Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sodium Valproate 200mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg Sodium Valproate.
Excipient: Amaranth (E123) 0.036 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet
Circular, biconvex, lilac-coloured tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For use in the treatment of epilepsy generalised, partial or other.

4.2 Posology and method of administration

Oral.

Dosage requirements vary with body weight and age.

Sodium valproate tablets may be given twice daily. The tablets should be swallowed whole and not crushed or chewed.

Monotherapy

Adults
Dosage should be commenced at 600mg daily in divided doses increasing at 3 day intervals by 200mg daily until control is achieved. The usual dosage range is 1000mg to 2000mg (20-30mg/kg) daily, but where adequate control is not achieved within this range the dose may be further increased to 2500mg per day.

Children over 20kg body weight
The usual initial dose should be 400mg daily (irrespective of weight) in divided doses with slow increments to the level of adequate control generally between 20 to 30mg/kg body weight daily.
Where adequate control is not achieved the dose may be increased to 35mg/kg body weight daily.

Children under 20kg body weight
20mg/kg body weight per day; in severe cases this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Elderly
Although the pharmacokinetics of Sodium Valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free drug is increased. This will affect the clinical

interpretation of plasma valproic acid levels.

In patients with renal insufficiency
It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2 Pharmacokinetic Properties).

Combined Therapy
When starting sodium valproate in patients already on other anticonvulsants, these should be tapered slowly; initiation of sodium valproate therapy should then be gradual, with target dose being reached after about 2 weeks.

In certain cases it may be necessary to raise the dose by 5 to 10mg/kg/day when used in combination with anticonvulsants which induce liver enzyme activity, (eg phenytoin, phenobarbitone and carbamazepine). Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of sodium valproate. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

NB: In children requiring doses higher than 40mg/kg/day clinical chemistry and haematological parameters should be monitored.

General Consideration
Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected (see section 5.2 Pharmacokinetic Properties).

4.3 Contraindications

Hypersensitivity to sodium valproate. Active liver disease**;** family history of severe hepatic dysfunction, particularly drug related**;** porphyria.

4.4 Special warnings and precautions for use

Hepatic: Routine measurement of liver function should be undertaken before therapy and periodically during the first 6 months especially in those who seem most at risk, and those with a prior history of liver disease; such patients should have close clinical supervision (see also section 4.8 Undesirable Effects).

Haematological: Prior to initiation of therapy and also before surgery, clinicians should assure themselves, using appropriate blood tests (blood cell count, bleeding time and coagulation tests), that there is no undue potential for bleeding complications (see also section 4.8 Undesirable Effects).

Pancreatitis: Severe pancreatitis, which may be fatal, has been very rarely reported. The risk of fatal outcome is greatest in young children and decreases with increasing age. Severe seizures or severe neurological impairment with combination anticonvulsant therapy may be risk factors for severe pancreatitis. Hepatic failure with pancreatitis increases the risk of fatal outcome. Patients should be advised to consult their doctor immediately if they develop symptoms suggestive of pancreatitis (e.g. abdominal pain, nausea and vomiting).

Medical evaluation (including measurement of serum amylase) should be undertaken in patients presenting with symptoms suggestive of pancreatitis and sodium valproate should be discontinued if pancreatitis is diagnosed.

Weight gain: Sodium valproate very commonly causes weight gain, which may be marked and progressive. All patients should be warned of this risk at the initiation of therapy and appropriate strategies adopted to minimise weight gain.

Pregnancy: It is recommended that sodium valproate be used in women of child-bearing age only in severe cases or those resistant to other treatment because of the potential teratogenic risk to the foetus exposed to valproate *in utero*. Women of child-bearing age should be informed of the potential risks and benefits of continuing anti-epileptic treatment throughout pregnancy (see also section 4.6 Pregnancy and Lactation).

Systemic lupus erythematosus: Caution should be observed when using the drug in patients with features which may suggest systemic lupus erythematosus because, rarely, signs of an immune disorder have occurred (see also section 4.8 Undesirable Effects).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with valproate.

Diabetic Patients
Sodium Valproate is eliminated mainly through the kidneys partly in the form of Ketone Bodies: this may give false positives in the urine testing of diabetics.

See also Section 4.6 Pregnancy and Lactation, and Section 4.8 Undesirable Effects.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Effects of Valproate on Other Drugs
-Neuroleptics, Monoamine Oxidase (MAO) inhibitors, antidepressants and benzodiazepines
Sodium Valproate 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*
Sodium Valproate 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*
Sodium Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

– *Phenytoin*
Sodium Valproate decreases phenytoin total plasma concentration. Moreover valproate 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 effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- *Lamotrigine*
Sodium Valproate may reduce lamotrigine metabolism and increase its mean half-life, dosages should be adjusted (lamotrigine dosage decreased) when appropriate. Co-administration of lamotrigine and Sodium Valproate might increase the risk of rash.

