For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

TORVATE

1. **Generic Name**
   Controlled Release Tablets of Sodium Valproate 200mg, 300mg, 500mg

2. **Qualitative and quantitative composition**

TORVATE 200
Each Controlled-release tablet contains:
Sodium Valproate I.P..... 200 mg Colour :
Titanium Dioxide I.P. Excipients q.s.

TORVATE 300
Each Controlled-release tablet contains:
Sodium Valproate I.P..... 300 mg Colour :
Titanium Dioxide I.P. Excipients q.s.

TORVATE 500
Each Controlled-release tablet contains:
Sodium Valproate I.P..... 500 mg Colour :
Titanium Dioxide I.P. Excipients q.s.

The excipients used are Ethyl cellulose, Colloidal silicon dioxide, Hydroxy propyl methyl cellulose, Methanol, Methacrylic .acid & methy methacrylate.copolymer, Talc, Titanium dioxide, Diethyl phthalate and Isopropyl alcohol.

3. **Dosage form and strength**
   Dosage Form: Controlled release tablets
   Strength: 200 mg, 300 mg and 500 mg

4. **Clinical particulars**

4.1 Therapeutic indication

Anti-epileptic drug- indicated in the treatment of all forms of epilepsis

4.2 Posology and method of administration

Torvate tablets are for oral administration.

Torvate tablet is a prolonged release formulation of sodium valproate which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Daily dosage requirements vary according to age and body weight.

Torvate tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed.

Dosage

Usual requirements are as follows: Adults

Dosage should start at 600 mg daily increasing by 200 mg at three-day intervals until control is achieved. This is generally within the dosage range 1000-2000 mg per day, i.e. 20-30 mg/kg/day body weight. Where adequate control is not achieved within this range the dose may be further increased to 2500 mg per day.

Children over 20 kg

Initial dosage should be 400 mg/day (irrespective of weight) with spaced increases until control is achieved; this is usually within the range 20-30 mg/kg body weight per day. Where adequate control is not achieved within this range the dose may be increased to 35 mg/kg body weight per day.

Children under 20 kg

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

Use in the elderly

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

In patients with renal insufficiency

It may be necessary to decrease the dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading.

In patients with hepatic insufficiency

Salicylates should not be used concomitantly with Torvate since they employ the same metabolic pathway.

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid.

Salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome). In addition in conjunction with Torvate, concomitant use in children under 3 years can increase the risk of liver toxicity.

Female children and women of childbearing potential

Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. 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. The benefits and risks should be carefully reconsidered at regular treatment reviews.

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.

Combined Therapy

When starting Torvate in patients already on other anti-convulsants, these should be tapered slowly; initiation of Torvate therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases, it may be necessary to raise the dose by 5-10 mg/kg/day when used in combination with anti-convulsants, which induce liver enzyme activity, e.g. phenytoin, phenobarbital and carbamazepine. Once known enzyme inducers have been withdrawn it may be possible to maintain seizure control on a reduced dose of Torvate. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children), the dosage of barbiturate should be reduced.

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

Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side effects are suspected.

Method of administration
Torvate Controlled Release Tablets are for oral administration.

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

4.3 Contraindications

Torvate is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment.
- In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.
- Active liver disease.
- Personal or family history of severe hepatic dysfunction, especially drug related.
- Patients with known urea cycle disorders.
- Hypersensitivity to sodium valproate.
- Porphyria.
- Valproate is contraindicated in 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.

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations be not normally recommended due to the clinical implications of possible variations in plasma concentrations.

Liver dysfunction:

Conditions of occurrence:

Severe liver damage, including hepatic failure sometimes resulting in fatalities, has been very rarely reported. Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anti-convulsant therapy, are infants and in particular young children under the age of 3 years and those with severe seizure disorders, organic brain disease, and (or) congenital metabolic or degenerative disease associated with mental retardation. After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decreases with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing Torvate, but the potential benefit of Torvate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

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, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.

- In patients with epilepsy, recurrence of seizures.

These are an indication for immediate withdrawal of the drug.

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 biological assessment of liver function should be undertaken immediately.

