1.4 PRODUCT INFORMATION

1.4.1 Prescribing information (Summary of products characteristics)

1. **Name of the medicinal product**

Valepsy-300 (Gastro-Resistant Sodium Valproate Tablets BP 300mg)

2. Qualitative and quantitative composition

MASTER FORMULA							
S. No.	Ingredients	Pharma copeia Grade	Label Claim	Mg/tab	Ovg. (%)/Factor	Qty. for 1.0 Lac (Kg)	Function
DRY MIXING							
1	Sodium Valproate*	BP	300 mg	300.00	NA	30.000	Active Pharmaceutical Ingredient
2	Microcrystalline Cellulose	BP	NA	77.700	NA	7.770	Diluent
3	Crospovidone	BP	NA	10.000	NA	1.000	Disintegrant
4	Lactose Monohydrate	BP	NA	75.000	NA	7.500	Diluent
5	Colloidal Silicon Dioxide	BP	NA	10.000	NA	1.000	Lubricant
6	Sodium Lauryl Sulphate	BP	NA	12.000	NA	1.200	Lubricant
7	Magnesium Aluminium Silicate	BP	NA	15.000	NA	1.500	Lubricant
BINDER							
8	Ethyl Cellulose	BP	NA	1.300	NA	0.130	Binder
9	Methylene Dichloride#	BP	NA	QS	NA	Q.S	Solvent
LUBRICATION							
10	Crospovidone	BP	NA	10.000	NA	1.000	Disintegrant
11	Microcrystalline Cellulose (PH-102)**	BP	NA	70.000	NA	7.000	Diluent
12	Colloidal Silicon Dioxide	BP	NA	12.000	NA	1.200	Lubricant
13	Croscarmellose Sodium	BP	NA	10.000	NA	1.000	Disintegrant
14	Sodium Starch Glycollate	IHS	NA	15.000	NA	1.500	Disintegrant
15	Purified Talc	BP	NA	20.000	NA	2.000	Lubricant
16	Magnesium Stearate	BP	NA	12.000	NA	1.200	Lubricant
Target Weight of Compressed Tablets				650.000	----	65.000	-
SEAL COATING MATERIAL							

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17	Seal Coat	IHS	NA	19.500	NA	1.950	Sealant
18	Isopropyl Alcohol#	BP	NA	QS	NA	QS	Solvent
19	Methylene Dichloride#	BP	NA	QS	NA	QS	Solvent
ENTERIC COATING MATERIAL							
20	Enteric Coated Titanium White Ready Mix	IHS	NA	84.500	NA	8.450	Coating material
21	Colour: Red Oxide of Iron	IHS	NA	2.500	NA	0.250	Colourant
22	Isopropyl Alcohol #	BP	NA	QS	NA	Qs	Solvent
23	Methylene Dichloride #	BP	NA	QS	NA	Qs	Solvent
24	Purified Talc	BP	NA	3.000	NA	0.300	For Dusting
Target Weight of Coated Tablets				728.000		72.800	

Standard quantity of Sodium Valproate* based on 100 % assay on as is basis, any increase or decrease in the quantity compensate with Purified Talc**.
Extra quantity of Microcrystalline Cellulose (PH-102)** to be taken to compensate loss on drying.
Methylene Dichloride and Isopropyl Alcohol used as solvent
Extra coating material used to compensate the loss during coating.

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3. Pharmaceutical form

Enteric coated Tablet.

Brick red coloured, capsule shaped, biconvex, enteric coated tablets having plain on both the sides

4. Clinical particulars

4.1 Therapeutic indications

In the treatment of generalized or partial epilepsy, particularly with the following patterns of seizures:

– absence

– tonic-clonic

– myoclonic

– atonic

– mixed

As well as, for partial epilepsy:

– simple or complex seizures

– secondary generalised seizures

– specific syndromes (West, Lennox-Gastaut)

Sodium Valproate is indicated for the treatment of the manic episodes associated with bipolar disorders.

4.2 Posology and method of administration

For Seizure Control Daily dosage should be established according to age and body weight; nevertheless the wide individual sensitivity to valproate should also be considered.

