUIP® and tricyclic antidepressants or benzodiazepines. ***Anti-Parkinson Drugs:*** Based on population pharmacokinetic assessment, there were no interactions between REQUIP® and drugs commonly used to treat Parkinson's disease, i.e., selegiline, amantadine, and anticholinergics. ***Levodopa:*** The potential pharmacokinetic interaction of levodopa/ carbidopa (100 mg/10 mg b.i.d.) and REQUIP® (2 mg t.i.d.) was assessed in levodopa naive (de novo) male and female patients with Parkinson's disease (n=30, mean age 64 years). The rate and extent of availability of REQUIP® at steady state were essentially the same with or without levodopa. Similarly, the rate and extent of availability of levodopa, as well as its elimination half-life, were essentially the same in the presence and absence of REQUIP®. ***Inhibitors of CYP1A2: Ciprofloxacin:*** The effect of ciprofloxacin (500 mg b.i.d.) on the pharmacokinetics of REQUIP® (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 55 years). The extent of systemic availability of REQUIP® was significantly increased when coadministered with ciprofloxacin (AUC increased by 1.84 fold). Thus, in patients already receiving CYP1A2 inhibitors such as ciprofloxacin, REQUIP® therapy may be instituted in the recommended manner and the dose titrated according to clinical response. However, if therapy with a drug known to be an inhibitor of CYP1A2 is stopped or introduced during treatment with REQUIP®, adjustment of the REQUIP® dosage will be required. ***Substrates of CYP1A2: Theophylline:*** The effect of oral theophylline (300 mg b.i.d.) on the pharmacokinetics of REQUIP® (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 59 years). There was no marked change in the rate or extent of availability of REQUIP® when coadministered with theophylline. Similarly, coadministration of REQUIP® with intravenous theophylline (5 mg/kg) did not result in any marked change in the pharmacokinetics of theophylline. It is therefore unlikely that substrates of CYP1A2 would significantly alter the pharmacokinetics of REQUIP®, and vice-versa. ***Digoxin:*** The effect of REQUIP® (2 mg t.i.d.) on the pharmacokinetics of digoxin (0.125–0.25 mg o.d.) was studied in male and female patients with Parkinson's disease (n=10, mean age 72 years). Coadministration at steady state with REQUIP® resulted in a 10% decrease in digoxin AUC although mean trough digoxin plasma concentrations were unaltered. However, the effect of higher recommended doses of REQUIP® on the pharmacokinetics of digoxin is not known. ***Alcohol:*** No information is available on the potential for interaction between REQUIP® and alcohol. As with other centrally active medications, patients should be cautioned against taking REQUIP® with alcohol. **Psycho-Motor Performance** – (see WARNINGS - Sudden Onset of Sleep).

ADVERSE REACTIONS: Adverse Reactions Associated with Discontinuation of Treatment – Of 1599 patients who received REQUIP® (ropinirole hydrochloride) during the premarketing clinical trials, 17.1% in early-therapy studies and 17.3% in adjunct-therapy studies discontinued treatment due to adverse reactions. The events resulting in discontinuation of REQUIP® in 1% or more of patients were as follows: ***Early therapy:*** nausea (6.4%), dizziness (3.8%), aggravated Parkinson's disease (1.3%), hallucination (1.3%), headache (1.3%), somnolence (1.3%) and vomiting (1.3%). ***Adjunct therapy:*** dizziness (2.9%), dyskinesia (2.4%), confusion (2.4%), vomiting (2.4%), hallucination (1.9%), nausea (1.9%), anxiety (1.9%), and increased sweating (1.4%). Patients over 75 years of age (n=130) showed slightly higher incidences of withdrawal due to hallucination, confusion and dizziness than patients less than 75 years of age. **Most Frequent Adverse Events** – Adverse events occurring with an incidence of greater than, or equal to, 10% were as follows: ***Early therapy:*** nausea, dizziness, somnolence, headache, peripheral edema, vomiting, syncope, fatigue and viral infection. ***Adjunct therapy:*** dyskinesia, nausea, dizziness, somnolence and headache. Dopamine agonists, with an ergoline chemical structure have been associated with adverse experiences such as retroperitoneal fibrosis, erythromelalgia and pulmonary reactions. REQUIP® has a novel, non-ergoline chemical structure and no reports of such events have been observed in clinical trials. **Incidence of Adverse Events in Placebo Controlled Trials** – The incidence of postural hypotension, an event commonly associated with initiation of dopamine agonist therapy, was not notably different from placebo in clinical trials. However, decreases in systolic blood pressure to < 90 mmHg have been observed in 13% (<65 years), 16% (65 – 75 years) and 7.6% (>75 years) of patients treated with REQUIP®. **Table 2** lists adverse events that occurred at an incidence of 1% or more among REQUIP®-treated patients who participated in placebo-controlled trials for up to one year. Patients were dosed in a range of 0.75 mg to 24 mg/day. Reported adverse events were classified using a standard World Health Organization (WHO)-based dictionary terminology. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies can not be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse events incidence rate in the population studied.

