discontinuing the treatment. Transient and/or dose
dependent side effects have been reported: hair
loss, fine postural tremor, and somnolence; isolated
and moderate hyperammonemia without change in
liver function tests.
Hyperammonemia associated with neurological
symptoms has also been reported. In such cases
further investigations should be considered.
Isolated reduction of fibrinogen or increase in bleed-
ing time have been reported, usually without asso-
ciated clinical signs and particularly with high doses
(sodium valproate has an inhibitory effect on the
second phase of platelet aggregation). Frequent
occurrence of thrombocytopenia, rare cases of ane-
ia, leucopenia or pancytopenia.
Cases of pancreatitis, sometimes lethal, have been
occasionally reported.
The occurrence of vasculitis has been reported.
Weight gain has been reported as well as amen-
orrhea and menstrual irregularities. Hearing loss,
either irreversible or reversible, have been reported
rarely. However the cause and effect relationship
has not been established.

Warnings
Liver damage: Conditions of occurrence
Hepatic lesions with a severe and sometimes fatal
course have been exceptionally reported. Infants
and young children aged less than 3 years with
severe epilepsy and notably epilepsy accompanied
by cerebral lesions, mental retardation and/or meta-
bole or degenerative disease of genetic origin are
the most exposed to this risk. Beyond the age of 3
years, the incidence of occurrence is significantly
reduced and decreases progressively with age. In
most cases, such hepatic lesions occur within the
first 6 months of treatment, most often between 2
and 12 weeks, and generally in cases of multiple
anticonvulsant therapy.
Suggestive signs: Early diagnosis is based above
In children under the age of 3 years, Depakine should be used only as monotherapy and after evaluation of the therapeutic value in relation to the risk of liver damage in such patients.

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see Side Effects/Precautions).

In patients with renal insufficiency, the increase in free serum concentrations of valproic acid should be taken into account, and the dosage decreased as a result.

In the presence of an “acute abdomen”, it is recommended that serum amylase levels can be checked before any surgery is undertaken, since exceptional cases of pancreatitis have been reported.

In young children the concomitant use of salicylates should be avoided due to the risk of liver toxicity.

Although immune disorders have been only exceptionally noted during the use of sodium valproate, the potential benefit of Depakine should be weighed against its potential risk in patients with systemic lupus erythematosus.

Pregnancy and Lactation

Pregnancy: Risk associated with epilepsy and antiepileptics: In offspring born of mothers with epilepsy receiving any antiepileptic treatment, the global rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3%) reported in the general population. Although an increased number of children with malformations has been reported in case of multiple drug therapy, the respective part of treatments and disease has not been formally established. Malformations most frequently encountered are labial clefts and cardiovascular malformations.

Sudden discontinuation of the antiepileptic therapy may be associated with a worsening of the disease in the mother and subsequent untoward effects in the fetus.

Risk Associated with Sodium Valproate
In animals: teratogenic effects have been demonstrated in the mouse, rat and rabbit. In humans: the global risk of malformations in women receiving valproate during the first trimester of pregnancy is not higher than the risk described with other antiepileptics. A few cases of facial dysmorphea and of multiple malformations have been reported. The frequency of these effects has not been yet clearly established. Nevertheless sodium valproate would appear to preferentially induce neural tube defects: myelomeningocele, spina bifida, malformations of which antenatal diagnosis is possible. The frequency of this effect is estimated to be 1%.

In view of the above data: it would not appear legitimate to advise against conception in an epileptic woman treated with valproate.

If a pregnancy is planned, it is the opportunity of reviewing the indication for anticonvulsant therapy. During pregnancy, valproate anticonvulsant treatment should not be discontinued if it has been effective. Monotherapy is to be recommended. The minimum effective daily dosage should be used, and administered in several divided doses.

Nevertheless, specialized antenatal monitoring should be instituted in order to detect any possible abnormalities of closure of the neural tube.

Risk in the Neonate: Exceptional cases of hemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This syndrome would not appear to be related to the decrease of vitamin K such as induced by phenobarbital and enzymatic inducers.

Platelet count, fibrinogen plasma level and coagulation test (temps de cephaleine activée: TCA) should be performed in mother prior to delivery. Normal results in mother do not allow to eliminate hemostasis abnormalities in neonate.