A good correlation has not been established between daily dose, serum concentration and therapeutic effect and optimum dosage should be determined essentially according to the clinical response; the determination of valproic acid plasma levels may be considered in addition to clinical monitoring when adequate seizure control is not achieved or when adverse effects are suspected. The reported effective range is usually between 40-100mg/litre (300-700mmol/litre)

Initiation of Sodium Valproate therapy

- In patients without other anti-epileptic drugs, the dosage should be preferably increased by successive dose levels at 2-3 day intervals in order to reach the optimum dosage in about 1 week.
- In patients previously receiving anti-epileptic agents, substitution with Sodium Valproate should be progressive, the optimum dosage being reached in about 2 weeks and other treatments being tapered and then stopped.
- Addition of another anti-epileptic agent should be done progressively where it is necessary (see "Interactions").

Practical Considerations

Dosage

Initial daily dosage is usually 10-15mg/kg, then doses are titrated up to the optimum dosage (see "Initiation of Sodium Valproate therapy")

This is generally within the range 20-30mg/kg. Nevertheless, where seizure control is not achieved within this range, the dose may be further increased adequately; patients should be carefully monitored when receiving daily doses higher than 50mg/kg (see "Precautions").

In children, usual dosage is about 30mg/kg per day.

In adults, usual dosage is within the range 20-30mg/kg per day.

Administration

The use of a controlled release form (Valparin Chrono) allows to give the drug once daily.

Sodium Valproate may be used in children provided that they are able to take such a form. The breakable forms of Valparin Chrono allow a fine dose adjustment

For Treatment of Mania

Initially dosage should start with 600mg daily increasing by 200mg / day at three-day intervals until control is achieved.

This is generally within the range 1000 to 2000mg/day (i.e., 20 to 30 mg/kg/day). Where adequate control is not achieved within this range the dose may be further increased to 2500mg /day

The Bowden et al study provides a strong support for a greater efficacy of serum levels above 45micrograms (these levels achieved 20% or greater improvement on both subscales of the Mania Rating Scale). Bowden noted that > 125 micrograms / ml had greater drug related adverse events. Between these extremes there does not appear to be a clear dose-response relationship

General

Hepatic Impairment: Hepatic dysfunction including hepatic failure resulting in fatal outcomes has occurred in patients whose treatment included valproic acid or sodium valproate.

Renal impairment: Lower doses may be required since free drug levels may be high owing to lowered serum albumin and poor urinary excretion of free drug metabolites.

Use in Elderly: Although the pharmacokinetics of Valparin 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.

Epilepsy indication: Among the oral pharmaceutical forms, the oral solution is more appropriate for administration to children less than 11 years.

Only for Bipolar indication In children and adolescents: The efficacy of Valparin for the treatment of manic episodes in bipolar disorder has not been established in patients aged less than 18 years. See also sections Warnings/Precautions and Adverse reactions for safety information.

Female children, women of childbearing potential and pregnant women

Sodium Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, Warnings" and Pregnancy)

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Program (PPP Section Warnings).

In the exceptional circumstance when valproate is the only treatment option during pregnancy in epileptic women, Valparin should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose of non-prolonged release formulations should be divided into at least two single doses during pregnancy

Estrogen-containing products

Valproate does not reduce efficacy of hormonal contraceptives.

However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels.

Administration

In view of the sustained release process and the nature of the excipients in the formula, the inert matrix of the granules is not absorbed by the digestive tract; it is eliminated in the stools after the active substances have been released.

4.3 Contraindications

Sodium Valproate is contraindicated in following situations:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see Sections Warnings and Pregnancy).

- • in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see Sections Warnings and Pregnancy).

Treatment of bipolar disorder

- in pregnancy .
- in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled.

4.4 Special warnings and precautions for use

Warning

Pregnancy Prevention Program

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 Pregnancy).

Valparin is contraindicated in the following situations:

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment
- in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled (see Sections Contraindications and Pregnancy).

Treatment of bipolar disorder

- in pregnancy
- in women of childbearing potential, unless the conditions of the pregnancy prevention program are fulfilled.

Conditions of Pregnancy Prevention Program:

The prescriber must ensure that

- Individual circumstances are evaluated in each case and discussed with the patient. This is to guarantee the patient's engagement and understanding of the therapeutic options together with the risks and the measures needed to mitigate the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient understands and acknowledges 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 (see subsection contraception of this 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 epilepsy, or 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.

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. Pharmacist or other health care professional (to be adapted locally) 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.

