IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0711/099/001
Case No: 2049598

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Valproat 300 mg Prolonged-Release Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **25/06/2008** until **27/07/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valproat 300 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release tablet contains 200 mg sodium valproate and 87 mg valproic acid, together equivalent to 300 mg sodium valproate

Excipients: 28 mg sodium

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet:
White, oblong prolonged-release tablet, with a score line

The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Primary form of generalized epilepsy
- typical and atypical absences (petit mal)
- myoclonic seizures
- tonic-clonic seizures (grand mal)
- mixed forms of tonic-clonic seizures and absences
- atonic seizures

May also be used for manifestations of epilepsy that do not adequately respond to other antiepileptic agents, such as:

Partial epilepsy
- both with elemental (focal) and complex (psychomotor) symptoms.
- Secondary forms of generalized epilepsy, especially akinetic and atonic seizures.

Monotherapy is often possible in the primary form of generalized epilepsy. In partial epilepsy combined therapy will have to be instituted more frequently, likewise in the secondary form of generalized epilepsy and in mixed forms of primary generalized and partial epilepsy

4.2 Posology and method of administration

The effective dose and duration of this long-term therapy has to be determined individually with the aim being free from seizures with the minimum dosage, particularly during pregnancy. Monitoring of the patients is recommended during the period of dose adjustment. Although a good correlation between daily dose, plasma level and therapeutic effect has not been demonstrated, generally a plasma level between 40 and 100 micrograms per ml (300-700 micromol/l) sodium valproate is attempted to be obtained. Nevertheless, favourable results with a lower or higher level have not been excluded, especially in children.

In cases of dosages of 35 mg sodium valproate/kg bodyweight per day or more, it is advisable to monitor the plasma level.

In some cases the full treatment response is achieved after 4-6 weeks. The daily doses should therefore not be increased too early beyond mean values.

A maximum daily dose of 60 mg sodium valproate/kg/day should not be exceeded.

When changing from pretreatment with (immediate release) pharmaceutical forms to Valproat 300/500 mg prolonged-release tablets, it must be ensured, that adequate serum levels are maintained.

In general, the following dosage regimen may be used:

Monotherapy

Initial dose:
Adults and children
Initially 10 -15 mg sodium valproate/kg bodyweight per day is taken in two or more doses during meals; increase the dose weekly in steps of 5-10 mg sodium valproate/kg bodyweight per day until the desired therapeutic effect is achieved.

Maintenance dose:
As average 20-30 mg sodium valproate/kg bodyweight per day is taken ranging as follows:
Adults : 9-35 mg sodium valproate/kg bodyweight per day
Children : 15-60 mg sodium valproate/kg bodyweight per day

The optimal daily maintenance dose is usually divided into 1 to 2 doses during meals.

Children under 20 kg bodyweight:
An alternative formulation of valproate should be used in this group of patients, due to the need for dose titration.

Elderly
The pharmacokinetics of valproate may be altered in the elderly. Dosage should be determined by seizure control. (See section 5.2).

The following average daily doses for sodium valproate are recommended (table for orientation purposes):

Age	Body weight (kg)	Average dose (mg/day)
3 – 6 months	≈ 5.5 - 7.5	150
6 - 12 months	≈ 7.5 – 10	150 - 300
1 – 3 years	≈ 10 – 15	300 - 450
3 – 6 years	≈ 15 – 20	450 - 600
7 - 11 years	≈ 20 – 40	600 - 1200
12 - 17 years	≈ 40 – 60	1000 - 1500
Adults and elderly	≥ 60	1200 - 2100

Use in renal impairment:
A dose reduction might be necessary in patients with renal impairment due to a possible increase in the level of free valproic acid in serum (see sections 4.4. and 5.2.).

Exact calculation of the dosage in mg/kg bodyweight is not strictly necessary. In some patients on lower doses, the daily dose may even be given in one administration, provided that this is well tolerated.

Combined therapy

If Valproat 300/500 mg prolonged-release tablets are administered in *combination with* or as *substitution therapy for*

previous medicinal products, it should be considered to reduce the dosage or the previously ordinated medicinal product (especially phenoparbitone) in order to avoid undesirable effects (see section 4.5) If the previous medicinal product is discontinued, this must be done gradually.

As the enzyme-inducing effect of other antiepileptics such as phenobarbitone, phenytoin, primidone and carbamazepine is reversible, the serum level of valproic acid should be measured approximately 4-6 weeks after the last intake of such an antiepileptic and the daily dose reduced if necessary.