TABLE 2
Adverse events with incidence ≥1% from all placebo-controlled early and adjunct therapy studies

	Early Therapy		Adjunct Therapy	
	REQUIP® N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP® N = 208 % occurrence	Placebo N = 120 % occurrence
Autonomic Nervous System				
Sweating Increased	6.4	4.1	7.2	1.7
Mouth Dry	5.1	3.4	5.3	0.8
Flushing	3.2	0.7	1.4	0.8
Body as a Whole General				
Peripheral Edema	13.4	4.1	3.9	2.5
Fatigue	10.8	4.1	–	–
Injury	–	–	10.6	9.2
Pain	7.6	4.1	5.3	3.3
Asthenia	6.4	1.4	–	–
Drug Level Increased	4.5	2.7	6.7	3.3
Chest Pain	3.8	2.0	–	–
Malaise	3.2	0.7	1.4	0.8
Therapeutic Response Decreased	1.9	0.7	–	–
Cellulitis	1.3	0.0	–	–
Influenza-like Symptoms	–	–	1.0	0.0
Fever	–	–	1.4	0.0
Cardiovascular General				
Syncope	11.5	1.4	2.9	1.7
Hypotension Postural	6.4	4.8	–	–
Hypertension	4.5	3.4	3.4	3.3
Hypotension	1.9	0.0	2.4	0.8
Cardiac Failure	–	–	1.0	0.0
Central and Peripheral Nervous System				
Dizziness	40.1	21.8	26.0	15.8
Dyskinesia	–	–	33.7	12.5
Headache	17.2	17.0	16.8	11.7
Ataxia (Falls)	–	–	9.6	6.7
Tremor	–	–	6.3	2.5
Paresthesia	–	–	5.3	2.5
Hyperesthesia	3.8	2.0	–	–
Dystonia	–	–	4.3	4.2
Hypokinesia	–	–	5.3	4.2
Paresis	–	–	2.9	0.0
Speech Disorder	–	–	1.0	0.0
Vertigo	1.9	0.0	–	–
Carpal Tunnel Syndrome	1.3	0.7	–	–
Gastrointestinal System				
Nausea	59.9	21.8	29.8	18.3
Vomiting	12.1	6.8	7.2	4.2
Dyspepsia	9.6	4.8	–	–
Constipation	8.3	7.5	5.8	3.3
Abdominal Pain	6.4	2.7	8.7	7.5
Diarrhea	–	–	4.8	2.5
Anorexia	3.8	1.4	–	–
Flatulence	2.5	1.4	1.9	0.8
Tooth Disorder	1.9	0.7	1.0	0.8
Saliva Increased	–	–	2.4	0.8
Colitis	1.3	0.0	-	-
Dysphagia	1.3	0.0	2.4	0.8
Periodontitis	1.3	0.0	1.4	0.8
Eructation	–	–	1.4	0.0
Fecal Incontinence	–	–	1.0	0.0
Hemorrhoids	–	–	1.0	0.0
Gastroesophageal Reflux	–	–	1.0	0.0
Gastrointestinal Disorder (NOS)	–	–	1.0	0.0
Tooth Ache	–	–	1.0	0.0
Hearing and Vestibular				
Tinnitus	1.3	0.0	–	–
Heart Rate and Rhythm				
Palpitation	3.2	2.0	2.9	2.5

