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The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association for Child Neurology

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VOLUME 9, NO. 3 AUGUST 1982

SERC®

(betahistine hydrochloride tablets)

For the management of Vertigo

■ Proven efficacy

"(Serc) is now a proven, useful therapeutic agent in the treatment of Ménière's disease, especially in the control of vertigo."[1]

■ Restores vestibular responses

"In a preliminary trial (Wilmot 1971) using objective testing of both auditory and vestibular function,...the results showed statistical significance in favour of Serc."[2]

■ Reduced severity of episodic vertigo

"...a significant improvement in favour of the drug (Serc) with regard to vertigo, tinnitus and deafness. Vertigo was the most responsive symptom."[1]

■ Well tolerated

"No adverse reactions were observed."[1]

REFERENCES:

1Frew, I.J.C. et al: Postgrad. Med. J.; 52:501-503, 1976.

2Wilmot, T.J. et al: J. Laryng. Otol; 9:833-840, 1976.

PRESCRIBING INFORMATION

INDICATIONS: SERC may be of value in reducing the episodes of vertigo in Meniere's disease. No claim is made for the effectiveness of SERC in the symptomatic treatment of any form of vertigo other than that associated with Meniere's disease.

DOSAGE AND ADMINISTRATION: The usual adult dosage has been one to two tablets (4 mg. each) administered orally three times a day.

Recommended starting dose is two tablets three times daily. Therapy is then adjusted as needed to maintain patient response. The dosage has ranged from two tablets per day to eight tablets per day. No more than eight tablets are recommended to be taken in any one day.

SERC (betahistine hydrochloride) is not recommended for use in children. As with all drugs, SERC should be kept out of reach of children.

CONTRAINDICATIONS: Several patients with a history of peptic ulcer have experienced an exacerbation of symptoms while using SERC. Although no causual relation has been established SERC is contraindicated in the presence of peptic ulcer and in patients with a history of this condition. SERC is also contraindicated in patients with pheochromocytoma.

PRECAUTIONS: Although clinical intolerance to SERC by patients with bronchial asthma has not been demonstrated, caution should be exercised if the drug is used in these patients.

USE IN PREGNANCY: The safety of SERC in pregnancy has not been established. Therefore, its use in pregnancy or lactation, or in women of childbearing age requires that its potential benefits be weighed against the possible risks.

ADVERSE REACTIONS: Occasional patients have experienced gastric upset, nausea and headache.

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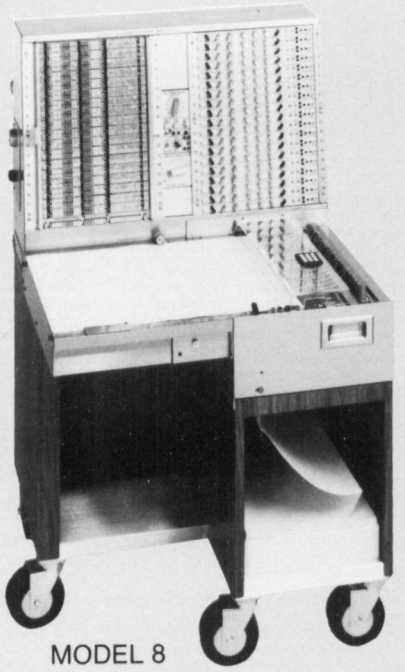

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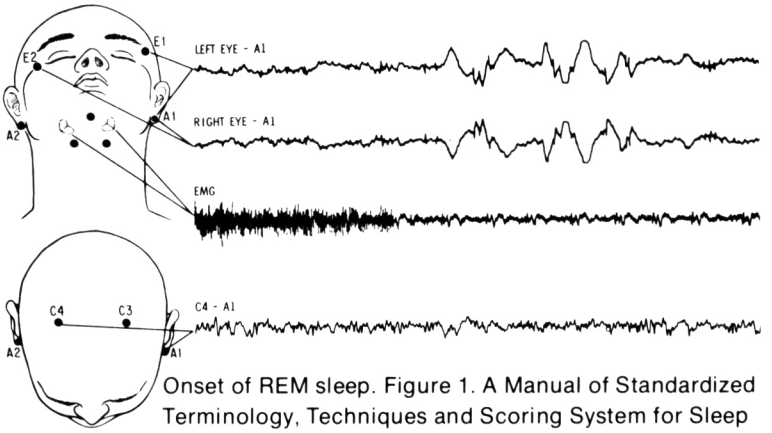
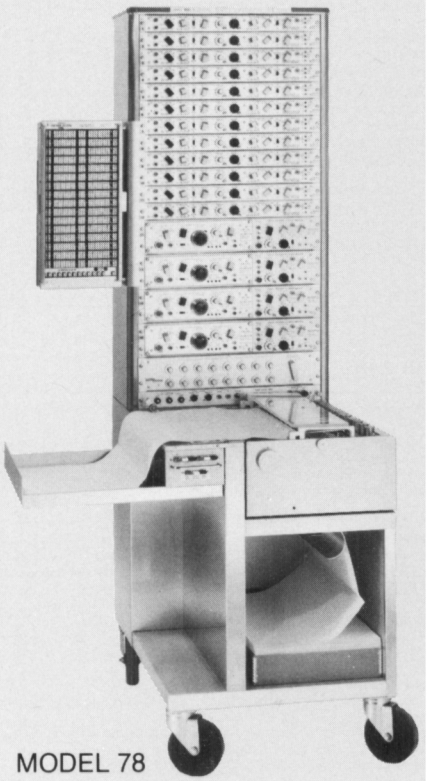