Detection:
Liver function should be measured before therapy and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst 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 Torvate therapy.

As a matter of precaution and in case they are taken concomitantly, salicylates should also be discontinued since they employ the same metabolic pathway.

As with most anti-epileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:
Pancreatitis, which may be severe and result in fatalities, has been very rarely reported. Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase).Young children are at particular risk; this risk decreases with increasing age. Severe seizures and severe neurological impairment with combination anti-convulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis, Torvate should be discontinued.

Female children, women of childbearing potential and pregnant women:

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.

Torvate is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment.
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled.

Conditions of Pregnancy Prevention

Programe: 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 minimize 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 epilepsy.
- 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 prescriber must ensure that:

- The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The 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 have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by

the specialist to switch 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 childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare 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.

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy. Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen- containing products.

On the opposite, valproate does not reduce efficacy of hormonal

contraceptives. Annual treatment reviews by a specialist

The specialist should review at least annually 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

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess 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. If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

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 treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

- The Patient Card is provided with every valproate dispensation and that patients

understand its content.

- 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, provide guidance regarding use of valproate in women of childbearing potential and provide 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.

  Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of epilepsy.

Aggravated convulsions:

As with other anti-epileptic 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.

Suicidal ideation and behaviour:

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 risk is not known and the available data does not exclude the possibility of an increased risk for sodium valproate.

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

Carbapenem agents:
The concomitant use of valproate 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, 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, opthalmoplegia, 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.

Precautions

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.

Renal insufficiency:
In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Patients with systemic lupus erythematosus:
Although immune disorders have only rarely been noted during the use of Torvate, the potential benefit of Torvate 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 hyperammonaemia with Torvate.

Weight gain:
Torvate very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy and appropriate strategies should be adopted to minimise it.

Diabetic patients:
Torvate is eliminated mainly through the kidneys, partly in the form of ketone bodies; this may give false positives in the urine testing of possible diabetics.

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 Torvate. Alcohol: Alcohol intake is not recommended during treatment with valproate

4.5 Drugs interactions

Effects of Torvate on other drugs

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
Torvate may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of other psychotropics should be adjusted when appropriate.
In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

Lithium
Torvate has no effect on serum lithium levels.

Olanzapine
Valproic acid may decrease the olanzapine plasma concentration.

Phenobarbital
Torvate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital

doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

Primidone
Torvate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Phenytoin
Torvate decreases phenytoin total plasma concentration. Moreover, Torvate increases 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 Torvate was administered with carbamazepine as Torvate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine
Torvate 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.

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

Rufinamide

Valproic acid may lead to an increase in plasma levels 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.

Zidovudine

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

Nimodipine

In patients concomitantly treated with sodium valproate and nimodipine the exposure to nimodipine can be increased by 50%. The nimodipine dose should therefore be decreased in case of hypotension.

Temozolomide

Co-administration of temozolomide and Torvate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other drugs on Torvate

Anti-epileptics

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

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

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

Anti-malarial agents

Mefloquine and chloroquine increase valproic acid metabolism and may lower the seizure threshold; therefore epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of Torvate may need adjustment.

Highly protein bound agents

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

Vitamin K-dependent factor anticoagulants

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

Cimetidine or erythromycin

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

Carbapenem antibiotics (such as panipenem, imipenem and meropenem)

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, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided. If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels 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 and ritonavir decrease valproate plasma level when co-administered.

Cholestyramine

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

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives

Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Consider monitoring of valproate serum levels.

On the opposite, valproate has no enzyme inducing effect; as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

Other Interactions
Caution is advised when using Torvate in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of valproate and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Quetiapine

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

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

- 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 Programme are fulfilled.

Pregnancy exposure risk related to valproate
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Teratogenicity and developmental effects
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.

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 anti-epileptics. 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 utero 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 utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential
Oestrogen-containing products
Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy.

If a woman plans a pregnancy
If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy must reassess 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. If switching is not possible, the woman should receive further counselling regarding the risks of valproate for the unborn child to support her informed decision-making regarding family planning.

