SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Belvo 250 mg gastro-resistant tablets
Belvo 500 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: valproate semisodium

Each gastro-resistant tablet of Belvo 250 mg contains 269.1 mg of valproate semisodium, equivalent to 250 mg of valproic acid.
Excipient(s) with known effect:
Sunset yellow (E110) – 0.2 mg
Sodium: contains 18.5 mg per tablet

Each gastro-resistant tablet of Belvo 500 mg contains 538.2 mg of valproate semisodium, equivalent to 500 mg of valproic acid.
Excipient(s) with known effect:
Carmoisine (E122) – 0.104 mg
Ponceau 4R (E124) - 0.091 mg
Sodium: contains 37.0 mg per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablets.

Belvo 250 mg gastro-resistant tablets:
Peach oblong tablet without inscriptions (approximated dimensions: length 14.5 mm, width 8 mm and thickness 5.5 mm).

Belvo 500 mg gastro-resistant tablets:
Pink oblong tablets without inscriptions (approximated dimensions: length 19 mm, width 10 mm and thickness 6.3 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate semisodium for acute mania.

4.2 Posology and method of administration

Posology:

Patients who have previously received treatment with valproic acid should initiate therapy with the same daily dose and regimen. After stabilization of the patient with the new product, a daily scheme of 2 to 3 doses may be established.

The frequency of the side effects (mainly increased levels of liver enzymes) may be related to the dose. The benefit of a more effective seizure control with higher doses should be evaluated in terms of the possibility of a higher incidence of adverse reactions.

With the progressive increase of the dosage of the product, phenytoin concentrations in the blood can be affected (see section 4.4).

For patients with gastrointestinal irritation complaints, it is recommended to administer the drug during meals and to progressively increase the dose starting off with a low initial dose.

Manic episodes in bipolar disorder:

Adults:

The daily dosage should be established and controlled individually by the treating physician.

The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg valproate semisodium/kg body weight, has also shown an acceptable safety profile. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adjusted to the clinical response in order to establish the lowest effective dose for the individual patient.

The mean daily dose usually ranges between 1000 and 2000 mg valproate semisodium. Patients receiving daily doses higher than 45 mg/kg body weight should be carefully monitored.

Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Paediatric population:

The safety and efficacy of Belvo for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

Female children and women of childbearing potential

Valproate must be initiated and supervised by a specialist experienced in the management of bipolar disorder. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (sections 4.3 and 4.4).

Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).

Method of administration:
The tablets are administered orally.
The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

4.3 Contraindications

Belvo is contraindicated in the following situations:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hepatic disease (acute or chronic) or significant dysfunction.
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).
- in pregnancy (see section 4.4 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.4 and 4.6).

4.4 Special warnings and precaution for use

Considering previously described cases of thrombocytopenia, inhibition of secondary phase of platelet aggregation and abnormal coagulation parameters, laboratory tests on coagulation and platelet count are recommended before initiating treatment and at periodic intervals, especially if the patient is to be submitted to surgery.

In case of appearance of bruising, bleeding or other changes in haemostasis/coagulation, the dose should be reduced or the treatment discontinued.

Hyperammoniaemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests. If a clinically significant increase occurs, the product should be discontinued.

Since valproate may react with concomitantly administered antiepileptic drugs, periodic plasma concentration determinations of the other administered drugs should be performed on a regular basis, especially during the early course of therapy (see section 4.5).

Valproate is partially eliminated in the urine, as a keto metabolite, which may lead to false positives in the analysis of urine for determination of ketone bodies.

There have been reports of altered thyroid function tests associated with valproate administration, although its clinical significance is unknown.

Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid.

These incidents have usually occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial oedema, anorexia and vomiting. Patients should be monitored closely for detection of these symptoms. Thus, it is recommended to perform liver function tests prior to therapy and at frequent

intervals thereafter, especially during the first six months. Additionally, a careful evaluation of the medical history as well as a physical examination is recommended.

