SUMMARY OF PRODUCT CHARACTERISTICS

ENCORATE CHRONO

(Sodium valproate and Valproic acid 200 mg, 300 mg and 500 mg Controlled release tablets)

1. NAME OF THE MEDICINAL PRODUCT

ENCORATE CHRONO

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ENCORATE CHRONO 200
Each film-coated controlled release tablet contains:
Sodium valproate BP…….133.2 mg
Valproic acid USP……... 58 mg

ENCORATE CHRONO 300
Each film-coated controlled release tablet contains:
Sodium valproate BP…….199.8 mg
Valproic acid USP……...87 mg

ENCORATE CHRONO 500
Each film-coated controlled release tablet contains:
Sodium valproate BP…….333 mg
Valproic acid USP……... 145 mg

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Controlled Release Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of generalised, partial or other epilepsy.

4.2 Posology and method of administration

Posology

Encorate Chrono is a controlled release formulation of sodium valproate which reduces peak concentration and ensures more even plasma concentrations throughout the day.

Encorate Chrono may be given once or twice daily.

Daily dosage requirements vary according to age and body weight.

In patients where, adequate control has been achieved, Encorate Chrono formulation is interchangeable with other conventional or prolonged release formulations of sodium valproate on an equivalent daily dosage basis.

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.

Special populations

Paediatric population

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

Elderly
Although the pharmacokinetics of valproate 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.

Renal impairment
It may be necessary in patients with renal insufficiency to decrease the dosage, or to increase the dosage in patients on haemodialysis. Valproate is dialysable (see **section 4.9**). Dosing should be modified according to clinical monitoring of the patient (see **section 4.4**).

Hepatic impairment
Salicylates should not be used concomitantly with valproate since they employ the same metabolic pathway (see **sections 4.4** and **4.8**).

Liver dysfunction, including hepatic failure resulting in fatalities, have been reported in patients whose treatment included valproic acid (see **sections 4.3 and 4.4**).

Salicylates should not be used in children under 16 years of age (see aspirin/salicylate product information on Reye's syndrome). In addition, in conjunction with valproate, concomitant use in children under 3 years of age can increase the risk of liver toxicity (see **section 4.4**).

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 (see **sections 4.3, 4.4** and **4.6**).

The benefits and risks should be carefully reconsidered at regular treatment reviews (see **section 4.4**).

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

Combined Therapy (see section 4.5)

When starting valproate in patients already on other anti-convulsants, these should be tapered slowly: initiation of valproate 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 to 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 valproate. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

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 (see **section 5.2**).

Method of administration
Encorate Chrono controlled release tablets are for oral administration. The tablets should be swallowed whole and not crushed or chewed.

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

Encorate Chrono is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment (see **sections 4.4 and 4.6**).
- Hypersensitivity to sodium valproate, valproic acid or any other excipients listed in **section 6.1.**
- Active liver disease, or personal or family history of severe hepatic dysfunction, especially drug related.
- Patients with known urea cycle disorders (see **section 4.4**).
- Porphyria.
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see **section 4.4**).

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 is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

Special warnings

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 reported to be significantly reduced and progressively decreases with age.

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

Monotherapy is recommended in children under the age of 3 years when prescribing valproate, but the potential benefit of valproate 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 reported 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 valproate 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, valproate should be discontinued.

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 (see **section 4.8**).

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 reported randomized placebo-controlled studies 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 reported 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 (see **section 4.3**).

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 (see **section 4.8**).

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 (see **sections 4.2** and **5.2**).

Patients with systemic lupus erythematosus
Although immune disorders have only rarely been reported during the use of valproate, the potential benefit of valproate should be weighed against its potential risk in patients with systemic lupus erythematosus (see **section 4.8**).

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 valproate (see **section 4.3**).

Weight gain
Valproate 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 (see **section 4.8**).

Diabetic patients
Valproate is reported to be 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 valproate.

Alcohol
Alcohol intake is not recommended during treatment with valproate.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Effects of valproate on other drugs</u>

Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
Valproate may potentiate the effect of other psychotropics such as antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and the dosage of the other psychotropics should be adjusted when appropriate.

In particular, a reported 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
Valproate has no effect on serum lithium levels.

Olanzapine
Valproic acid may decrease the olanzapine plasma concentration.

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

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

Lamotrigine
Valproate 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
Valproate 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 valproate may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other drugs on sodium valproate

Anti-epileptics
Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbital, 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 valproate decreases valproic acid clearance by 22%-50% and consequently increase the valproic acid plasma concentrations. Valproate 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 valproate may need adjustment.

Highly protein bound agents
In case of concomitant use of valproate 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 imipenem, panipenem 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 (see **section 4.4**). 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 (see **section 4.4**). 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.

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) and consider monitoring valproate serum levels as appropriate.