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

- Use the lowest effective dose and divide the daily dose 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 valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised 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 haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This haemorrhagic 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.

Breast-feeding
Valproate is excreted in human milk with a concentration ranging from 1% – 10% of maternal serum levels. Haematological disorders have been shown in breastfed newborns/infants of treated women.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Torvate 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. Valproate administration may also impair fertility in men. Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 Effects on ability to drive and use machines

Use of Torvate may provide seizure control such that the patient may be eligible to hold a driving licence.
Patients should be warned of the risk of transient drowsiness, especially in cases of anti-convulsant polytherapy or association with benzodiazepines.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).
Congenital malformations and developmental disorders.

Hepatobiliary disorders:
Common: liver injury
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported. Increased liver enzymes are common, particularly early in treatment, and may be transient.

Gastrointestinal disorders:
Very common: nausea

Common: vomiting, gingival disorder (mainly gum hyperplasia), stomatitis, gastralgia, diarrhoea

The above adverse events frequently occur at the start of treatment but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Torvate with or after food.

Uncommon: pancreatitis, sometimes lethal

Nervous system disorders:
Very common: tremor
Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus

Uncommon: coma*, encephalopathy, lethargy* (see below), reversible Parkinsonism, ataxia, paraesthesia, aggravated convulsions

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

Sedation has been reported occasionally, usually when in combination with other anti-convulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:
Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*
Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:
Common: hyponatraemia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome.

Rare: hyperammonaemia*, obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Torvate should be discontinued?

Hyperammonaemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered.

Endocrine disorders:
Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)
Rare: hypothyroidism

Blood and lymphatic system disorders:
Common: anaemia, thrombocytopenia,

Uncommon: pancytopenia, leucopenia

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

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

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Torvate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations.

Skin and subcutaneous tissue disorders:
Common: hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become curlier than previously.

Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

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

Reproductive system and breast disorders:
Common: dysmenorrhea
Uncommon: amenorrhea
Rare: male infertility, polycystic ovaries Very

rarely gynaecomastia has occurred.

Vascular disorders:
Common: haemorrhage

Uncommon: vasculitis

Eye disorders:
Rare: diplopia

Ear and labyrinth disorders:
Common: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:
Common: urinary incontinence

Uncommon: renal failure

Rare: enuresis, tubulointerstitial nephritis, reversible Falconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Torvate therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:
Uncommon: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:
Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Torvate. The mechanism by which Torvate affects bone metabolism has not been identified.

Rare: systemic lupus erythematosus, rhabdomyolysis

Respiratory, thoracic and mediastinal disorders:
Uncommon: pleural effusion

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)

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: myelodysplastic syndrome

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

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

Signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual, however some deaths have occurred following massive overdose.

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 oedema have been reported.

The presence of sodium content in the Torvate formulations may lead to hypernatraemia when taken in overdose.

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 – 12 hours following ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5. Pharmacological properties

5.1 Mechanism of Action

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

5.2 Pharmacodynamic properties

In certain reported in-vitro studies it was reported that Torvate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV-infected subjects show that Torvate does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of Torvate on HIV replication ex-vivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.3 Pharmacokinetic properties

In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

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

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

Metabolism

The major pathway of valproate biotransformation is glucuronidation (~ 40%), mainly via UGT1A6, UGT1A9 and UGT2B7.

The half-life of Torvate is usually reported to be within the range 8-20 hours. It is usually shorter in children.

Interaction with oestrogen-containing products

Inter-individual variability has been noted. There are insufficient data to establish a robust PK-PD relationship resulting from this PK interaction.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

No data available.

7. Description

The chemical name of Sodium Valproate is sodium 2-propylpentanoate (IUPAC). Its molecular formula is C8H15NAO2 and its molecular weight is 166.2. The chemical structure is:

Sodium Valproate is a white or almost white, crystalline powder; hygroscopic.

Product Description:

Torvate 200 and 300:

White round biconvex, coated tablets plain on both sides.

Torvate 500:

White capsule shaped, biconvex, coated tablets with break line on both sides.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry

8.3 Packaging information

Available in strip pack of 10 Tablets.