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 program 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 epilepsy indication, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess the valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section Pregnancy). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

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

In case of pregnancy

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to reevaluate 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 / pre-natal medicine for evaluation and counselling regarding the exposed pregnancy (see section 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 program. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

A risk acknowledgement form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist, and when a woman is planning a pregnancy or is pregnant.

• Severe liver damage

-Conditions of occurrence:

Severe liver damage resulting sometimes in fatalities has exceptionally been reported. Experience indicates that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disease.

After the age of 3 years, the risk is significantly reduced and it progressively decreases with age. In most cases, such liver damage occurred during the first 6 months of therapy.

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular, the following conditions which may precede jaundice should be taken into consideration, especially in patients at risk (see above "Conditions of occurrence"):

- non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy, drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- in patients with epilepsy, recurrence of seizures.

Patients (or their family for children) should be instructed to report immediately any such signs to a physician should they occur. Investigations including clinical examination and laboratory assessment of liver functions should be undertaken immediately.

Detection :

Liver function tests should be performed before therapy and then periodically during the first 6 months of therapy, especially in patients at risk (see also Section "Interactions"). Among the usual

investigations, tests which reflect protein synthesis particularly prothrombin rate, are most relevant. Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of Valparin therapy. As a matter of precaution and in case they are taken concomitantly, salicylates should also be discontinued since they follow the same metabolic pathway.

• Pancreatitis

Severe pancreatitis, which may result in fatalities, has been very rarely reported. Young children are at particular risk but this risk decreases with increasing age. Severe seizures, neurological impairment or anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.Patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, valproate should be discontinued.

• Estrogen-containing products

Valproate does not reduce efficacy of hormonal contraceptives.

However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels.

• Suicidal ideation and behavior

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this effect is not known.

Therefore, patients should be monitored for signs of suicidal ideation and behaviour, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

• Carbapenem agents

The concomitant use of Valparin and carbapenem agents is not recommended

• 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, acute liver failure and liver-related deaths have been associated with valproate treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for 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 un-explained 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 "Contraindications").

• Aggravated convulsions

As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with valproate. In case of aggravated convulsions, the patients should be advised to consult their physician immediately.

PRECAUTIONS

• Liver function tests

Liver function tests should be carried out before therapy and periodically during the first 6 months especially in patients at risk. As with most antiepileptic drugs, a slight increase in liver enzymes may be noted, particularly at the beginning of the therapy; they are transient and isolated. More extensive biological investigations (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

• Haematological tests

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

• Patients with systemic lupus erythematosus

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

• Urea cycle disorders

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

• Weight gain

Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimize the risk. (see "Adverse Reactions")

• Carnitine palmitoyltransferase (CPT) type II deficiency

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. (see"Contraindications") • Alcohol Alcohol intake is not recommended during treatment with valproate.

• Children:

Monotherapy is recommended in children under the age of 3 years when prescribing Valparin, but the potential benefit of Sodium Valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy. The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity.

• Renal insufficiency: It may be necessary to decrease the dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of valproate on other drugs

• Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines

Valparin 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.

• Lithium

Valparin has no effect on serum lithium levels.

• 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

• Phenytoin

Valparin decreases phenytoin total plasma concentration. Moreover Valparin increases the phenytoin free form with possible overdose 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 co-administered with carbamazepine as valproate may potentiate the toxic effect of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

• Lamotrigine

Valparin reduces the metabolism of lamotrigine and increases the lamotrigine mean half-life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and dosages should be adjusted (lamotrigine dosage decreased) when appropriate.

• Zidovudine

Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

• Felbamate

Valproic acid may decrease the felbamate mean clearance by up to 16%.

• Olanzapine

Valproic acid may decrease the olanzapine plasma concentration.

• Rufinamide

Valproic acid may lead to an increase in plasma level of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

• Propofol

Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

• Nimodipine Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration by 50 %

Effects of other drugs on valproate

• Antiepileptics

Antiepileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproic acid serum concentrations. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.

On the other hand, combination of felbamate and valproate decreases valproic acid clearance by 22% to 50%, and consequently increase the valproic acid plasma concentrations. Valproate dosage should be monitored.