Other interactions

Newer anti-epileptics (including topiramate and acetazolamide)

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

Concomitant administration of valproate and **topiramate** or **acetazolamide** has been reported to be 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 valproate and quetiapine may increase the risk of neutropenia/leucopenia.

4.6 Fertility, pregnancy and lactation

- Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.

Teratogenicity and developmental effects

Pregnancy exposure risk related to valproate
Both valproate monotherapy and valproate polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Reported data suggest that, both valproate monotherapy and polytherapy are associated with an increased risk of major congenital malformations and neuro-developmental disorders compared to the population not exposed to valproate.

Valproate was reported to cross the placental barrier in both animal species and humans (see **section 5.2**).

In animals: teratogenic effects have been reported in mice, rats and rabbits (see **section 5.3**).

Congenital malformations
Data derived from a reported meta-analysis (including registries and cohort studies) showed that approximately 11% of children of women with epilepsy exposed to valproate monotherapy during pregnancy had major congenital malformations. This is reported to be greater than the risk of major malformations in the general population (approximately 2-3%).

The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate.

This risk is dose-dependent in valproate monotherapy, and available data suggests it is dose-dependent in valproate polytherapy. However, a threshold dose below which no risk exists cannot be established.

Available reported data show an increased incidence of minor and major malformations. The most common types of reported 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.

In utero exposure to valproate may also result in hearing impairment or deafness 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 did not recover.

In utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

Neuro-developmental disorders
It has been reported that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk of neuro-developmental disorders (including that of autism) seems to be dose-dependent when valproate is used in monotherapy, but a threshold dose below which no risk exists, cannot be established based on reported data. When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neuro-developmental disorders in the offspring were also been reported to increase as compared with those in children from the general population or born to untreated women with epilepsy.
The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

When valproate is administered in monotherapy, studies reported in children exposed *in utero* to valproate showed 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 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 reported on the long-term outcomes.

It has been reported 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 study population.

It has been reported 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.

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

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 (see **sections 4.4** and **4.5**).

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 (see **section 4.4**). 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 (see **sections 4.3** and **4.4**). 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 (see **section 4.2**).

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 reported to be excreted in human milk with a concentration ranging from 1-10% of maternal serum levels. Haematological disorders have been reported in breastfed newborns/infants of treated women (see **section 4.8**).

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

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see **section 4.8**).

Valproate administration may also impair fertility in men (see **section 4.8**). Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited number of case reports suggest that a strong dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.

4.7 Effects on ability to drive and use machines

Use of valproate 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 anticonvulsant polytherapy or association with benzodiazepines (see **section 4.5**).

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 (see **sections 4.4** and **4.6**).

Hepato-biliary disorders
Common: liver injury (see **section 4.4**).
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see also **sections 4.2, 4.3** and **4.4**). Increased liver enzymes are common, particularly early in treatment, and may be transient (see **section 4.4**).

Gastrointestinal disorders
Very common: nausea,
Common: Vomiting, gingival disorder (mainly gingival hyperplasia) stomatitis, gastralgia, diarrhoea

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

Uncommon: pancreatitis, sometimes lethal (see **section 4.4**).

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 (see **section 4.4**).
Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder.

Sedation has been reported occasionally, usually when in combination with other anticonvulsants. In monotherapy it was reported to have 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 reported. These cases have often been reported to be 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

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 4.4).*
Rare: hyperammonaemia*(see **section 4.4**), 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 valproate should be discontinued.*

Hyperammonaemia associated with neurological symptoms has also been reported (see **section 4.4**). 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 (see **section 4.6**)

Blood and lymphatic system disorders
Common: anaemia, thrombocytopenia (see **section 4.4**).
Uncommon: pancytopenia, leucopenia

Rare: bone marrow failure, including pure 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 (valproate has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see **section 4.6**).

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 more curly 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: polycystic ovaries, male infertility (see **section 4.6**),
Very rarely gynaecomastia has been reported.

Vascular disorders
Common: haemorrhage (see **sections 4.4** and **4.6**).
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 Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) reported to be associated with valproate 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 valproate. The mechanism by which valproate affects bone metabolism has not been identified.
Rare: systemic lupus erythematosus, rhabdomyolysis (see **section 4.4**)

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) (see **section 4.4** and **4.6**)

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

Paediatric population

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

4.9 Overdose

Symptoms

Cases of accidental and deliberate valproate 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 been reported following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels (see **section 5.2**). Cases of intracranial hypertension related to cerebral oedema 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, including cardio-respirato-gastric monitoring. Gastric lavage may be useful up to 10 to 12 hours following ingestion.

Naloxone has been reported to be 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 reported to be used successfully.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, Fatty acid derivatives, ATC code: N03A G01.

Mechanism of action

Sodium valproate and valproic acid are anti-convulsants.

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

metabolism of GABA.

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

5.2 Pharmacokinetic properties

The reported effective therapeutic range for plasma valproic acid levels is 40-100 mg/litre (278-694 µmol/litre). This reported range may depend on time of sampling and presence of co-medication.