	Early Therapy		Adjunct Therapy	
	REQUIP® N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP® N = 208 % occurrence	Placebo N = 120 % occurrence
Heart Rate and Rhythm				
Extrasystoles	1.9	0.7	–	–
Tachycardia	1.9	0.0	1.0	0.0
Fibrillation Atrial	1.9	0.0	–	–
Tachycardia Supraventricular	1.3	0.0	–	–
Bradycardia	–	–	1.0	0.0
Liver and Biliary System				
Gamma - GT Increased	1.3	0.7	1.0	0.0
Hepatic Enzymes Increased	1.3	0.0	–	–
Metabolic and Nutritional				
Alkaline Phosphate Increased	2.5	1.4	1.0	0.0
Weight Decrease	–	–	2.4	0.8
Hypoglycemia	1.3	0.0	–	–
Musculoskeletal System				
Arthralgia	–	–	6.7	5.0
Arthritis	–	–	2.9	0.8
Arthritis Aggravated	1.3	0.0	1.4	0.0
Myocardial, Endocardial, Pericardial Valve				
Myocardial Ischemia	1.3	0.7	–	–
Psychiatric				
Somnolence	40.1	6.1	20.2	8.3
Anxiety	–	–	6.3	3.3
Confusion	5.1	1.4	8.7	1.7
Hallucination	5.1	1.4	10.1	4.2
Nervousness	–	–	4.8	2.5
Yawning	3.2	0.0	–	–
Amnesia	2.5	1.4	4.8	0.8
Dreaming Abnormal	–	–	2.9	1.7
Depersonalization	–	–	1.4	0.0
Paranoid Reaction	–	–	1.4	0.0
Agitation	1.3	0.7	1.0	0.0
Concentration Impaired	1.9	0.0	1.0	0.0
Illusion	1.3	0.0	–	–
Thinking Abnormal	–	–	1.4	0.8
Apathy	–	–	1.0	0.0
Increased Libido	–	–	1.0	0.0
Personality Disorder	–	–	1.0	0.0
Red Blood Cell				
Anemia	–	–	2.4	0.0
Reproductive Male				
Impotence	2.5	1.4	–	–
Prostatic Disorder	–	–	1.0	0.0
Penis Disorder	–	–	1.3	0.0
Resistance Mechanism				
Upper Respiratory Tract Infection	–	–	8.7	8.3
Infection Viral	10.8	3.4	7.2	6.7
Respiratory System				
Pharyngitis	6.4	4.1	–	–
Rhinitis	3.8	2.7	–	–
Sinusitis	3.8	2.7	–	–
Dyspnea	3.2	0.0	2.9	1.7
Bronchitis	2.5	1.4	–	–
Respiratory Disorder	1.9	1.4	1.9	0.0
Pneumonia	1.3	0.7	1.0	0.8
Coughing	–	–	1.4	0.8
Skin/Appendages				
Pruritis	–	–	1.0	0.0
Urinary System				
Urinary Tract Infection	5.1	4.1	6.3	2.5
Cystitis	1.3	0.7	–	–
Micturition Frequency	–	–	1.4	0.0
Pyuria	–	–	1.9	0.8
Urinary Incontinence	–	–	1.9	0.8
Urinary Retention	1.3	0.7	–	–
Dysuria	–	–	1.0	0.0
Vascular Extracardiac				
Peripheral Ischemia	2.5	0.0	–	–
Vision				
Vision Abnormal	5.7	3.4	–	–
Eye Abnormality	3.2	1.4	–	–
Diplopia	–	–	1.9	0.8
Xerophthalmia	1.9	0.0	1.4	0.8
Cataract	–	–	1.4	0.8
Lacrimation Abnormal	–	–	1.4	0.0
White Cell and Reticuloendothelial System				
Eosinophilia	–	–	1.4	0.0

a: Incidence of adverse event <1%.

Post-Marketing Experience - Patients treated with REQUIP® have rarely reported suddenly falling asleep while engaged in activities of daily living, including operation of motor vehicles which has sometimes resulted in accidents (see WARNINGS).

DOSAGE AND ADMINISTRATION: REQUIP® (ropinirole hydrochloride) should be taken three times daily. While administration of REQUIP® with meals may improve gastrointestinal tolerance, REQUIP® may be taken with or without food. The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose as described in the table below. After week 4, daily dosage may be increased by 0.5 to 1.0 mg per dose on a weekly basis until an optimal therapeutic response is established. Smaller dose increments are recommended for patients who may be at risk for orthostatic symptoms.

	Week			
	1	2	3	4
Unit Dose (mg)	0.25	0.5	0.75	1.0
Total Daily Dose (mg)	0.75	1.5	2.25	3.0

In clinical trials, initial benefits were observed with 3 mg/day and higher doses. Doses greater than 24 mg/day have not been included in clinical trials. In a 5-year, double-blind study of early therapy in Parkinson's disease patients, the average daily dose of REQUIP® (based on the observed data set) was 10.1 mg at 6 months (median dose = 9.0 mg), 14.4 mg at 3 years (median dose = 15.0 mg), and 16.6 mg at 5 years (median dose = 18.0 mg), regardless of levodopa supplementation. When REQUIP® is administered as adjunct therapy to levodopa, the dose of levodopa may be decreased gradually as tolerated once a therapeutic effect with REQUIP® has been observed. REQUIP® should be discontinued gradually over a 7-day period. The frequency of administration should be reduced from three times daily to twice daily for 4 days. For the remaining 3 days, the frequency should be reduced to once daily prior to complete withdrawal of REQUIP®. **Renal and Hepatic Impairment:** In patients with mild to moderate renal impairment, REQUIP® may be titrated in the recommended manner according to clinical response. Patients with severe renal impairment or on hemodialysis have not been studied and administration of REQUIP® to such patients is not recommended. Patients with hepatic impairment have not been studied and administration of REQUIP® to such patients is not recommended. **Estrogen Replacement Therapy:** In patients already receiving estrogen replacement therapy, REQUIP® may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or started during treatment with REQUIP®, adjustment of the REQUIP® dosage may be required. **AVAILABILITY OF DOSAGE FORM:** REQUIP® is supplied as a pentagonal film-coated Tiltab® tablet with beveled edges containing ropinirole (as ropinirole hydrochloride) as follows: 0.25 mg – white imprinted with SB and 4890; 1.0 mg – green imprinted with SB and 4892; 2.0 mg – pale pink imprinted with SB and 4893; 5.0 mg – blue tablets imprinted with SB and 4894. REQUIP® is available in bottles in the pack size of 100 tablets. Full Product Monograph available to practitioners upon request.