Onset of REM sleep. Figure 1. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. UCLA-BIS-DHEW.



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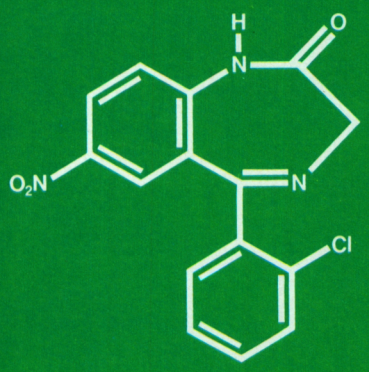

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Petit Mal
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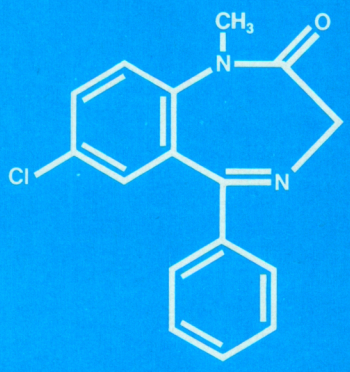

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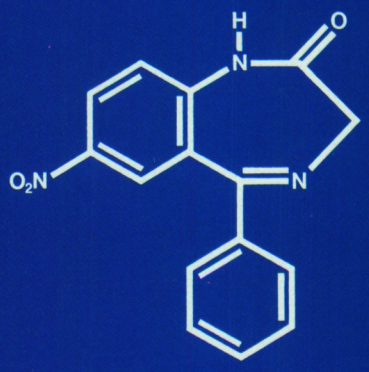

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Myoclonic Seizures

Availability:
5 mg and 10 mg tablets

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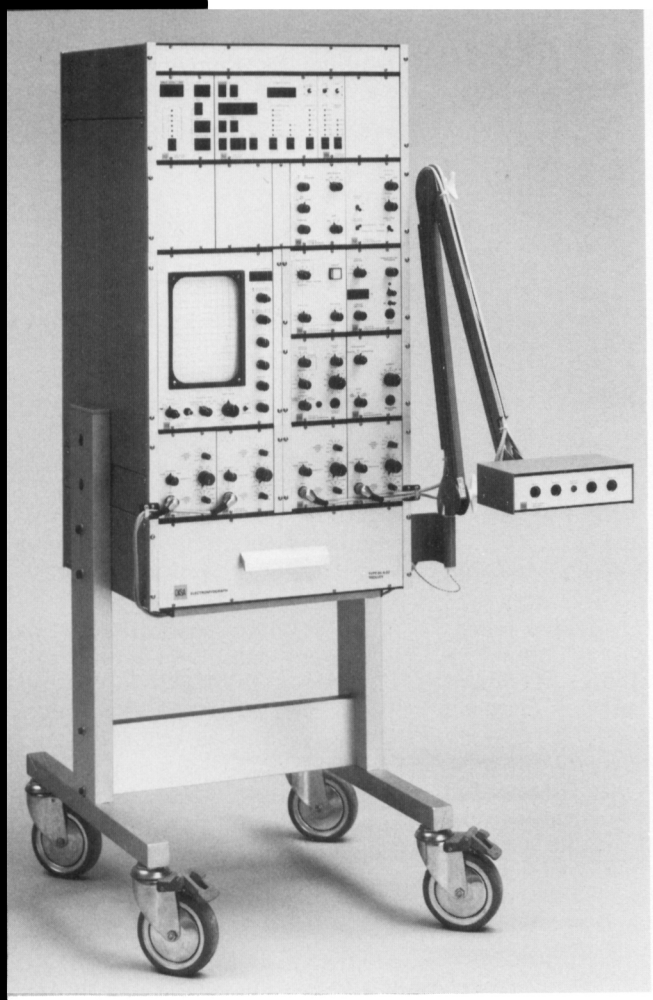

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THE EDITORIAL BOARD wishes to publish original work in the basic and clinical neurosciences on the understanding that it has not been and will not be published elsewhere Review articles on timely subjects will be accepted. Manuscripts must be in triplicate including illustrations. One of the copies must be the original, ribbon copy. Manuscripts should be typed double spaced, on white paper.