- *Zidovudine*
Sodium Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

- *Vitamin K-dependent anticoagulants*
The anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproic acid. The prothrombin time should be closely monitored.

- *Temozolomide*
Co-administration of temozolomide and valproate may cause a small decrease in the clearance of temozolomide that is

not thought to be clinically relevant.

4.5.2 Effects of Other Drugs on Valproate
Antiepileptics with enzyme inducing effect (including *phenytoin, phenobarbital, carbamazepine*) decrease valproic acid plasma 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 valproic acid plasma concentration. Valproate dosage should be monitored.

Both *mefloquine* and *chloroquine* may lower the seizure threshold. In addition, mefloquine may decrease valproate levels. The dosage of sodium valproate may need adjustment accordingly.

In case of concomitant use of valproate and *highly protein bound agents (e.g. aspirin)*, free valproic acid plasma levels may be increased.

Valproic acid plasma levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with *cimetidine* or *erythromycin*.

Carbapenem antibiotics may reduce plasma valproic acid to sub-therapeutic levels. If these antibiotics have to be administered, close monitoring of valproic acid plasma levels is recommended.

Cholestyramine may decrease the absorption of valproate.

4.5.3 Other Interactions
Caution is advised when using sodium valproate in combination with newer anti-epileptics whose pharmacodynamics may not be well established.
Valproate does not significantly induce hepatic enzymes; the efficacy of oral contraceptive agents does not appear to be affected.

4.6 Pregnancy and lactation

An increased incidence of congenital abnormalities (including facial dysmorphia, neural tube defects and multiple malformations, particularly of the limbs) has been demonstrated in offspring born to mothers with epilepsy both untreated and treated, including those treated with sodium valproate.

The incidence of neural tube defects in women receiving valproate during the first trimester has been estimated to be in the region of 1-2%. Folate supplementation has been demonstrated to reduce the incidence of neural tube defects in the offspring of women at high risk. No direct evidence exists of such effects in women receiving anti-epileptic drugs, however there is no reason to contraindicate folic acid in these women.

The available evidence suggests that anticonvulsant monotherapy is preferred. Dosage should be reviewed before conception and the lowest effective dose used, in divided doses as abnormal pregnancy outcome tends to be associated with higher total daily dosage. Women of child bearing age should be informed of the risks and benefits of continuing anti-epileptic treatment throughout pregnancy. Pregnancies should be carefully screened by alpha-foetoprotein measurement, ultrasound and other techniques if appropriate (see Section 4.4 Special Warnings and Special Precautions for Use).

There have been rare reports of haemorrhagic syndrome in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinaemia. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Note however, that haemorrhagic syndrome may also be induced by phenobarbitone and other enzyme-inducers.

Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.

Breast feeding
The concentration of valproic acid found in the breast milk is very low, between 1% and 10% of total maternal plasma

levels. There appears to be no contraindication to breast feeding by patients on valproate. The decision to allow the patient to breast feed should be taken with regard to all the known facts.

4.7 Effects on ability to drive and use machines

Not applicable. Use of sodium valproate may provide seizure control such that the patient may again be eligible to hold a driving licence.

However, patients should be warned of the risk of transient drowsiness especially in cases of anticonvulsant polytherapy or association with benzodiazepines.

4.8 Undesirable effects

Neurological
Ataxia and tremor have been occasionally reported and appear to be dose-related effects. Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In sodium valproate monotherapy it occurred early in treatment on rare occasions and is usually transient. Rare cases of lethargy and confusion occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants, notably phenobarbitone. They have usually been reversible on withdrawal of treatment or reduction of dosage.

Very rare cases of reversible extrapyramidal symptoms including parkinsonism, or reversible dementia associated with reversible cerebral atrophy have been reported.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported. Hearing loss, either reversible or irreversible has been reported rarely, though a causal relationship has not been established.

Hepatic
Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid or sodium valproate. Patients most at risk are children particularly those under the age of three and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation.

The incidents mainly occurred during the first six months of therapy, the period of maximum risk being 2-12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.