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario
L5N 6L4

REQUIP® is a registered trademark, used under license by GlaxoSmithKline Inc.
Date of preparation: June 18, 2001
Date of revisions: March 31, 2004

GlaxoSmithKline

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ADVERTISERS INDEX

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Table 1 (continued)
Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study of Relapsing MS

Adverse Event	Placebo (N = 143)	AVONEX® (N = 158)
Abdominal pain	6%	9%
Chest pain	4%	6%
Injection site reaction	1%	4%
Malaise	3%	4%
Injection site inflammation	0%	3%
Hypersensitivity reaction	0%	3%
Ovarian cyst	0%	3%
Ecchymosis injection site	1%	2%
Cardiovascular System		
Syncope	2%	4%
Vasodilation	1%	4%
Digestive System		
Nausea	23%	33%
Diarrhea	10%	16%
Dyspepsia	7%	11%
Anorexia	6%	7%
Hemic and Lymphatic System		
Anemia*	3%	8%
Eosinophils ≥ 10%	4%	5%
HCT (%) ≤ 32 (females) or ≤ 37 (males)	1%	3%
Metabolic and Nutritional Disorders		
SGOT ≥ 3 x ULN	1%	3%
Musculoskeletal System		
Muscle ache*	15%	34%
Arthralgia	5%	9%
Nervous System		
Sleep difficult	16%	19%
Dizziness	13%	15%
Muscle spasm	6%	7%
Suicidal tendency	1%	4%
Seizure	0%	3%
Speech disorder	0%	3%
Ataxia	0%	2%
Respiratory System		
Upper respiratory tract infection	28%	31%
Sinusitis	17%	18%
Dyspnea	3%	6%
Skin and Appendages		
Urticaria	2%	5%
Alopecia	1%	4%
Nevus	0%	3%
Herpes zoster	2%	3%
Herpes simplex	1%	2%
Special Senses		
Otitis media	5%	6%
Hearing decreased	0%	3%
Urogenital		
Vaginitis	2%	4%

* Significantly associated with AVONEX® treatment ($p \leq 0.05$).

Post-Marketing Experience

Anaphylaxis and other allergic reactions have been reported in patients using AVONEX® (see **WARNINGS**: Anaphylaxis). Decreased peripheral blood counts have been reported in patients using AVONEX® (see **WARNINGS**: Decreased Peripheral Blood Counts). Seizures, cardiovascular adverse events, and autoimmune disorders also have been reported in association with the use of AVONEX® (see **PRECAUTIONS**).

Single Demyelinating Event

The adverse events observed in the placebo-controlled study of patients with a single demyelinating event were similar to those observed in the placebo-controlled study of relapsing MS patients. Patients in this trial (N = 193) initiated AVONEX® treatment while on oral prednisone, which was used to treat the initial demyelinating event. The most common adverse events associated with AVONEX® ($p \leq 0.05$) during the first 6 months of treatment were flu-like syndrome (AVONEX®: 39%, placebo: 22%), fever (AVONEX®: 17%, placebo: 6%), and chills (AVONEX®: 17%, placebo: 3%). A higher proportion of patients treated with AVONEX® (20%) experienced depression, as compared with placebo (13%) ($p = 0.05$) (see **WARNINGS**).

DOSAGE AND ADMINISTRATION

The recommended dosage of AVONEX® (Interferon beta-1a) is 30 mcg injected intramuscularly once a week. AVONEX® is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in IM injection technique.

Before initiating a patient on AVONEX® therapy, please note the following **CONTRAINDICATIONS**.

- AVONEX® is contraindicated in patients with a known hypersensitivity to natural or recombinant interferon beta, albumin (human), or any other component of the formulation. Anaphylaxis has been observed with the use of AVONEX®.

Please also review the **WARNINGS** and **PRECAUTIONS** sections and ensure appropriate monitoring of patients with depression, hepatic dysfunction, a history of seizures, cardiac disease, thyroid dysfunction, myelosuppression, and female patients of child-bearing potential.