8.4 Storage and handing instructions

Keep in a dry place at a temperature not exceeding 30^{o}C.

9. Pharmaceutical particulars

Package leaflet: Information for the user

TORVATE

Controlled Release Tablets of Sodium Valproate

Torvate, sodium valproate, can seriously harm an unborn baby when taken during pregnancy. If you are a female able to have a baby you must use an effective method of birth control (contraception) without interruption during your entire treatment with Torvate. Your doctor will discuss this with you but you must also follow the advice in section 2 of this leaflet. Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant. Do not stop taking Torvate unless your doctor tells you to as your condition may become worse. If you are a parent or caregiver of a female child treated with Torvate, you must also read section 2 of this leaflet carefully and contact your child's doctor once they experience their first period.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What Torvate Tablets are and what they are used for.

The name of your medicine is Torvate Tablets. These are Prolonged-Release Sodium Valproate Tablets. "Prolonged release" means that the active ingredient sodium valproate is slowly released from the tablets over a period of time.

What Torvate contains

Torvate contains sodium valproate. It belongs to a group of medicines called anti- convulsants or anti-epileptic agents. It works by helping to calm the brain down.

What Torvate is used for

Torvate is used to treat epilepsy (fits) and prevent and treat mania (over-excitability and exaggerated emotions).

9.2 What you need to know before you use Torvate Tablets.

Do not use Torvate Tablets:

- You are allergic (hypersensitive) to sodium valproate or any of the other ingredients of Torvate. Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- You have liver problems or you or your family have a history of liver problems
- You have a rare illness called porphyria.
- You have a known metabolic disorder, i.e. a urea cycle disorder.
- You have a genetic problem caused by a mitochondrial disorder (e.g. Alpers- Huttenlocher syndrome).
- You are pregnant, unless nothing else works for you (see 'Pregnancy, breast-feeding and fertility-Important advice for women' below).

If you are a woman able to have a baby you must nottake Torvate unless you use an effective method ofbirth control (contraception) at all times during your treatment with Torvate. Do not stop taking Torvate or your contraception until you have discussed this with your doctor. Your doctor will advise you further (see below under 'Pregnancy, breast-feeding and fertility-Important advice for women').

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Torvate.

Warnings and precautions

- A small number of people being treated with anti-epileptics such as sodium valproate have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.
- As with other anti-epileptic drugs, convulsions may become worse or happen more frequently whilst taking this medicine. If this happens contact your doctor immediately.
- Talk to your doctor or pharmacist before taking Torvate if:
- You have diabetes. This medicine may affect the results of urine tests.
- You have a carnitine palmitoyltransferase type II deficiency.
- You have kidney problems. Your doctor may give you a lower dose.
- You have a brain disease or a metabolic condition affecting your brain.
- You have a 'urea cycle disorder' where too much ammonia builds up in the body.
- You have an illness called 'systemic lupus erythematosus (SLE)' – a disease of the immune system which affects skin, bones, joints and internal organs.
- You know that there is a genetic problem caused by a mitochondrial disorder in your family. If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Torvate.

Weight gain

Taking Torvate may make you put on weight. Talk to your doctor about how this will affect you.

Blood tests

Your doctor may wish to do blood tests before you start taking Torvate and during your treatment.

Other medicines and Torvate

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Torvate can affect the way some other medicines work. Also some medicines can affect the way Torvate works.

The following medicines can increase the chance of you getting side effects, when taken with Torvate:

- Some medicines used for pain and inflammation (salicylates) such as aspirin
- Some other medicines used to treat fits (epilepsy). This includes medicines such as phenobarbital, primidone, phenytoin, carbamazepine, rufinamide, topiramate, acetazolamide, lamotrigine and felbamate.

Torvate may increase the effect of the following medicines:

- Medicines used for thinning the blood (such as warfarin).
- Zidovudine-used for HIV infection.
- Temozolomide used to treat cancer.
- Medicines for depression.
- Monoamine oxidase inhibitors (MAOI) such as moclobemide, selegiline, linezolid.
- Medicines used to calm emotional and mental health problems (including schizophrenia, bipolar disorder and depression) such as quetiapine, diazepam and olanzapine.
- Nimodipine. • Propofol – used for anaesthesia.