Valproic acid serum levels may be increased in case of concomitant use with phenytoin or phenobarbital. Therefore patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemia

• Mefloquine

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

• Highly protein bound agents

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

• Vitamin K dependent factor anticoagulant

Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent factor anticoagulant.

• Cimetidine or Erythromycin

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

• Carbapenem agents

Carbapenem (panipenem, meropenem, imipenem…): 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 sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, coadministration of carbapenem agents in patients stabilized on valproic acid should be avoided (see Warnings). If treatment with these antibiotics cannot be avoided, close monitoring of Valparin blood level should be performed.

• Rifampicin

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.

• Protease inhibitors

Protease inhibitors such as lopinavir, ritonavir decrease valproate plasma level when co-administered.

• Cholestyramine

Cholestyramine may lead to a decrease in plasma level of valproate when co-administered.

• Estrogen-containing products

Estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control), when adding, or discontinuing estrogen-containing products. Consider monitoring of valproate plasma levels Valproate usually has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agentsin women receiving hormonal contraception.

• Metamizole

Metamizole may decrease valproate serum levels when co-administered, which may result in potentially decreased valproate clinical efficacy. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate

Other Interactions

- Risk of liver damage

The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity (see Section Warnings/Precautions- “Severe liver damage” and “children”).

Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see Section Warnings/Precautions- “Severe liver damage” and “children”).

In patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, clinical trials have reported ALT increases greater than 3 times the upper limit of normal in 19% of patients. Appropriate liver monitoring should be exercised when valproate is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters.

• Topiramate and acetazolamide

Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonemia. Patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonemic encephalopathy.

• Quetiapine

Co-administration of valproate and quetiapine may increase the risk of neutropenia/leucopenia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Valproate is contraindicated as treatment for bipolar disorder during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled (see Sections Contraindications and Warnings).

Teratogenicity and Developmental Effects

Valproate was shown to cross the placental barrier both in animal species and in humans.

Pregnancy Exposure Risk related to valproate

Both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate may be associated with a greater risk of congenital malformations than valproate monotherapy.

In animals: Teratogenic effects have been demonstrated in mice, rats and rabbits.

Congenital malformations

Data 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 or major malformations. The most common types of malformations include neural tube defects, facial dysmorphism,cleft lip palate, craniostenosis, cardiac, renal and urogenital defects, limb defects(including bilateral aplasia of the radius), and multiple anomalies involving various body systems. In utero exposure to valproate may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases had not resolved. Monitoring of signs and symptoms of ototoxicity is recommended.

Developmental disorders

Data have shown that exposure to valproate in utero 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 utero 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 utero 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 from a study conducted using registries in Denmark show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately 3-fold)and childhood autism (approximately 5-fold) compared to the unexposed population in the study.

Available data from a second study conducted using registries in Denmark show that children exposed to valproate in utero are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

If a woman plans a pregnancy

For the epilepsy indication, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess the valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see Section Warnings). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

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

Pregnant women

Valproate as treatment for bipolar disorder is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment

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.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in / pre-natal medicine 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 (5 mg daily) 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

Exceptional cases of hemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to 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 the pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of pregnancy.

• Estrogen-containing products

Valproate does not reduce efficacy of hormonal contraceptives. However, estrogen-containing products, including estrogen-containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy Prescribers should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum level

FERTILITY

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see “Adverse Reactions”). Valproate administration may also impair fertility in men.

In the few cases in which valproate was switched/discontinued or the daily dose reduced, the decrease in male fertility potential was reported as reversible in most but not all cases, and successful conceptions have also been observed

Breast-feeding

Excretion of valproate in breast milk is low, with a concentration between 1% to 10% of maternal serum levels. Based on literature and clinical experience, breastfeeding can be envisaged, taking into account the Valparin safety profile, especially hematological disorders.

4.7 Effects on ability to drive and use machines

The patient should be warned of the risk of somnolence especially in cases of anticonvulsant polytherapy or association with benzodiazepines.

4.8 Undesirable effects

Blood and lymphatic system disorders

Common: anaemia thrombocytopenia. (see "Precautions")

Uncommon: pancytopenia, leucopenia

Rare: bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis.

Investigations

Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see also "Precautions" and "Pregnancy"),biotin deficiency/biotinidase deficiency.