Patients should be advised of the side-effects of AVONEX® and instructed on the use of aseptic technique when administering AVONEX®. The AVONEX® Patient Leaflet should be carefully reviewed with all patients, and patients should be educated on self-care and advised to keep the Leaflet for continued reference during AVONEX® therapy.

AVAILABILITY OF DOSAGE FORMS

AVONEX® (Interferon beta-1a) is available as:

Package (Administration Pack) containing 4 Administration Dose Packs (each containing one vial of AVONEX®, one 10mL (10cc) diluent vial, two alcohol wipes, one 3cc syringe, one Micro Pin®, one needle, one adhesive bandage, one gauze pad).

Product Monograph available upon request.

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3 Robert Speck Parkway, Suite 300, Mississauga, Ontario L4Z 2G5

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DOSAGE AND ADMINISTRATION

REMINYL (galantamine hydrobromide) tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

Adults

The dosage of REMINYL shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a b.i.d. regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL might provide additional benefit for some patients.

The recommended starting dose of REMINYL is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) after a minimum of 4 weeks at the previous dose may be considered following appropriate assessment of clinical benefit and tolerability.

REMINYL should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be warned that if therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

The abrupt withdrawal of REMINYL in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL are lost, however, when the drug is discontinued.

Concomitant Treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered.

Special Populations

Dose escalation for elderly patients (>85 years old) with low body weight (especially females) or serious comorbid diseases should be undertaken with particular caution.

Hepatic Impairment

Galantamine plasma levels may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), dosing could begin with 4 mg once daily for at least 1 week. Then the dosage should be increased to 4 mg twice a day for at least 4 weeks. In these patients, daily doses should not exceed 8 mg twice a day (16 mg/day). Since no data are available on the use of REMINYL in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL is not recommended for this population (see PRECAUTIONS).

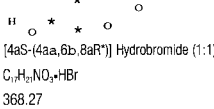
Renal Impairment

For patients with renal impairment (creatinine clearance of 9 to 60 mL/min), dose escalation should proceed cautiously and the maintenance dose should generally not exceed 16 mg/day. Since no data are available on the use of REMINYL in patients with a creatinine clearance less than 9 mL/min, REMINYL is not recommended for this population (see PRECAUTIONS).

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name:	REMINYL
Common Name:	galantamine hydrobromide
Chemical Name:	(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide
Structural Formula:	 [4aS-(4aa,6b,8aR*)] Hydrobromide (1:1)
Molecular Formula:	$C_{17}H_{21}NO_3 \cdot HBr$
Molecular Weight:	368.27
Ionization Constant:	pKa=8.2 (azepine moiety)
Partition Coefficient:	log P=1.09, between n-octanol and an aqueous buffer solution at pH=12.0
Melting Point:	257.3°C
Description:	Galantamine hydrobromide is a white to almost white powder. It is freely soluble in water (pH=5.2), 0.1 N hydrochloric acid (pH=1.0) and 0.1 N sodium hydroxide (pH=8.3).

Composition

REMINYL (galantamine hydrobromide) tablets are available in three strengths containing 4, 8, 12 mg of galantamine per tablet, as galantamine hydrobromide. The inactive ingredients are lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, propylene glycol, talc, and titanium dioxide. The 4 mg tablet also contains yellow ferric oxide. The 8 mg tablet also contains red ferric oxide. The 12 mg tablet also contains red ferric oxide and FD & C yellow #6 (also known as orange yellow S aluminum lake).

Stability and Storage Recommendations

REMINYL tablets should be stored between 15°C–30°C.

AVAILABILITY OF DOSAGE FORMS

REMINYL (galantamine hydrobromide), expressed as galantamine base, is available as film-coated tablets in the following strengths:

4 mg tablets which are off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side;
8 mg tablets which are pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side;
12 mg tablets which are orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side.
REMINYL is available in bottles of 60 tablets and in blisters of 56 tablets per carton.

Product Monograph available to healthcare professionals upon request.

JANSSEN ORTHO

19 Green Belt Drive, Toronto, Ontario M3C 1L9

Date of Issuance: September 2003
RMPI031032A

See OBC

continué à page A-27

seringue et un adaptateur de flacon stériles afin de prélever 1,1 mL du diluant fourni (eau stérile pour injection) et de l'injecter dans le flacon de COPAXONE®. Agiter très délicatement, par un mouvement de rotation, le flacon de COPAXONE® et le laisser reposer à la température ambiante jusqu'à dissolution complète du lyophilisat. Inspecter visuellement le produit reconstitué et le jeter ou le retourner au pharmacien avant l'utilisation s'il renferme des particules. Administrer dans les huit heures suivant la reconstitution. Prélever 1,0 mL de la solution à l'aide d'une seringue stérile. Retirer l'adaptateur de flacon, connecter une aiguille de calibre 27 et injecter la solution par voie sous-cutanée. Les points d'auto-administration comprennent les bras, l'abdomen, les fesses et les cuisses. Un flacon ne convient qu'à une seule utilisation; toute portion inutilisée doit être jetée (voir **INFORMATION À L'INTENTION DU PATIENT, Produit reconstitué**).