Patients taking several anticonvulsants, children, patients with congenital metabolic disorders, patients with severe seizures disorders accompanied by mental retardation, and patients with organic brain disease are those that may be at particular risk.
Experience has indicated that patients most at risk of fatal hepatotoxicity are young children under the age of 2 years, particularly those with previous mentioned conditions. In these patients Belvo should be prescribed as monotherapy and clinical monitoring is advised. Benefit and risk should be carefully reconsidered. The incidence of hepatotoxicity is significantly reduced and progressively decreases with age.

The drug should be discontinued immediately on suspicion or evidence of hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed despite discontinuation of therapy.

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

Belvo is contraindicated in the following situations:

- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

The prescriber must ensure that

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of bipolar disorders.

- the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her physician in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

- The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of child bearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee

her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by a specialist

The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

For the indication bipolar disorder if a woman is planning to become pregnant a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

In case of pregnancy

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. The patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in <teratology> {to be adapted depending on health care system} for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that

- the patient card is provided with every valproate dispensing and that the patients understand its content.
- the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

An annual risk acknowledgement form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Suicidal behaviour and ideation and have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an

increased risk for sodium valproate. Therefore, patients should be monitored for signs of suicidal ideation and suicidal behaviour, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice as soon as signs of suicidal ideation and behaviour emerge.

The concomitant use of valproate acid/sodium valproate and carbapenem agents is not recommended (see section 4.5).

Patients with known or suspected mitochondrial disease

Valproate may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, valproate-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy, cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Belvo 250 mg gastro-resistant tablets contains Sunset yellow (E110) and Belvo 500 mg gastro-resistant tablets contains Carmoisine (E122) and Ponceau 4R (E124) that may cause allergic reactions.

Sodium content
Belvo 500 mg gastro-resistant tablets: this medicinal product contains 37.0 mg sodium per tablet, equivalent to 1.85% of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Valproate may potentiate the CNS depressant action of alcohol.

The concomitant administration of valproate with other drugs that binds extensively to plasma proteins (e.g. acetylsalicylic acid, carbamazepine, dicumarol and phenytoin) may result in alteration of serum drug concentrations. There is evidence that valproate can cause an increase in serum phenobarbital concentrations by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproate and phenobarbital has also been reported to produce CNS depression but however without significant elevations of barbiturate or valproate serum concentrations.

All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity, reducing the dosage of the barbiturate as needed. Primidone is metabolized to a barbiturate and, therefore, may also be involved in a similar or identical interaction.

Changes of phenytoin serum concentrations have been reported, when administered concomitantly. However there have also been reports of both increasing and lowering phenytoin concentrations with further increase. In addition, a decrease in total serum phenytoin with an

increase in the free versus protein-bound phenytoin concentrations has been observed. The dosage of phenytoin should be readjusted as required by the clinical situation.

The concomitant use of valproate and clonazepam may produce absence seizures.

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide concentrations. Patients receiving treatment with valproate and ethosuximide, concomitantly with other anticonvulsants, should be carefully monitored for alterations in serum concentrations of both drugs.

Caution is recommended when valproate is administered concomitantly with drugs affecting coagulation (e.g., acetylsalicylic acid and warfarin). (See section 4.8).

In some cases it was found that there is an association between the use of certain antiepileptics (valproate semisodium has also antiepileptic effects) and the ineffectiveness of oral contraceptives. One explanation for this interaction is based on the fact that most of antiepileptics are enzyme inducers and therefore reduce plasma concentrations of steroid hormones, which consequently results in inefficient inhibition of ovulation. Valproate is not an enzyme inducer and so it does not cause a decrease in concentrations of steroid hormones. Comparative clinical studies have shown that valproate is the only antiepileptic that does not interfere with the efficacy of oral contraceptive drugs.

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100% decrease in valproic acid levels within two days. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilized on valproic acid is not considered to be manageable and therefore should be avoided (see section 4.4).

4.6 Fertility, pregnancy and lactation

Valproate is contraindicated as treatment for bipolar disorder during pregnancy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4).