Nervous system disorders

Very common: tremor

Common:extrapyramidal disorder, stupor*,somnolence,convulsion*,memory impairment, headache, nystagmus, dizziness Uncommon coma*, encephalopathy*, lethargy*(see below), reversible parkinsonism, ataxia, paresthesia

Uncommon: Aggravated convulsions (see "Warnings").

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.

*Stupor and lethargy sometimes leading to transient coma /encephalopathy; they were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and they decreased on withdrawal of treatment or reduction of dosage. These cases mostly occurred during combined therapy (in particular with phenobarbital or topiramate) or after a sudden increase in valproate doses.

Eye disorders

Not known: diplopia

Ear and labyrinth disorders

Common: deafness

Respiratory, thoracic and mediastinal disorders

Uncommon: pleural effusion

Gastrointestinal disorders

Very common: nausea

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, abdominal pain upper, diarrhea frequently occur in some patients at the start of treatment, but they usually disappear after a few days without discontinuing the treatment.

Uncommon: pancreatitis, sometimes lethal. (see "Warnings")

Renal and urinary disorders

Common: urinary incontinence

Uncommon: renal failure

Rare : enuresis, tubulointerstitial nephritis,reversible Fanconi syndrome but the mode of action is as yet unclear.

Skin and subcutaneous tissue disorders

Common: hypersensitivity, transient and /or dose related alopecia, nail and nail bed disorders. Uncommon: angioedema, rash, hair disorder (such as hair texture abnormal, hair colour changes, hair growth abnormal)

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Musculoskeletal and connective tissue disorders

Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on longterm therapy with sodium valproate. The mechanism by which sodium valproate affect bone metabolism has not been identified.

Rare: systemic lupus erythematosus (see "Precautions"), rhabdomyolysis (See "Precautions")

Endocrine disorders

Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acnea, male pattern alopecia, and/or androgen increased)

Rare: hypothyroidism.

Metabolism and nutrition disorders

Common: hyponatraemia, weight increased.

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see Section "Precautions").

Rare: hyperammonaemia(see section Precautions), obesity

*Cases of isolated and moderate hyperammonemia without change in liver function tests may occur and should not cause treatment discontinuation. Hyperammonemia associated with neurological symptoms has also been reported. In such cases, further investigations should be considered (see "Precautions")

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Rare: myelodysplastic syndrome

Vascular disorders

Common: haemorrhage (see Precautions & Pregnancy)

Uncommon: vasculitis

General disorders and administration site conditions

Uncommon: hypothermia, non severe oedema peripheral

Hepatobiliary disorders

Common: liver injury .

Reproductive system and breast disorders

Common: dysmenorrhea

Uncommon : amenorrhea Rare: male infertility, polycystic ovaries

Psychiatric disorders

Common: confusional state, hallucinations, aggression*, agitation*,disturbance in attention*

Rare: abnormal behavior*, psychomotor hyperactivity*, learning disorder

*These ADRs are principally observed in the paediatric population.

Pediatric population

The safety profile of valproate in the pediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the pediatric 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 Warnings/Precautions). Psychiatric disorders such as aggression, agitation, disturbance in attention abnormal behavior, psychomotor hyperactivity and learning disorder are principally observed in the pediatric population.

4.9 OVERDOSE

Signs and Symptoms

Signs of acute massive overdose usually include a coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions, metabolic acidosis, hypotension and circulatory collapse/shock Deaths have occurred following massive overdose; nevertheless, a favorable outcome is usual.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral edema have been reported. The presence of sodium content in the valproate formulations may lead to hypernatraemia when taken in overdose

Management:

Hospital management of overdose should be symptomatic: gastric lavage may be useful up to 10 to 12 hours following ingestion, cardio-respiratory monitoring. Naloxone has been successfully used in a few isolated cases. In case of massive overdose, hemodialysis and hemoperfusion have been used successfully.

GENOTOXICITY

Valproate was not mutagenic in bacteria (Ames test), or mouse lymphoma L5178Y cells at thymidine kinase locus (mouse lymphoma assay), and did not induce DNA repair activity in primary culture of rat hepatocytes. After oral administration, valproate did not induce either chromosome aberrations in rat bone marrow, or dominant lethal effects in mice. In literature, after intraperitoneal exposure to valproate, increased incidences of DNA and chromosome damage (DNA strand-breaks, chromosomal aberrations or micronuclei) have been reported in rodents. However, the relevance of the results obtained with the intraperitoneal route of administration is unknown. Statistically significant higher incidences of sister-chromatid exchange (SCE) have been observed in patients exposed to valproate as compared to healthy subjects not exposed to valproate. However, these data may have been impacted by confounding factors. Two published studies examining SCE frequency in epileptic patients treated with valproate versus untreated epileptic patients, provided contradictory results. The biological significance of an increase in SCE frequency is not known.

