1.3 South African Labelling And Packaging

1.3.1 South African Package Insert

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The package insert follows on page 2.

SCHEDULING STATUS: S3

PROPRIETARY NAME: EPIROL

COMPOSITION: Each tablet contains 200 mg sodium valproate.

PHARMACOLOGICAL CLASSIFICATION:

2.5 Anticonvulsants, including antiepileptic.

PHARMACOLOGICAL ACTION:

Sodium valproate has anticonvulsant action and causes an increase in the concentration of gamma-aminobutyric acid in the brain.

Since its chemical structure differs from that of other currently available anticonvulsant drugs studies suggest that it may have a different mode of action.

INDICATIONS:

Petit mal, grand mal and temporal lobe epilepsy.

CONTRA-INDICATIONS:

Use should be avoided in pregnancy unless, in the judgement of the prescribing physician, continued seizures constitute a risk to both patient and foetus.

DOSAGE AND DIRECTIONS FOR USE:

Epirol should preferable be taken with or after food. The tablets should be swallowed, preferably with water, but not with aerated water.

Adult dose:

Dosage should start at 600 mg per day in divided doses. The dosage may then be increased by 200 mg per day at three day intervals until control has been established.

Optimum control is usually obtained with doses of 1000 to 1600 mg per day. If adequate control has not been achieved after two weeks, the dose may be further increased, by stages, to a maximum of 2600 mg per day, or one other anti-epileptic agent may be added at a low dosage. In patients already receiving other therapy, the same pattern should be followed. Dosage of both Epirol and other agents should be adjusted, during the stabilisation period to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with Epirol alone.

Children:

Over 20 kg - Initial dosage should be 400 mg per day irrespective of mass, in divided doses with spaced increases until control is achieved. This is usually within the range of 20 to 30 mg per kg body mass per day.

Under 20 kg – 20 mg per kg of body mass per day. In severe cases up to 50 mg/kg/day. A dose of 50 mg/kg should be exceeded only in patients in whom plasma valproate levels are measured; plasma levels of 200 µg/ml should be exceeded only with caution and with monitoring of clinical chemistry and haematological function.

Once known enzyme-inducers (e.g. phenytoin, phenobarbitone, carbamazepine) have been withdrawn, or if side effects, such as tremor, are experienced, it may be possible to reduce the dose of Epirol, while still maintaining seizure control. A method of measuring plasma levels is available, should this be considered helpful; however, seizure control must ultimately determine the optimum dosage.

Side effects and special precautions:

Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients whose treatment included valproic acid or sodium valproate. These incidents occurred during the first six months of therapy, the period of maximum risk being 2 -12 weeks. No deaths have occurred in patients receiving the drug continuously for more than 6 months. Biochemical tests may not always become abnormal early in the evaluation of hepatic failure; non-specific findings such as loss of seizure control, malaise, anorexia and vomiting, developing after a period of satisfactory Epirol treatment alert the clinician to the possibility of hepatic damage.

Epirol should not be administered to patients with pre-existing hepatic dysfunction. All patients for whom treatment with Epirol is contemplated should have base line liver function assessed (including serum fibrinogen and albumin levels) prior to commencement of therapy. Liver function should be carefully monitored, particularly during the first six months of therapy, and when dosage is being titrated upwards. Patients with a prior history of liver disease or with severe or unusual seizure disorders, e.g. those accompanied by mental retardation and/or organic brain disease, should be followed particularly carefully.

Transient elevations of liver enzymes are not uncommon during early treatment with Epirol. However, if liver enzymes, elevations are accompanied by other evidence of hepatic dysfunction; especially raised serum bilirubin or lowered serum fibrinogen then the drug should be immediately withdrawn.

Hyperammonaemia without hepatic damage can occur in patients during treatment with valproic acid or sodium valproate. It has been suggested that this may be related to interference with propionic acid metabolism. This may manifest clinically as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, Epirol should be discontinued. Valproic acid inhibits second stage of platelet aggregation.

Reversible prolongation of bleeding time, sometimes with thrombo-cytopenia, has occurred rarely at high dosage. Spontaneous bruising or bleeding is an indication for withdrawal of medication pending

investigation. It is recommended that patients receiving Epirol should be monitored for platelet function before surgery.

Red cell hypoplasia and leucopenia have been reported with Epirol.

The blood picture returned to normal when the drug was discontinued.

There have been reports of pancreatitis occurring in patients receiving valproic acid or sodium valproate. Patients experiencing acute abdominal pain should have the serum amylase estimated.

No cardiac effects attributed to Epirol have been reported. Minor gastric irritation, and, less frequently, nausea have been observed in some patients at the start of treatment, but these problems can usually be overcome by administering Epirol tablets with or after food. Should such symptoms persist they can be relieved by standard medication.

Transient hair loss has been noted in some patients. This effect does not appear to be dose-related and regrowth normally begins within 6 months, although the hair may become more curly than previously. Tremor has occasionally been observed at high dosages which may be controlled by reduction of dosage.

Oedema has been reported. Increase in alertness, appetite and mass may occur.

WOMAN OF CHILDBEARING AGE:

EPIROL had been associated with teratogenicity when given to women in the first trimester of pregnancy. Its use should be avoided in pregnant women and women likely to become pregnant unless its continued use is considered essential by the doctor. Women who have been exposed to Epirol in the first trimester of pregnancy should be informed of the risk and offered prenatal counselling.

COMBINED MEDICATION

Owing to the interaction known to occur with other anti-epileptic compounds it may sometimes be necessary to reduce the dosage of other drugs when adding Epirol to existing anticonvulsant

therapy. If the sedative effects of barbiturates are found to be enhanced, dosage of these compounds should be reduced. Like many other drugs, Epirol may also potentiate the effect of monoamine oxidase inhibitors (MAO) and other antidepressants, and dosage of such compounds should therefore also be reduced.

DIABETIC PATIENTS

Epirol is eliminated mainly through the kidneys, partially in the form of ketone bodies, and this may give false positive readings in the urine-testing of possible diabetics.

Known symptoms of overdosage and particulars of its treatment:

For symptoms of overdosage - see side-effects.

Treatment consists of induced vomiting, gastrict lavage, assisted ventilation, forced diureses and other supportive measures. Naloxone has been used successfully in one patient.

It has been suggested that gastric lavage may be of limited value in view of the rapid absorption of valproic acid. Thus particular attention should be paid to maintaining an adequate urinary output.

CONDITIONS OF REGISTRATION:

Advertising to the Professions only.

IDENTIFICATION:

White biconvex tablets 11 mm in diameter.

PRESENTATION:

Amber glass bottles containing 100 and 500 tablets plus a dessicant or packs of 100 and 500 tablets of 200 mg packed in foil strips.

STORAGE INSTRUCTIONS:

Store in a dry place below 25 °C and protect from light. Keep out of reach of children.

As the tablets are hygroscopic they must not be removed from their foil wrapper until ready for administration.

REGISTRATION NUMBER:

S/2.5/72

NAME AND BUSINESS ADDRESS OF APPLICANT:

Oethmaan Biosims (Pty) Ltd

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Emmarentia

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