Pour obtenir les directives concernant la préparation et l'injection de COPAXONE® au moyen de la seringue préremplie, voir **INFORMATION À L'INTENTION DU PATIENT, Seringue préremplie.**

RENSEIGNEMENTS PHARMACEUTIQUES

Substance médicamenteuse :

Nom propre : Acétate de glatiramère

Dénomination Chimique : L'acétate de glatiramère est le sel acétate de polypeptides synthétiques.

Description : L'acétate de glatiramère est préparé par réaction chimique des dérivés activés de quatre acides aminés : l'acide L-glutamique (L-Glu), la L-alanine (L-Ala), la L-tyrosine (L-Tyr) et la L-lysine (L-lys) dans une proportion spécifique. La fraction molaire de chaue résidu d'acide aminé s'échelonne comme suit : L-Glu, de 0,129 à 0,153 ; L-Ala, de 0,392 à 0,462 ; L-Tyr, de 0,086 à 0,100 et L-Lys, de 0,300 à 0,374.

Formule Developpée : $Poly[L\text{-}Glu^{3-15}, L\text{-}Ala^{39-46}, L\text{-}Tyr^{8.6-10}, L\text{-}Lys^{30-37}]\bullet nCH_3CO_2H$ *(n=15-24)*

Poids moléculaire : Le poids moléculaire moyen du polypeptide se situe entre 4 700 et 11 000 daltons, au moins 68% du matériel se situant entre 2 500 et 22 500 daltons.

Description Physique : Lyophilisat de couleur blanche à légèrement jaunâtre.

Solubilité : Légèrement soluble dans l'eau, insoluble dans l'acétone.

ph : Le pH d'une solution à 0,5 % p/V d'acétate de glatiramère dans de l'eau se situe entre 5,5 et 8,0.

Composition : COPAXONE® (acétate de glatiramère pour injection) est un lyophilisat stérile destiné à l'injection sous-cutanée après reconstitution avec de l'eau stérile pour injection. Un flacon de lyophilisat renferme *20 mg d'acétate de glatiramère et un surtitrage de 2 mg pour tenir compte des pertes possibles pendant la* reconstitution et le prélèvement ainsi que 40 mg de mannitol. Un flacon d'eau stérile pour injection renferme 1,1 mL d'eau stérile pour injection et un surtitrage de 0,35 mL pour tenir compte des pertes possibles pendant la reconstitution et le prélèvement.

COPAXONE® (acétate de glatiramère injectable) est présenté en seringue préremplie à usage unique renfermant 20 mg/1,0 mL de solution stérile équivalant à la solution reconstituée de COPAXONE® (c.-à-d., 20 mg/mL d'acétate de glatiramère et 40 mg de mannitol dans de l'eau stérile pour injection).

Stabilité et conditions d'entreposage : Les flacons de lyophilisat de COPAXONE® doivent être réfrigérés (entre 2 et 8° C). *COPAXONE®* peut également être conservé à la température ambiante (entre 15 et 30° C) pendant un maximum de 14 jours. Les flacons de diluant (eau stérile pour injection) doivent être conservés à la température ambiante.

Les seringues préremplies de COPAXONE® doivent être réfrigérées dès leur réception (entre 2 et 8° C). NE PAS CONGELER.

S'il n'est pas possible de conserver les seringues préremplies de COPAXONE® au réfrigérateur, elles peuvent être conservées à la température ambiante (entre 15 et 30° C) pendant un maximum d'une semaine. Ne pas conserver les seringues préremplies de COPAXONE® à la température ambiante pendant plus de sept jours. Remarque : ce médicament est sensible à la lumière, le protéger de la lumière lorsqu'on ne fait pas d'injection. Une seringue préremplie ne doit servir qu'une seule fois.

Reconstitution du lyophilisat : Pour reconstituer le lyophilisat de COPAXONE®, avant l'injection, utiliser une seringue et un adaptateur de flacon stériles afin de prélever le diluant fourni (eau stérile pour injection) et de l'injecter dans le flacon de COPAXONE®. Agiter très délicatement, par un mouvement de rotation, le flacon de COPAXONE® et le laisser reposer à la température ambiante jusqu'à dissolution complète du lyophilisat. Inspecter visuellement le produit reconstitué et le jeter ou le retourner au pharmacien avant l'utilisation s'il renferme des particules. Une fois le produit complètement dissous, prélever 1,0 mL de la solution à l'aide d'une seringue stérile. Retirer l'adaptateur de flacon, connecter une aiguille de calibre 27 et injecter la solution par voie sous-cutanée. Un flacon ne convient qu'à une seule utilisation ; toute portion inutilisée doit être jetée. La solution reconstituée ne doit pas être conservée plus de huit heures à la température ambiante.