CARCINOGENICITY

The 2-year carcinogenicity studies were conducted in mice and rats given oral valproate doses of approximately 80 and 160 mg/kg/day (which are the maximum tolerated doses in these species but less than the maximum recommended human dose based on body surface area). Subcutaneous

fibrosarcomas were observed in male rats and hepatocellular carcinomas and bronchiolo-alveolar adenomas were observed in male mice at incidences slightly higher than concurrent study controls but comparable to those in registries of historical controls.

REPRODUCTIVE & DEVELOPMENTAL TOXICITY

Teratogenic effects (malformations of multiple organ systems) have been demonstrated in mice, rats, and rabbits. In published literature, behavioral abnormalities have been reported in first generation offspring of mice and rats after in utero exposure to clinically relevant doses/exposures of valproate. In mice, behavioral changes have also been observed in the 2nd and 3rd generations, albeit less pronounced in the 3rd generation, following an acute in utero exposure of the first generation326. The relevance of these findings for humans is unknown.

5.0 CLINICAL PHARMACOLOGY

5.1 Pharmacodynamic properties

Broad spectrum anti-epileptic agent.- Sodium valproate exerts its effects mainly on central nervous system. Pharmacological studies in animalshave demonstrated that valproate has anticonvulsant properties in various models of experimental epilepsy (generalized and partial seizures). In humans, sodium valproate has demonstrated anti-epileptic activity in various types of epilepsy. - Its main mechanism of action seems to be related to a reinforcement of the GABAergic pathway.

5.2 Pharmacokinetic properties

- Sodium valproate bioavailability is close to 100% following oral administration.
- The volume of distribution is mainly limited to blood and extracellular fluid. Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentration in plasma (about 10% of the total concentration) Valproate is transferred through placenta. When given to breast feeding mothers, valproate is excreted in breast milk at low concentrations (between 1 to 10% of the total serum concen-tration).
- Steady state plasma concentration is reached rapidly (3 to 4 days) following oral administration.
- Valproate is highly bound to plasma proteins; protein binding is dose dependent and saturable.
- Valproate molecule can be dialysed but only the free form (approximately 10%) is excreted.
- Unlike other anti-epileptics, sodium valproate does not increase its own degradation, neither that of other agents such as oestroprogestatives. This is due to the absence of enzyme inducing effect involving cytochrome P450.
- Half life is approximately 8 to 20 hours. It is usually shorter in children.

- Sodium valproate is mainly excreted in urine following metabolization via glucuro conjugation and betaoxidation.

5.3 Preclinical safety data

NA

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose

Colloidal Silicon Dioxide

Sodium lauryl Sulphate

Magnesium Aluminium Silicate

Ethyl Cellulose

Methylene Dichloride

Cross carmellose Sodium

Doshion Resin

Purified Talc

Magnesium stearate

Seal coat

Isopropyl Alcohol

Enteric coated Titanium White Ready Mix

Red Oxide of Iron Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

10 Tablets are packed in alu/alu blister. Such 10 blister packed in an outer carton.

6.6 Special precautions for disposal

Tablets should be handled with care.

Keep the medicine out of reach of children

7. REGISTRANT

Name of Registrant:

Maxtar Bio-Genics

Address of Office:

310, Pearls Corporate (W Mall),

Manglam Place ,Sector- 3,Rohini,

Delhi-85 India.

8. MANUFACTURER

Name of Manufacturer:

Maxtar Bio-Genics

Address of Manufacturer:

K. No. 705, Nalagarh road, Malku Majra,

(Baddi), Tehsil Nalagarh ,Distt. Solan,

Himachal Pradesh - 173205

INDIA

9. DATE OF REVESION OF THE TEXT

Not applicable

MARKETING AUTHORIZATION NUMBER

DATE OF FIRST AUTHORIZATION

DATE OF REVISION OF THE TEXT