The following medicines can affect the way Torvate works:

- Oestrogen-containing products (including some birth control pills).
- Some medicines used for the prevention and treatment of malaria such as mefloquine and chloroquine.
- Cimetidine – used for stomach ulcers.
- Protease inhibitors such as lopinavir and ritonavir – used for HIV infection and AIDS.
- Carbapenem agents (antibiotics used to treat bacterial infections) such as imipenem, meropenem, rifampicin and erythromycin. The combination of Torvate and carbapenems should be avoided because it may decrease the effect of your medicine.
- Cholestyramine used to lower blood fat (cholesterol) levels.

Taking Torvate with food and drink

Alcohol intake is not recommended during treatment.

Pregnancy, breast-feedingand fertility important advice for women

- You must not use Torvate if you are pregnant, unless nothing else works for you.
- If you are a woman able to have a baby, you must not take Torvate unless you use an effective

method of birth control (contraception) during your entire treatment with Torvate.

- Do not stop taking Torvate or your birth control (contraception), until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy

- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don't have epilepsy.
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine or your method of birth control (contraception) until you have discussed this with your doctor.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact their doctor once your child experiences their first period (menarche).
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of birth control (contraception) that is the most appropriate for you.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Please choose the situations which apply to you and read the descriptions below:

- **I AM STARTING TREATMENT WITH TORVATE**
- **I AM TAKING TORVATE AND NOT PLANNING TO HAVE A BABY**
- **I AM TAKING TORVATE AND PLANNING TO HAVE A BABY**
- **I AM PREGNANT AND I AM TAKING TORVATE**
- **I AM STARTING TREATMENT WITH TORVATE**

If this is the first time you have been prescribed Torvate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of birth control (contraception)

Without interruption throughout your treatment with Torvate. Talk to your doctor or family

planning clinic if you need advice on birth control (contraception).

Key messages:

- Pregnancy must be excluded before start of treatment with Torvate with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with Torvate.
- You must discuss appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy. • Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING TORVATE AND NOT PLANNING TO HAVE A BABY

If you are continuing treatment with Torvate but you are not planning to have a baby make sure you are using an effective method of birth control (contraception) without interruption during your entire treatment with Torvate. Talk to your doctor or family planning clinic if you need advice on birth control (contraception).

Key messages:

- You must use an effective method of birth control (contraception) during your entire treatment with Torvate.
- You must discuss birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control (contraception).
- You must get regular (at least annual) appointments with a specialist experienced in the management of epilepsy. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy. • Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING TORVATE AND PLANNING TO HAVE A BABY

If you are planning to have a baby, first schedule an appointment with your doctor. Do not stop taking Torvate or your birth control (contraception) until you have discussed this with your doctor. Your doctor will advise you further. Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development, which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of epilepsy, so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible. Your specialist may decide to change the dose of Torvate, switch you to another medicine, or stop treatment with Torvate a long time before you become pregnant – this is to make sure your illness is stable. Ask your doctor

about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Do not stop taking Torvate unless your doctor tells you to.
- Do not stop using your birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware of and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine or stop treatment with Torvate a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING TORVATE

Do not stop taking Torvate unless your doctor tells you to as your condition may become worse.

Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. You will be referred to a specialist experienced in the management of epilepsy so that alternative treatment options can be evaluated. In the exceptional circumstances when Torvate is the only available treatment option during pregnancy, you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing. You and your partner should receive counselling and support regarding the valproate exposed pregnancy. Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. • Do not stop taking Torvate unless your doctor tells you to. • Make sure you are referred to a specialist experienced in the treatment of epilepsy to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of Torvate during pregnancy, including malformations and developmental effects in children. • Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations

Make sure you read the Patient Guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.Newborn babies of mothers who took valproate during pregnancy may have:

- Blood clotting problems (such as blood not clotting very well). This may appear as bruising or bleeding which takes a long time to stop.
- Hypoglycaemia (low blood sugar). • Hypothyroidism (underactive thyroid gland, which can cause tiredness or weight gain).
- Withdrawal syndrome (including agitation, irritability, hyperexcitability, jitteriness, hyperkinesia, muscle problems, tremor, convulsions and feeding problems). In particular, this

may occur in newborns whose mothers have taken valproate during the last trimester of their pregnancy.