As far as possible, avoid traumatic delivery. Platelet count, fibrinogen plasma level and coagulation test (TCA) should be investigated in neonates.

Lactation: Excretion of sodium valproate in breast milk is low with a concentration of 1 to 10% of the serum level. Up to now, breast-fed children that have been monitored during the neonatal period have not experienced clinical effects.

**Overdosage**
Clinical signs of acute massive overdosage usually includes a coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions. Symptoms may, however, be variable and seizures have been reported in the presence of very high plasma levels. Hospital management of overdosage should include gastric lavage, that is useful up to 10 to 12 hours following ingestion, osmotic diuresis, cardiac and respiratory monitoring. In very severe cases, dialysis or exchange transfusion may be performed. Naloxone has been successfully used in one case. Deaths have occurred following massive overdosage, nevertheless, a favourable outcome is usual.

**Storage Conditions**
Depakine should be stored in the original packaging, in a dry place, at room temperature (below 25°C).

**Drug Interactions**
Effects of Valproate on Other Drugs

**Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines:**
Depakine may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines; therefore clinical monitoring is advised and dosage should be adjusted when appropriate.

**Phenobarbital:** Depakine increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

**Primidone:** Depakine increases primidone plasma levels with exacerbation of its side effects (such as sedation): these signs cease with long-term treatment. Clinical monitoring is recommended especial-
ly at the beginning of combined therapy with dosage adjustment when appropriate.

Phenytoin: Depakine increases phenytoin total plasma concentration.

Moreover Depakine increases phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should be evaluated.

Carbamazepine: Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effect of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine: increased risk of severe cutaneous reactions (Lyell syndrome). Besides, valproate may reduce lamotrigine hepatic metabolism; close clinical monitoring should be instituted.

Zidovudine: Valproate may raise zidovudine plasma concentration leading to increase zidovudine toxicity.

Effects of Other Drugs on Valproate
Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproate serum concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.

On the other hand, combination of felbamate and valproate may increase valproate serum concentration. Valproate dosage should be monitored.

Mefloquine increases valproic acid metabolism and has a convulsant effect; therefore epileptic seizures may occur in cases of combined therapy.

In case of concomitant use of valproate and highly protein bonded agents (aspirin), valproate free serum levels may be increased.

Valproate serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.

Other interactions: Valproate usually has not enzyme inducing effect; as a consequence, valproate does not reduce efficacy of estroprogestative agents in women receiving hormonal contraception. Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent factor anticoagulant.

Dosage and Administration
Depakine
Average daily dosage is to be administered in divided doses (2 to 3 daily), preferably with meals.

Infants and young children: 30 mg/kg

Use either
Depakine oral solution: Prescription is to be stated in mg (or eventually ml) but not in drops. A measuring syringe marked and graduated to indicate the levels in ml on one side, and in mg on the other, is supplied with the oral solution. The solution may be diluted with water or nongaseous fruit juices.

or
Depakine Syrup: A measuring spoon marked with a 200 mg and a 100 mg graduation is supplied with the syrup. Prescription is to be stated in mg. Treatment should be effected by successive increases at 5 day intervals.

Administer the dosage in divided doses two daily for patients under 1 year of age and three daily for patients above 1 year.

Children: 30 mg/kg. Use in preference Depakine 200 mg tablets.

For Adults, Adolescents and Children Over 25 kg.
Use in preference Depakine 500 mg tablets.

Depakine Chrono 500

Daily Dosage and Administration: 20 to 30 mg/kg to be taken in 1 or 2 doses.

Initiation of Sodium Valproate Therapy: In patients previously receiving antiepileptic drugs, substitution with Depakine should be progressive, the optimum dosage being reached in about 2 weeks and other treatments being tapered then stopped.

In patients without other antiepileptic drugs, the dosage should be preferably increased by successive dose levels at 2-3 days intervals in order to reach the optimum dosage in about one week.
**Recommendations for Use**
Tablets should not be broken or chewed, but taken with water or non-gaseous liquids; solution may be diluted in water or non-gaseous fruit juices.

**Packaging**
- sn: 200 mg/ml x 40 ml
- sy: 100 mg/5 ml x 150 ml
- t: 200 mg x 40 (Enteric Coated)
- sy: 200 mg/5 ml x 150 ml
- t: 500 mg x 30 (Depakine Chrono)