Papers will be accepted in French or English. All papers should be accompanied by a short résumé in both languages. The résumé translation will be done by the editorial board if requested.

Papers should be identified only by the full name of the author, or authors, and the name of the place in which the work was done.

ILLUSTRATIONS: Photographs should be unmounted on glossy paper and show magnification scale. They should be marked on the back with figure number, title of paper and name of author.

Diagrams should be in India ink and large enough to be informative after reduction.

All illustrations should be referred to as figures, numbered consecutively, not included in the body of the text and all captions should be typed on a separate piece of paper.

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REFERENCES to authors outside the context of the sentence should read (Name, Year). i.e. *"However, a recent study (Bird and Iverson, 1975) showed a decreased, etc."* Authors mentioned within the context of the sentence should read Name (Year), *"i.e. ...twenty years since Ecker and Reimenshender (1951) demonstrated, etc."* References should be typed in alphabetical order on a separate sheet and include author's name, initials, year, title, publication, volume first and last page, i.e. Isacson, P. (1967). Myx-oviruses and autoimmunity. Progress in Allergy, 10, 256-292. Abbreviations should be the same as those used in Cumulated Index Medicus.

Textbook references should include name of text, author's name, page number, publisher and city.

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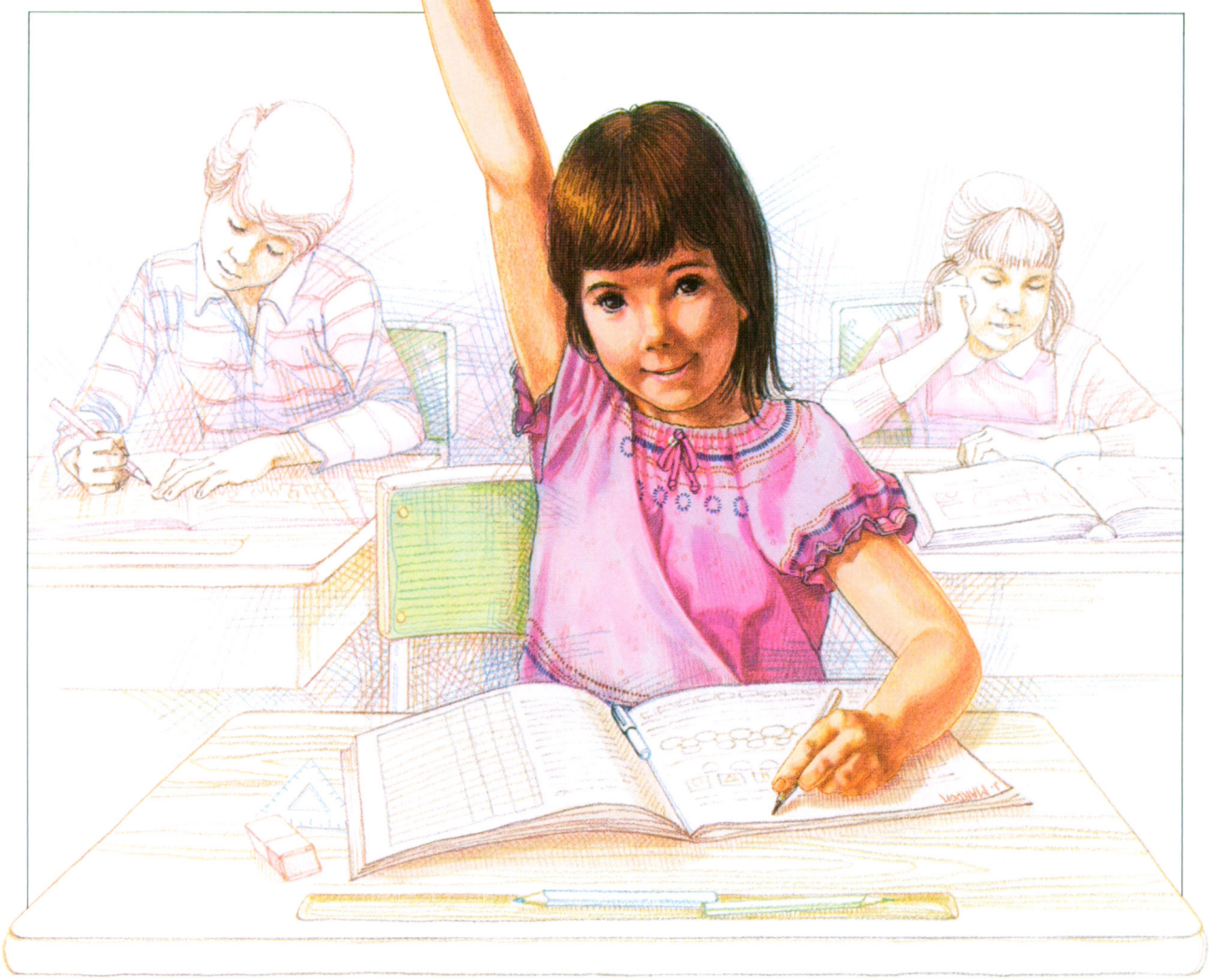
you wouldn't guess Jane's an epileptic