Clinical symptoms are more helpful than laboratory investigations in the early stages of hepatic failure. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms, usually of sudden onset, such as loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. These are an indication for immediate withdrawal of the drug. Patients should be instructed to report any such signs to the clinician for investigation should they occur. Whilst it is difficult to establish which, if any, investigation is predictive, tests which reflect protein synthesis e.g., prothrombin time may be most relevant.

Raised liver enzymes are not uncommon during treatment with Sodium Valproate and are usually transient or respond to reduction in dosage of Sodium Valproate. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function including prothrombin time should be monitored until they return to normal. However an abnormally prolonged prothrombin time particularly in association with other relevant abnormalities requires cessation of treatment. Any concomitant use of salicylates should be stopped, since they employ the same metabolic pathway.

Pancreatic
Very rare cases of pancreatitis, sometimes fatal, have been reported (see section 4.4 Special Warnings and Special Precautions for Use).

Metabolic
Hyperammonaemia without change in liver function tests may occur. Isolated and moderate hyperammonaemia may occur frequently, is usually transient and should not cause treatment discontinuation. However, it may occasionally present clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur sodium valproate should be discontinued. Hyperammonaemia associated with neurological symptoms has also been reported (see Section 4.4 Special Warnings and Special Precautions for Use). Oedema has been rarely reported.

Haematological
Valproic acid inhibits the second stage of platelet aggregation leading to prolongation of bleeding time and frequently to thrombocytopenia. These are usually associated with doses above those recommended and are reversible. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigation. Red cell hypoplasia**,** leucopenia and pancytopenia have been reported rarely; the blood picture returned to normal when the drug was discontinued. Isolated reduction of fibrinogen may also occur.

Gastrointestinal
Appetite may increase and sodium valproate very commonly causes weight gain which may be marked and progressive (see section 4.4 Special Warnings and Special Precautions for Use). Frequently at the start of treatment minor gastrointestinal irritation and, less commonly, nausea may occur. These problems can usually be overcome by taking Sodium Valproate with or after food or by using Enteric Coated Sodium Valproate.

Renal
There have been isolated reports of a reversible Fanconi's syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with valproate therapy, but the mode of action is as yet unclear.

Endocrine
There have been isolated reports of irregular periods or amenorrhoea. Very rarely gynaecomastia has occurred.

Dermatological
Transient hair loss has often been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within six months, although the hair may become more curly than previously. Hirsutism and acne have been very rarely reported.

Cutaneous reactions such as exanthematous rash have been reported rarely. In exceptional cases toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported.

Other
The occurrence of vasculitis has occasionally been reported**.** Allergic reactions (ranging from rash to hypersensitivity reactions) have been reported.

4.9 Overdose

Cases of accidental and deliberate overdosage have been reported. At plasma concentrations of up to 5 to 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

In massive overdose i.e. with plasma concentrations 10 to 20 times maximum therapeutic levels, there may be serious CNS depression and respiration may be impaired. However, the symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see also section 5.2 Pharmacokinetic Properties). Cerebral oedema and intracranial hypertension have been reported. A number of deaths have occurred following large overdoses. Hospital management of overdose including induced vomiting, gastric lavage, assisted ventilation and other supportive measures is recommended.

Haemodialysis and haemoperfusion have been used successfully. Intravenous naloxone has also been used sometimes in association with activated charcoal given orally.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sodium valproate is an anticonvulsant.

The most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

In certain *in vitro* studies, it has been reported that sodium valproate can stimulate HIV. However this effect is modest, variable, unrelated to the dose and not documented in man.

5.2 Pharmacokinetic properties

The half life of sodium valproate is usually reported to be within the range 8-20 hours. It is usually shorter in children. In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free serum valproic acid levels.

The reported effective therapeutic range for plasma valproic acid levels is 40-100mg/litre (278-694 micromol/litre). This reported range may depend on time of sampling and presence of co-medication. The percentage of free (unbound) drug is usually between 6% and 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of sodium valproate may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Povidone K30
Talc
Calcium silicate
Magnesium stearate

Subcoat:
Hypromellose 6
Anhydrous Citric acid
Macrogol 6000
*Violet Lake Solids

Enteric coat:
Polyvinyl acetate phthalate
Diethyl Phthalate
Stearic acid 50

* containing titanium dioxide, amaranth (E123) aluminium lake, indigo carmine aluminium lake and hyprolose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Sodium Valproate Tablets are packed in a blister strip of polyamide aluminium heat seal lacquer blister laminate with aluminium heat seal lacquer lidding foil. Ten tablets in each blister strip. Each blister strip is embossed with the batch number and expiry date. Ten blister strips are packed in a 350 micron folding cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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