Produits parentéraux : COPAXONE® ne doit être reconstitué qu'avec le diluant fourni (eau stérile pour injection).

Format du flacon	Volume de diluant à ajouter	Volume à injecter	Concentration nominale par mL
2 mL	*1,1 mL*	*1,0 mL*	*20 mg*

PRÉSENTATION

COPAXONE® (acétate de glatiramère pour injection) est offert sous la forme d'une dose de 20 mg de lyophilisat stérile d'acétate de glatiramère avec du mannitol, le produit étant conditionné dans des flacons unidoses de 2 mL de couleur ambre. Un deuxième flacon renfermant 1,1 mL de diluant (eau stérile pour injection) et un surtitrage de 0,35 mL accompagne chaque flacon de médicament et est inclus dans la trousse d'auto-administration. COPAXONE® (acétate de glatiramère pour injection) est offert en emballages de 32 flacons de couleur ambre renfermant le lyophilisat stérile destiné à l'injection sous-cutanée. Le diluant (eau stérile pour injection) accompagnant COPAXONE® est offert en emballages de 32 flacons transparents qui sont inclus dans la trousse d'auto-administration.

COPAXONE® (acétate de glatiramère injectable) est présenté en seringues préremplies à usage unique renfermant 20 mg/1,0 mL de solution stérile équivalant à la solution reconstituée de COPAXONE®. COPAXONE® (acétate de glatiramère injectable) est offert en emballages de 30 seringues en verre préremplies à usage unique (20 mg/1,0 mL), accompagnées de 33 tampons d'alcool.

Monographie fournie sur demande.

Bibliographie :

1. Monographie de COPAXONE® (acétate de glatiramère), Teva Neuroscience.

Teva Neuroscience
999, boul. de Maisonneuve Ouest, bureau 550
Montréal (Québec) H3A 3L4

CCPP

HEADACHE AND PAIN FELLOWSHIP

A 1-2 year fellowship in headache and pain is available starting July 2005 at the Wasser Pain Management Centre at Mount Sinai Hospital in Toronto, Canada. Candidates must have completed a recognized neurology training program and be eligible to practice medicine in the province of Ontario. The successful candidate will be expected to participate in outpatient clinics and manage patients with headache and neuropathic pain disorders, undertake research in headache and pain disorders, and contribute to headache and pain teaching within the neurology division. The Wasser Pain Management Centre is affiliated with the Division of Neurology at the University Health Network/Mount Sinai Hospital and the University of Toronto Centre for the Study of Pain (UTCSP).

Interested applicants should contact Ralph Z. Kern MD MHSc FRCPC at 416 586-3218 or by email at rkern@mtsinai.on.ca

Palliser Health Region

NEUROLOGIST

The Palliser Health Region invites applications for a Neurologist position.

Activities would be concentrated at Medicine Hat Regional Hospital, a 213 acute care bed regional referral centre, in a community of 51,000 located in southeastern Alberta, and a referral area with a population of 105,000.

Candidate should possess a recognized Fellowship and be eligible for licensure by The College of Physicians and Surgeons of Alberta. Attractive relocation package with site paid visits for approved candidates. Remuneration is fee for service.

Inquiries and c.v. can be directed to :

Dr.V.L. Di Ninno, B.Sc., Ph.D., M.D., C.C.F.P.
Vice President – Medical Services
PALLISER HEALTH REGION
666 – 5 Street S.W.
Medicine Hat, Alberta, T1A 4H6
Tel: 403-529-8024; Fax: 403-529-8998
e-mail: chiefofstaffpalliserhealth.ca
www.palliserhealth.ca

Voir page A-16

INTRODUCING NEW IMITREX DF™
ITS AIM IS STILL SPEED TO ZERO PAIN™

New IMITREX DF™ tablets are designed to promote tablet disintegration and dispersion.[1†]

In fact, *in vitro* dissolution showed that nearly 100% of the sumatriptan was dissolved within 2 minutes[1†*]
(†Clinical significance not yet established).

With IMITREX DF™ 100 mg tablets, close to 45% of attacks were reduced to ZERO PAIN™** at 1 hour; 66% reduced to ZERO PAIN™ at 2 hours when patients were instructed to initiate migraine treatment during the mild pain phase[2Δ≈]

IMITREX DF™ tablets were shown to be bioequivalent to conventional IMITREX® tablets[1ß◊]
(◊Comparative clinical significance is unknown).