Pregnancy Exposure Risk related to valproate

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and

palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Teratogenicity and Developmental Effects

Data have shown that exposure to valproate in uterus can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in uterus to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in uterus was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in uterus are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to valproate in uterus may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see above and section 4.4)

If a woman plans a pregnancy
For the indications bipolar disorder if a woman is planning to become pregnant a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

Pregnant women
Valproate as treatment for bipolar disorder attacks is contraindicated for use during pregnancy.

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

• Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in <teratology> {to be adapted depending on health care system} for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies.
However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

Risk in the neonate

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

Breastfeeding

Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Belvo therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Since valproate semisodium may have a depressant effect on the central nervous system, especially when taken with alcohol or other CNS depressant drug, patients are advised not to take part in hazardous work, such as operating machines or driving, until they are certain that the medication does not cause drowsiness to them.

4.8 Undesirable effects

Since valproate semisodium is frequently administered concomitantly with other antiepileptics, in most of the cases it not possible to determine whether the following adverse reactions can be ascribed to valproate semisodium alone or to the combination of drugs.

Blood and lymphatic system disorders:
There have been reports of cases of thrombocytopenia and inhibition of secondary phase of platelet aggregation, which may be reflected in altered bleeding time, petechiae, bruising, hematoma formations and frank haemorrhage (see section 4.4).
Rarely, lymphocytosis, hipofibrinogenaemia, leukopenia, eosinophilia, anaemia and bone marrow suppression have been reported.

Endocrine disorders:
There have been reports of irregular menstruation and secondary amenorrhea, breast enlargement, galactorrhea. Abnormal thyroid function tests (see section 4.4) were reported.

Metabolism and nutrition disorders:
Hyperammonaemia (see section 4.4). Obesity (rare). Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent non-ketotic hyperglycinemia.

Psychiatric disorders:
There have been reports of cases of emotional disorder, depression, psychosis, aggression, hyperactivity and dementia.

Nervous system disorders:
In some cases, sedative effects have occurred in patients receiving monotherapy, but such effects occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication.
The most common effects on the CNS are: ataxia, headache, confusion, nystagmus, “visual spots”, asterixis, dysarthria, dizziness and incoordination. Rare cases of coma have been reported in patients receiving valproate sodium as monotherapy or in combination with phenobarbital.
Nausea, sedation, extrapyramidal disorders.

Gastrointestinal disorders:
The most commonly reported side effects at initiation of therapy are: nausea, vomiting and indigestion. These effects are usually transient and rarely require suspension of therapy. Diarrhoea, abdominal cramps and constipation have been reported. Both anorexia with immediate weight loss and increased appetite with weight gain have also been reported. The administration of delayed-release valproate semisodium generally results in reduction of gastrointestinal side effects.
Acute pancreatitis may be observed (including fatal cases but rarely).

Hepatobiliary disorders:
Small increases in the level of transaminases (SGOT and SGPT) and LDH are frequent and appear to be dose-dependent.

Occasionally, laboratory tests may indicate an increase in serum bilirubin and abnormal changes in other liver function. In this case, the results may reflect a potential severe liver toxicity (see section 4.4

Skin and subcutaneous tissue disorders:
Transient alopecia, rash, photosensitivity, generalized pruritus and erythema multiform may be observed and, frequently, nail and nail bed disorders. A case of fatal epidermal necrolysis has been reported in a six months old child taking valproate concomitantly with and other drugs.

Musculoskeletal and connective tissue disorders:
General weakness may be observed.
There have been reports of decreased Bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with valproate semisodium. The mechanism by which valproate semisodium affects bone metabolism has not been identified.

Other: Oedema of the extremities.
Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

Paediatric population
The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see Section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The clinical condition of an overdose of valproate may lead to deep coma. The benefit of gastric lavage or induction of vomiting will depend on the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output. It has been observed that naloxone has the ability to reverse the depressant effects of valproate on the CNS.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Central nervous system. Antiepileptic and anticonvulsant
ATC code: N03 AG01

Mechanism of action

Valproate semisodium dissociates to the valproate ion in the gastrointestinal tract.