Epileptic therapy doesn't have to interfere with her life. Depakene can effectively control seizures, with little risk of disturbed behaviour or poor performance.

Depakene provides broad-spectrum seizure control Depakene is considered a drug of first choice for simple and complex absence seizures[1,2] and has been successfully used in tonic-clonic or myoclonic seizures with absence components.[3,4]

No impairment of learning Depakene has made patients more alert, more lively and better able to perform daily tasks.[5]

Positive effect on behaviour Depakene, unlike phenobarbital, rarely affects behaviour, and may actually improve it.[5]

Low incidence of disturbing side effects Depakene does not cause hirsutism, gum hyperplasia or acne, nor has it been associated with aplastic anemia or agranulocytopenia.

Minimizes problems of polypharmacy Depakene is often effective as single therapy. When other anticonvulsants are necessary, their dosage may be reduced.

New dosage convenience A 500-mg enteric-coated capsule is now available.

valproic acid

Depakene*

brings many epileptic patients closer to normal

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Prescribing information on page . . .

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Depakene

valproic acid

Brief prescribing information

INDICATIONS AND CLINICAL USE: Depakene (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. Valproic acid may also be used adjunctively in patients with multiple-seizure types which include absence.
In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS: Depakene (valproic acid) should not be administered to patients with hepatic disease or significant dysfunction; it is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Hepatic failure resulting in fatalities has occurred in patients receiving Depakene. These incidences usually have occurred during the first six months of treatment with Depakene. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia and vomiting. Patients and parents should be instructed to report such symptoms. Because of the nonspecific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious causes while taking sodium valproate.
Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed when administering Depakene to patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.
In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decrease in concentrations and serum ammonia for increases in concentration. If changes occur, valproic acid should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.
The drug should be discontinued immediately in the presence of significant hepatic dysfunctions, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug. The frequency of adverse effects particularly elevated liver enzymes may increase with increasing dose. Therefore, the benefit gained by increased seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

USE IN PREGNANCY: The safety of Depakene (valproic acid) during pregnancy has not been established, however, animal studies have demonstrated teratogenicity. Therefore, the physician should weigh the potential benefits against the possible risks in treating or counselling women of childbearing age who have epilepsy.
Recent reports indicate an association between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women, this incidence may be increased two to three-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.
Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsant drugs, including trimethadione and paramethadione. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.
Anticonvulsant drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.
Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation might be indicated.

NURSING MOTHERS: Depakene is secreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving valproic acid.

FERTILITY: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown that doses up to 350 mg/kg/day for 60 days have no effect on fertility. The effect of Depakene (valproic acid) on the development of the testes and on sperm production and fertility in humans is unknown.
LONG TERM TOXICITY STUDIES IN RATS INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS: HEPATIC DYSFUNCTION: SEE CONTRAINDICATIONS AND WARNINGS

GENERAL: Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients receiving Depakene (valproic acid) be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of Depakene (valproic acid) dosage or withdrawal of therapy pending investigation.
Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests; if elevation occurs, the valproic acid should be discontinued.
Because Depakene (valproic acid) may interact with other anticonvulsant drugs, periodic serum level determinations of such other anticonvulsants are recommended during the early part of therapy (see DRUG INTERACTIONS). There have been reports of breakthrough seizures occurring with the combination of Depakene and phenytoin.
Depakene (valproic acid) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