Method of administration
The tablets - or half tablets if required - should be taken with a glass of plain water (carbonated drinks should not be used) and swallowed without chewing. If at the start or during treatment gastrointestinal irritation occurs, the tablets should be taken with or after food.

4.3 Contraindications

Hypersensitivity to sodium valproate, valproic acid or any of the excipients
- hepatic and/or pancreatic impairment
- personal or family history of severe hepatic dysfunction, especially drug related.
- hepatic porphyria
- haemorrhagic diathesis

4.4 Special warnings and precautions for use

Haematological
Monitoring of the blood count, including platelet count, bleeding time and coagulation tests, is advisable prior to initiation of therapy and before a surgical or dental operation, and in cases of spontaneous haematomas or bleeding (see section 4.8).

Bone marrow damage
Patients with previous bone marrow damage must be strictly monitored.

Hepatic dysfunction
Rare cases of severe liver damage following ingestion of sodium valproate, sometimes with a fatal outcome, have been reported.

Infants and children of less than 3 years of age with severe epilepsy, and especially epilepsy in combination with cerebral abnormalities, mental retardation, genetic degenerative conditions and/or known metabolic disturbances such as carnitine deficiency, deficiency of urea cycle enzymes, and/or a history of hepatic dysfunction, have the highest risk of hepatotoxicity, especially during the first 6 months of treatment. Above 3 years, the risk decreases with increasing age. The risk of hepatotoxicity is greater in combined treatment with other antiepileptic agents, especially in very young children.
In children of less than 3 years of age, concomitant use of salicylates is not recommended on account of the possibility of hepatotoxicity.

Monotherapy is recommended for children of less than 3 years of age if prescribing of Valproat is considered. However, the possible benefits must be weighed against the risk of liver damage and pancreatitis in such patients before treatment is initiated.

Valproat should not be normally used in small children less than 3 years of age as a first line therapy. Valproat should be used with caution in small children, only if benefits outweigh the risks, and if possible monotherapy should be preferred.

Clinical symptoms
Clinical symptoms are essential for early diagnosis. In particular, attention must be paid to the following disorders, which may precede jaundice:

- non-specific symptoms such as asthenia, anorexia, apathy, somnolence, sometimes accompanied by repeated vomiting and abdominal pain
- recurrence or exacerbation of convulsions
- prolongation of the bleeding time.

It is also advisable to warn the patient or parents about these symptoms, and to instruct them that, if they occur, the attending physician must be informed immediately.

Monitoring of liver function for hepatotoxicity
Liver function should be monitored prior to initiation of therapy and then periodically during the first 6 months. In particular, abnormally high thromboplastin time, representative of disturbed protein synthesis, is important. In cases of severely disturbed liver function tests (transaminases and/or bilirubin, and/or fibrinogen coagulation factors), treatment should be discontinued. As a precaution, concomitant use of salicylates (if these are used) should also be stopped, as hepatotoxicity caused by valproic acid can strongly resemble Reye's syndrome.

As with most antiepileptic agents, at the beginning of treatment an isolated transient increase in the transaminases may occur without clinical symptoms.

If this occurs, more extensive investigations (including determination of PTT) are recommended; adjustment of the dosage may be considered, and the investigations should be repeated if necessary.

Pancreatitis
Severe pancreatitis, which may be fatal, has been reported in rare cases. In particular young children are at risk. This risk decreases with increasing age. Severe seizures, neurological abnormalities in combination with other antiepileptic agents can be risk factors. Liver failure in combination with pancreatitis increases the risk of a fatal outcome.

Patients with acute abdominal pain during valproic acid treatment should therefore be examined without delay, and in the event of pancreatitis, treatment with sodium valproate should be stopped.

Immediate withdrawal of therapy should also be considered if any of the following symptoms occur:
unexplained impairment of the general condition, clinical signs of hepatic and/or pancreatic damage, coagulation disturbance, more than 2- to 3-fold increase of SGPT or SGOT even without clinical signs (induction of hepatic enzymes by concomitant medicinal products is to be taken into consideration), moderate (1- to 1,5-fold) increase of SGPT or SGOT accompanied by an acute feverish infection, marked impairment of the coagulation parameters, occurrence of dose-independent undesirable effects.