Breast-feeding

Very little Torvate gets into the breast milk. However, talk to your doctor about whether you should breast-feed your baby. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You may feel sleepy when taking Torvate. If this happens to you, do not drive or use any tools or machines. Taking other medicines used to treat fits or calm emotional and mental health problems may increase sleepiness.

9.3 How to use Torvate Tablets

Always take Torvate exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Torvate treatment must be started and supervised by a doctor specialised in the treatment of epilepsy.

Taking this medicine

- Your doctor will decide how much Torvate to give you or your child depending on your or your child's body weight.
- Take this medicine by mouth.
- Do not crush or chew the tablets. • If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself but ask your doctor.

How to take this medicine

- The dose is normally split and given half in the morning and half in the evening.

How much to take

Adults (including the elderly)

- The starting dose is 600mg daily. Your doctor should gradually increase this dose by 200mg every 3 days depending on your condition.
- The usual dose is 1000-2000mg (20-30mg per kilogram of body weight) each day.
- This may be increased to 2500mg each day depending on your illness.

Children over 20 kilograms

- The starting dose should be 400mg daily. Your doctor should increase this dose depending on your child's illness.
- The usual dose is then 20-30mg for each kilogram of body weight each day.
- This may be further increased to 35mg for each kilogram of body weight each day
- Depending on your child's illness.

Children under 20 kilograms

- The usual dose is 20mg for each kilogram of body weight each day.
- Depending on the child's condition your child's doctor may decide to increase this dose.

Patients with kidney problems

- Your doctor may decide to adjust your or your child's dose.

Patients taking other medicines for fits (epilepsy)

- You or your child may be taking other medicines for epilepsy at the same time as Torvate. If

so, your doctor should gradually initiate treatment depending on your or your child's condition.

- Your doctor may increase the dose of Torvate by 5-10mg for each kilogram of body weight each day depending on which other medicines you are taking.

If you take more Torvate than you should
If you take more Torvate than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken.

The following effects may happen: feeling sick or being sick, pupils of the eye become smaller, dizziness, loss of consciousness, weak muscles and poor reflexes, breathing problems, headaches, fits (seizures), confusion, memory loss and unusual or inappropriate behaviour.

If you forget to take Torvate
If you forget to take a dose, take it as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Torvate
Keep taking until your doctor tells you to stop. Do not stop taking Torvate just because you feel better. If you stop your fits may come back.

Tests
Make sure you or your child keep your regular appointments for a check-up. They are very important as your or your child's dose may need to be changed. Torvate can change the levels of liver enzymes shown up in blood tests. This can mean that your or your child's liver is not working properly. If you or your child go into hospital or visit another doctor or a dentist, tell them you are taking Torvate. If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 Possible Side Effects

Like all medicines, these tablets can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following serious side effects- you may need

- You have an allergic reaction. The signs may include: a rash, joint pain, fever (systemic lupus erythematosus), swallowing or breathing problems, swelling of your lips, face, throat or tongue. Hands, feet or genitals may also be affected. More severe allergic reactions can lead to lymph node enlargement and possible impairment of other organs.

- Liver problems and problems of the pancreas may show as a sudden illness, which may happen in the first six months of treatment. This happens in a very small number of people taking Torvate. It includes feeling and being sick many times; being very tired, sleepy and weak; stomach pain including very bad upper stomach pain; jaundice (yellowing of the skin or whites of the eyes); loss of appetite; swelling (especially of the legs and feet but may include other parts of the body); worsening of your fits or a general feeling of being unwell. Your doctor may tell you to stop taking Torvate immediately if you have these symptoms.

- You have a skin rash or skin lesions with a pink/red ring and a pale centre which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'.

- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome'.

- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'.