DRIVING AND HAZARDOUS OCCUPATIONS: Valproic acid may produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

DRUG INTERACTIONS: DEPAKENE (VALPROIC ACID) MAY POTENTIATE THE CNS DEPRESSANT ACTION OF ALCOHOL.
THERE IS EVIDENCE THAT VALPROIC ACID MAY CAUSE AN INCREASE IN SERUM PHENOBARBITAL LEVELS, ALTHOUGH THE MECHANISM IS UNKNOWN. PATIENTS RECEIVING CONCOMITANT BARBITURATE THERAPY SHOULD BE CLOSELY MONITORED FOR NEUROLOGICAL TOXICITY. SERUM BARBITURATE DRUG LEVELS SHOULD BE OBTAINED, IF POSSIBLE, AND THE BARBITURATE DOSAGE DECREASED, IF INDICATED.
Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction.
THERE IS CONFLICTING EVIDENCE REGARDING THE INTERACTION OF VALPROIC ACID WITH PHENYTOIN. IT IS NOT KNOWN IF THERE IS A CHANGE IN UNBOUND (FREE) PHENYTOIN SERUM LEVELS. THE DOSE OF PHENYTOIN SHOULD BE ADJUSTED AS REQUIRED BY THE CLINICAL SITUATION.
THE CONCOMITANT USE OF VALPROIC ACID AND CLONAZEPAM MAY PRODUCE ABSENCE STATUS.
Caution is recommended when valproic acid is administered with drugs affecting coagulation, e.g. acetylsalicylic acid and warfarin (see ADVERSE REACTIONS).

ADVERSE REACTIONS: The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since Depakene (valproic acid) has usually been used with other anticonvulsants, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

GASTROINTESTINAL: Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS EFFECTS: Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes", tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients who were also on phenobarbital.

DERMATOLOGIC: Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

ENDOCRINE: There have been reports of irregular menses and secondary amenorrhea in patients receiving Depakene.

PSYCHIATRIC: Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration have been reported.

MUSCULOSKELETAL: Weakness has been reported.

HEMATOPOIETIC: Thrombocytopenia has been reported. Valproic acid inhibits the second phase of platelet aggregation (see DRUG INTERACTIONS). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

HEPATIC: Minor elevations of transaminases (e.g. SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity. (See WARNINGS).

METABOLIC: Hyperammonemia. (See PRECAUTIONS). Hyperglycinemia has been reported and associated with a fatal outcome in a patient with pre-existing nonketotic hyperglycinemia.

PANCREATIC: Isolated reports of pancreatitis in association with valproic acid therapy have been received.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: In a reported case of overdosage with Depakene (valproic acid) after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.
Naloxone has been reported to reverse the CNS depressant effects of Depakene overdose. Because naloxone could theoretically also reverse the anticonvulsant effects of Depakene it should be used with caution.
As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION: Depakene (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one-week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases.
The maximal recommended dose is 60 mg/kg/day. When the total daily dose exceeds 250 mg, it is given in a divided regimen. A 500-mg enteric coated capsule may be substituted for two 250-mg capsules.
The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control must be weighed against the increased incidence of adverse effects.

Table of Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily Dose (mg)	Number of Capsules or Teaspoonfuls of Syrup		
kg	lb		Dose 1	Dose 2	Dose 3
10 – 24.9	22 – 54.9	250	0	0	1
25 – 39.9	55 – 87.9	500	1	0	1
40 – 59.9	88 – 131.9	750	1	1	1
60 – 74.9	132 – 164.9	1,000	1	1	2
75 – 89.9	165 – 197.9	1,250	2	1	2

As the dosage of valproic acid is raised, blood levels of phenobarbital and/or phenytoin may be affected (see PRECAUTIONS).
Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. Such patients may benefit from administration of the enteric-coated capsule. The capsules should be swallowed without chewing to avoid local irritation of the mouth and throat.

AVAILABILITY: Depakene (valproic acid) is available as orange-coloured, soft-gelatin capsules of 250 mg in bottles of 100 capsules (Number 5681; DIN 443840); pale yellow, oval soft gelatin enteric-coated capsules of 500 mg in bottles of 100 capsules (Number D795; DIN 507989) and as a red syrup containing the equivalent of 250 mg valproic acid, as the sodium salt, per 5 mL in bottles of 450 mL (Number 5682; DIN 443832).

Depakene is now available in a 500-mg enteric-coated capsule.

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2. Data on file, Abbott Laboratories.
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