Hyperammonaemia with neurological symptoms
If an enzyme disturbance in the urea cycle is suspected, metabolic investigation should take place before treatment is started on account of the risk of hyperammonaemia as a result of valproic acid.

If valproic acid has to be discontinued suddenly on account of symptoms of toxicity such as increased apathy, somnolence, vomiting, hypotension and an increase in the frequency of seizures, withdrawal should take place while administering an adequate dose of another antiepileptic agent.

Diabetic patients
Use of Valproat can cause false-positive reactions when using the standard nitroprusside method of measuring ketone bodies in urine.

Thyroid hormone:
Dependent on its plasma concentration valproate may displace thyroid hormones from plasma protein binding sites and increase their metabolism which may lead to the false presumption diagnosis of hypothyroidism.

Renal impairment
Dose reduction may be necessary in patients with renal impairment, since the level of free valproic acid in serum is increased (see sections 4.2 and 5.2).

Weight gain
Patients should be warned of the possibility of weight gain at the beginning of treatment, and the necessary measures must be taken to limit this to a minimum (see section 4.8). Since it is a risk factor for polycystic ovary syndrome, weight gain should be carefully monitored.

Provocation of seizures
Valproat does not promote the development of tonic-clonic or partial complex seizures, a factor that is important in patients with absences.

Astatic-myoclonic seizures may be provoked, although this is rare.

Reactions of the immune system
Valproic acid can, although rarely, induce systemic lupus erythematosus and cause existing systemic lupus erythematosus to flare up. Therefore, in patients with systemic lupus erythematosus, the benefit of Valproat must be weighed against possible risks.

The combination of lamotrigine and valproic acid causes an increased risk of (severe) skin reactions, especially in children.

Each Valproat 300 mg prolonged-release tablet contains 1,227 mmol (28 mg) sodium. This has to be taken into consideration by patients on a controlled sodium diet.

Note:
The tablet matrix of Valproat may be recovered in the faeces.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of valproate on other medicinal products

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
Valproic acid may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines. Clinical monitoring is therefore advised. The dosage of these medicinal products should be adjusted if necessary.

In healthy test persons valproate displaced diazepam from the plasma albumin bond and inhibited its metabolism. In combination treatment the concentration of unbound diazepam may be increased and the plasma clearance and distribution volume of the free diazepam fraction lowered (by 25 %; 20 %). However, the half life remains unchanged.

In healthy individuals, simultaneous treatment with valproate and lorazepam led to a reduction in the plasma clearance of lorazepam by up to 40 %.

The serum level of phenytoin in children may be increased after the simultaneous administration of clonazepam and valproic acid

Phenobarbital
Valproic acid increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) as a result of which sedation may occur, particularly in children. Clinical monitoring is therefore recommended throughout the first 15 days of concomitant treatment, and if sedation occurs, the dose of phenobarbital should be reduced immediately. If necessary, the phenobarbital plasma levels should be determined.

Primidone
Valproic acid increases primidone plasma concentrations with an increase in its undesirable effects (such as sedation). These disappear in longer-term treatment. Clinical monitoring is recommended especially at the beginning of concomitant therapy. The dosage should be adjusted if necessary.

Phenytoin

Valproic acid decreases the total plasma concentration of phenytoin. Moreover, valproic acid increases the free form of phenytoin 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 also be evaluated.

Carbamazepine
Clinical toxicity has been reported when valproate was administered concomitantly with carbamazepine. Valproic acid may potentiate the toxic effect of carbamazepine. Clinical monitoring is recommended, especially at the beginning of concomitant therapy. The dosage should be adjusted if necessary.

Lamotrigine
Valproic acid may reduce lamotrigine metabolism. The dosage should be adjusted (lamotrigine dosage decreased) if necessary.

Combination of lamotrigine and valproic acid causes an increased risk of (severe) skin reactions, especially in children.

Felbamate
Valproic acid may increase the serum level of felbamate by approximately 30-50 %.

Zidovudine
Valproic acid may raise zidovudine plasma concentrations, leading to toxicity as a result of zidovudine. Reduction in the zidovudine dose may be necessary.

Effects of other medicinal products on valproic acid
Antiepileptics with an enzyme-inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid serum concentrations. In case of combined therapy, the dosages should be adjusted to the blood levels.

Felbamate increases the serum concentrations of free valproic acid linearly by 18% in relation to the dose. The valproic acid dosage should be reviewed.