- Bruising more easily and getting more infections than usual. This could be a blood problem called 'thrombocytopenia'. It can also be due to a fall in the number of white blood cells, bone marrow depression or another condition that affects red blood cells, white blood cells and platelets (pancytopenia) or how the blood clots.
- Blood clotting problems (bleeding for longer than normal), bruising or bleeding for no reason.
- Changes in mood, loss of memory, lack of concentration and deep loss of consciousness (coma).
- Underactive thyroid gland, which may cause tiredness or weight gain (hypothyroidism).
- Breathing difficulty and pain due to inflammation of the lungs (pleural effusion).

Tell your doctor as soon as possible if you have any of the following side effects:

- Changes in behaviour including being very alert, and sometimes also aggressive, hyperactive and unusual or inappropriate behaviour. This is more likely if other medicine to treat fits such as phenobarbital and topiramate are taken at the same time or if the Torvate starting dose is high or has been suddenly increased.
- Changes in the amount of ammonia in the blood. Symptoms of this condition are being sick, problems with balance and co-ordination, feeling lethargic or less alert.
- Feeling shaky (tremor), sleepy or unsteady when walking or jerky muscle movements.
- Feeling tired or confused with loss of consciousness sometimes accompanied by hallucinations or fits.
- Blisters with the skin flaking away.
- Rapid, uncontrollable movement of the eyes.
- An increase in the number and severity of convulsions

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet:

- Feeling sick (nausea), being sick (vomiting), stomach ache or diarrhoea, especially when starting treatment. This may be helped by taking the tablets with food.
- Swelling of gums or sore mouth
- Fainting
- Hearing loss
- Double vision
- Nail and nail bed disorders
- Skin problems such as rashes. These happen rarely, but more often in people also taking lamotrigine
- Hair disorders (changes in texture, colour or growth), hair loss which is usually temporary. When it grows back it may be more curly than before.
- Increased levels of some hormones (androgens), which may lead to increased hair growth on the face, breasts or chest, acne or thinning hair.
- Skin rash caused by narrow or blocked blood vessels (vasculitis).
- Changes in women's periods and increased hair growth in women.
- Breast enlargement in men • Swelling of the feet and legs (oedema)

- Obesity, weight gain – as your appetite may be increased
- Kidney disease, kidney problems, blood in the urine, bedwetting or increased need to pass urine, urinary incontinence (unintentional passing of urine)
- Headache
- Seeing or hearing things that are not there (hallucinations)
- Aggression,agitation, disturbance in attention, abnormal behaviour, restlessness/hyperactivity and learning disorder
- Tingling or numbness in the hands and feet
- Lowering of normal body temperature
- Abnormal blood clotting factors
- Muscle pain and weakness (rhabdomyolysis)

Bone disorders
There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term anti-epileptic medication, have a history of osteoporosis, or take steroids.

Tests
Torvate can change levels of liver enzymes, salts or sugars shown up on blood and urine tests.

Male fertility
Taking Torvate can be a contributing factor in male infertility.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Torvate Tablets

Keep out of the sight and reach of children. Do not take this medicine after the expiry date shown on the strip and carton after EXP. The expiry date refers to the last day of that month. Do not remove the tablets from the foil until just before you take them. Do not cut the blister strips. Keep in a dry place at a temperature not exceeding 30°C. Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

9.6 Contents of the pack and other information

What Torvate Tablets contains:

The active substance in this product is Sodium Valproate.

The other ingredients are Ethyl cellulose, Colloidal silicon dioxide, Hydroxy propyl methyl cellulose, Methanol, Methacrylic .acid & methy methacrylate.copolymer, Talc, Titanium dioxide, Diethyl phthalate and Isopropyl alcohol.

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd. 32
No.Middle camp, NH-10,

East District, Gangtok, Sikkim-737 135

OR

Manufactured in India by:

Windlas Biotech Limited (Plant-IV)

Plot No. 183 & 192, Mohabewala Industrial Area, Dehradun-248110, Uttarakhand

11.Details of permission or licence number with date

Mfg.Lic.No.M/563/2010 06-Dec-2021

12.Date of revision

JUN 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TORVATE 200, 300, 500mg/JUN-2022/09/PI