5.2 Pharmacokinetic properties

Equivalent oral doses of valproate semisodium and valproic acid deliver equivalent quantities of valproate ion systemically. However, the rate of valproate ion absorption may vary with the conditions of use (e.g. fasting or postprandial).

When patients are in a fasting stage, peak plasma concentrations of valproate ion are observed after 3 to 4 hours following administration of the drug. Clinic studies indicate that feeding can influence the absorption rate of valproate.

While absorption rate from the gastrointestinal tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate in chronic use is not affected.

The plasma half-life of valproate is typically in the range of 6 to 16 hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic drugs capable of enzyme induction.

Valproate is primarily metabolized in the liver. The major metabolic routes are: glucuronidation, mitochondrial β-oxidation and microsomal oxidation.

The major metabolites formed are the glucuronide conjugate, 2-propyl-3-keto-pentanoic acid and 2-propyl-hydroxypentanoic acid. Other unsaturated metabolites have been observed. The major route of elimination of these metabolites is in the urine.

Patients on monotherapy have generally longer half-life times and higher concentrations of valproate at a given dosage than patients receiving polytherapy. This is primarily due to enzyme induction caused by other antiepileptics, which results in enhanced clearance of valproate by glucuronidation and microsomal oxidation.

Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

The therapeutic range is believed to be from 50 to 100 μg/ml of total valproate, although some patients may be controlled with plasma concentrations lower or higher than this range. Valproate is highly bound (90%) to plasma proteins in the therapeutic range. However, protein binding is concentration-dependent and decreases at high valproate concentrations. The binding is variable among patients, but can be influenced by fatty acids or by highly bound drugs such as salicylate. Some clinicians advise monitoring free valproate concentrations, which may more accurately reflect CNS penetration of valproate. As yet, a consensus on the therapeutic range of free concentrations has not yet been established. However, monitoring total and free valproate may be informative when there are changes in clinical status, concomitant medication or valproate dosage.

5.3 Preclinical safety data

Carcinogenicity studies revealed a statistically significant increase in the incidence of subcutaneous fibrosarcomas in male rats and a significant trend to dose-dependent appearance of lung adenomas and carcinomas in male mice treated with valproic acid. The clinical relevance of these findings is unknown.

Valproate d revealed no evidence of genotoxic potential in vitro and in vivo studies.

Toxicity studies in the reproduction and development revealed teratogenic effects in the mouse, rat and dog. Chronic toxicity studies in rats and young and adult dogs showed a decrease of spermatogenesis and testicular atrophy

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

250 mg gastro-resistant tablets:

Tablet core:
silicon dioxide
pregelatinized starch
povidone

Tablet coat:
titanium dioxide (E171)
talc
povidone
hypromellose phthalate
diacetylated monoglycerides
Yellow Aluminium Lake (Sunset yellow (E110) and Aluminium)
vanillin

500 mg gastro-resistant tablets:

Tablet core:
silicon dioxide
pregelatinized starch
povidone

Tablet coat:
titanium dioxide (E171)
talc
povidone
hypromellose phthalate
diacetylated monoglycerides
Carmoisine lake (Carmoisine (E122) and Aluminium)
Ponceau 4R lake (Ponceau 4R (E124) and Aluminium)

vanillin

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

250 mg: 24 months
500 mg: 18 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original blister in order to protect from moisture. Keep blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

Gastro-resistant tablets 250 mg and 500 mg are packed in Aluminium/PVDC+PVC/PE/PVDC blisters.

The primary packaging material (blister) is packed in cartons together with the patient leaflet.

Packs of 20, 30, 60 and 90 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Consilient Health Limited
5th Floor, Beaux Lane House,
Mercer Street Lower,
Dublin 2,
Ireland

8. MARKETING AUTHORISATION NUMBERS

250 mg: PL 24837/0108
500 mg: PL 24837/0109

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/04/2019

10. DATE OF REVISION OF THE TEXT

15/03/2021