Mefloquine increases the metabolism of valproic acid and has a convulsant effect. As a result, epileptic seizures may occur in case of concomitant therapy.

The serum levels of valproic acid may be increased due to concomitant use of medicinal products inhibiting the liver enzyme system, such as cimetidine or erythromycin.

Carbapenem antibiotics, e.g. meropenem, panipenem and imipene*:* a decrease in the valproic acid blood levels, sometimes accompanied by convulsions, has been observed when panipenem and meropenem were combined with valproic acid. Close monitoring of the valproic acid blood levels is recommended if these antibiotics have to be used.

<u>Anticoagulants, antiplatelet agents</u>
In case of concomitant use of a vitamin K antagonist, the thromboplastin time should closely be monitored (enhanced effect). Valproic acid can also potentiate the effect of acetylsalicylic acid. These interactions may result in increased haemorrhagic diathesis.

<u>Cholestyramine:</u>
The absorption of valproate may be decreased.

<u>Other interactions</u>
Valproic acid does usually not have an enzyme-inducing effect. Reduction in the efficacy of oestro-progestogenic agents is therefore not to be expected in women using hormonal contraception.

In case of concomitant use of valproate and agents strongly binding to proteins (such as acetylsalicylic acid), the serum levels of unbound valproate may be increased. Co-administration of medicinal products containing valproic acid and acetylsalicylic acid should be avoided in case of fever and pain, particularly in infants and toddlers.

Absence status occurred during the simultaneous treatment of patients with seizures of the absence type in their anamnesis with medicinal products containing valproic acid and clonazepam.

Alcohol:
Valproate may potentiate the effects of alcohol.

4.6 Pregnancy and lactation

Pregnancy
The need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. Due to increased risk of congenital abnormalities in offspring of mothers treated with antiepileptics, specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential

From observations in humans, there has been evidence that valproic acid can be harmful for the unborn foetus, especially after exposure in the first trimester of pregnancy. It is known that neonates born to mothers who take antiepileptic agents display developmental disturbances more frequently than other infants. In cases of valproic acid monotherapy the risk of abnormalities is 2-3 times greater than for untreated, non-epileptic pregnant women. In this respect, in humans valproic acid is particularly associated with the occurrence of spina bifida (estimated risk 1-2 %) and other abnormalities including cranio-facial abnormalities and malformations of the heart and limbs. The possibility of harmful effects occurring in the unborn foetus appears to be greater in cases of combination with other anti-epileptic agents.

Neonatal withdrawal symptoms may occur after use of valproic acid until the end of the pregnancy.

In general, it is not desirable to discontinue anticonvulsant therapy during pregnancy as this may lead to breakthrough seizures which could have serious consequences for both mother and child. Where possible, during pregnancy preference should be given to monotherapy. The lowest effective doses of valproic acid must be given, in divided doses and if possible, as prolonged release preparation in order to avoid high peak plasma levels. The plasma concentrations must be monitored since considerable variations were observed during early and late pregnancy despite equal doses. More malformations have been seen with plasma levels above 70 μg/ml and dosages above 1000 mg per day.

Some anti-epileptic agents possibly cause folate deficiency. Folate supplementation, in dosages that are usual (5 mg folic acid/day) for every pregnant woman, is recommended. Prenatal diagnostic measures to early diagnose damage (ultrasound and alpha-fetoprotein measurement) should be carried out.

Very rare cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenemia; afibrinogenemia has also been reported and may be fatal. These are possibly associated with a decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin-K factors induced by phenobarbitone and other enzyme inducing drugs. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Lactation
Valproic acid passes in low concentrations into breast milk. The advantages of breast-feeding should be weighed against the (slight) possibility of undesirable effects occurring in the infant. Mothers being treated with valproic acid may breast-feed provided that checks are carried out to ascertain whether undesirable effects (such as drowsiness, difficulty in drinking, vomiting, petechiae) are occurring.

4.7 Effects on ability to drive and use machines

Valproat has major influence on the ability to drive and use machines.
In view of the undesirable effects profile (vertigo, fatigue, and somnolence), a negative effect is to be expected. This should be taken into account when driving and operating machines.

Epilepsy itself is also a reason to be cautious about performing these activities, especially if someone has not been seizure-free for a long period.

Combined therapy, including use of benzodiazepines, may potentiate this effect (see section 4.5).

5 PHARMACOLOGICAL PROPERTIES

6 PHARMACEUTICAL PARTICULARS