IMITREX DF™ (sumatriptan succinate) is a selective 5-HT_1 receptor agonist indicated for the acute treatment of migraine attacks with or without aura.[3] IMITREX DF™ is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic, basilar, or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache.[3]

IMITREX DF™ is contraindicated in patients with history, symptoms or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX DF™. IMITREX DF™ is also contraindicated in patients with uncontrolled or severe hypertension.[3]

The most common adverse events with IMITREX DF™ 100 mg tablets included: nausea (11.0% vs 5.8% placebo), malaise/fatigue (9.5% vs 5.1% placebo), sensations (body regions unspecified) (9.0% vs 4.5% placebo).[3]

*Dissolution testing was performed using USP II apparatus in 0.01M HCL (aq) at 30 rpm.[1]
Δ 2-hour post-dose time point was the primary endpoint.[2]
≈Prospective, double-blind, placebo-controlled, parallel-group, single attack study in migraine patients randomized to receive either placebo or the new formulation of sumatriptan 50 mg or 100 mg tablets (n = 432). Patients were instructed to treat during the mild pain phase and within 1 hour of onset of pain. Results presented are for the intent-to-treat population (IMITREX DF 100 mg, n = 142; placebo, n = 153; $p<0.001$ vs placebo).[2]
**ZERO PAIN™ refers to complete relief of pain or "0" (zero) on a 4-point scale where 0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain.[2]
ß Randomized, open-label, 4-way crossover study (n=32) showed the new formulation of sumatriptan tablets to be bioequivalent to the conventional tablets as demonstrated by the finding that the 90% confidence intervals for sumatriptan $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} fell within the predetermined bounds defining bioequivalence (0.80 to 1.25) for both 50 mg and 100 mg doses.[1]

IMITREX DF™
SUMATRIPTAN SUCCINATE

GlaxoSmithKline

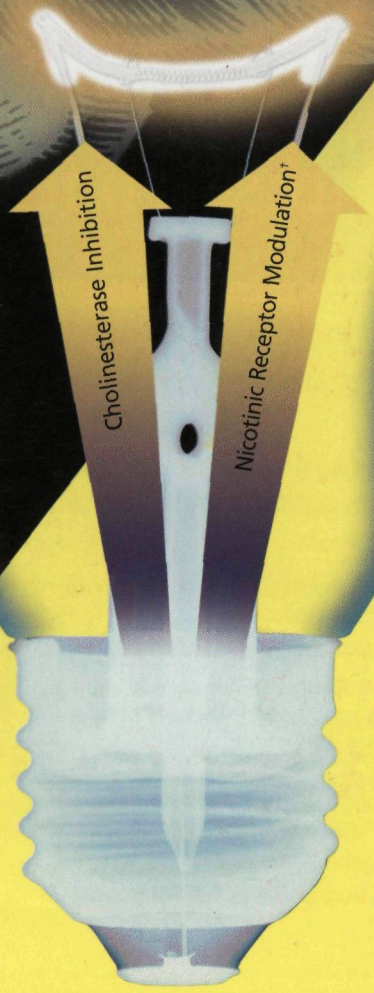
OUR GOAL: SPEED TO ZERO PAIN™

PAAB Member R&D

For brief prescribing information see pages A-20, A-21

REMINYL*: FOR THE TREATMENT OF ALZHEIMER'S DISEASE

††Now on provincial formularies for Ontario, Quebec, Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia and Newfoundland



Unique proposed mode of action:

Cholinesterase inhibition and nicotinic modulation[1,2†]

New REMINYL: The difference may be nicotinic modulation†

More than just cholinesterase inhibition, REMINYL enhances the action of acetylcholine through binding to an allosteric site on the nicotinic receptors[1,2†]

† Based on *in vitro* data. The clinical relevance to humans is unknown. The majority of common side effects occurred during the dose-escalation period and were primarily gastrointestinal. During maintenance therapy, the most common side effects were: REMINYL 16 mg/day-nausea (4%) and diarrhea (5%); REMINYL 24 mg/day-nausea (6%), vomiting (6%) and anorexia (5%).

REMINYL (galantamine hydrobromide) is indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL has not been studied in controlled clinical trials for longer than 6 months. There is no evidence that galantamine alters the course of the underlying dementing process.

References:
1. REMINYL* (galantamine hydrobromide) Product Monograph, JANSSEN-ORTHO Inc., October 29,2003.
2. Maelicke A, Albuquerque EX. *Eur J Pharmacol* 2000;393:165-170.

†† Exception drug status

RMJA041001A

JANSSEN-ORTHO Inc.
19 Green Belt Drive,
Toronto, ON M3C 1L9
www.janssen-ortho.com

Pr Reminyl* Galantamine hydrobromide tablets

Think Cognition

For brief prescribing information see pages A-34, A-35, A-36, A-39