Distribution

The percentage of free (unbound) drug is usually reported between 6-15% of 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 valproate and valproic acid-controlled release tablets may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

*Placental transfer (see **section 4.6**)*

Valproate crosses the placental barrier in animal species and in humans:

- In animal species, valproate crosses the placenta to a similar extent as in humans.
- In humans, several publications assessed the concentration of valproate in the umbilical cord of neonates at delivery. Valproate serum concentration in the umbilical cord, representing that in the fetuses, was similar to or slightly higher than that in the mothers.

Metabolism

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

Elimination

The half-life of sodium valproate and valproic acid is usually reported to be within the range of 8 – 20 hours.

Interaction with oestrogen-containing products

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

Special populations

Renal insufficiency

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

Paediatric population

Above the age of 10 years, children and adolescents have valproate clearances similar to those reported in adults. In paediatric patients below the age of 10 years, the systemic clearance of valproate varies with age. In neonates and infants up to 2 months of age, valproate clearance is decreased when compared to adults and is lowest directly after birth. In a review of the scientific literature, valproate half-life in infants under two months reported considerable variability ranging from 1 – 67 hours. In children aged 2 – 10 years, valproate clearance is 50% higher than in adults.

Encorate Chrono tablets, are controlled release formulations which reported less fluctuation in plasma concentration compared with other conventional and modified release sodium valproate formulations.

In cases where measurement of plasma levels is considered necessary, the pharmacokinetics of sodium valproate and valproic acid-controlled release formulation make the measurement of plasma levels less dependent upon time of sampling.

5.3 Preclinical safety data

Valproate was neither reported to be mutagenic in bacteria, nor in the mouse lymphoma assay *in vitro* and did not induce DNA repair in primary rat hepatocyte cultures. *In vivo*, however, contradictory results were reported at teratogenic doses depending on the route of administration. After oral administration, the predominant route of administration in humans, valproate did not reported to induce chromosome aberrations in rat bone marrow or dominant lethal effects in mice. Intraperitoneal injection of valproate was reported to increase DNA strand-breaks and chromosomal damage in rodents. In addition, increased sister-chromatid exchanges in patients with epilepsy exposed to valproate as compared to untreated healthy subjects have been reported in published studies. However, conflicting results were reported when comparing data in patients with epilepsy treated with valproate with those in untreated patients with epilepsy. The clinical relevance of these DNA/chromosome findings is unknown.

Reported non-clinical data reveal no special hazard for humans based on conventional carcinogenicity studies.

Reproductive and developmental toxicity
Valproate was reported to induce teratogenic effects (malformations of multiple organ systems) in mice, rats and rabbits.

Animal studies reported that *in utero* exposure to valproate results in morphological and functional alterations of the auditory system in rats and mice.

Behavioural abnormalities have been reported in first generation offspring of mice and rats after *in utero* exposure. Some behavioural changes have also been reported in the second generation and those were less pronounced in the third generation of mice following acute *in utero* exposure of the first generation to teratogenic valproate doses. The underlying mechanisms and the clinical relevance of these findings are unknown.

Testicular toxicity
In reported sub-chronic/chronic toxicity studies, testicular degeneration/atrophy or spermatogenesis abnormalities and a decrease in testes weight were reported in adult rats and dogs after oral administration starting at doses of 465 mg/kg/day and 150 mg/kg/day, respectively. The safety margin based on plasma concentrations has been reported to be unknown, however body-surface-area comparisons indicate that there may be no safety margin.

In juvenile (sexually immature) and young adult rats (pubertal), a significant dose-related reduction in testes weight has been reported at 240 mg/kg/day following i.v. and i.p. administration with no apparent histopathological changes. However, testicular atrophy has been reported in the young adult rat at an i.v. dose of 480 mg/kg/day. Despite the absence of apparent histopathology changes, the testicular weight reductions have been reported to be considered part of a dose-related spectrum leading to testicular atrophy. There is no safety margin reported for the effect on testicular weight.

There is a limited number of published papers which report findings in juvenile animals consistent with those reported in the GLP adult and juvenile studies, with respect to testicular weights. Reductions in testicular weights are associated with adverse effects on the adult male reproductive tract in reported animal studies and impaired fertility in adult patients (see **section 4.6**).

The toxicological significance of the testicular findings in juvenile animals has not been reported to be evaluated and hence the relevance to human testicular development,

particularly in the pediatric population, has been reported to be unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicon dioxide (Syloid 244 FP), Hypromellose (2208, K4M), Ethyl Cellulose (20 cps), Opadry 200 Orange 200F230000, Isopropyl alcohol & Purified Water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Keep all medicines out of the reach of children.

6.5 Nature and contents of container

10 Tablets are packed in Alu/Alu blister pack and such 3/5 blisters are further packed in carton along with package insert.

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Ranbaxy Nigeria Ltd. (A SUN PHARMA company)
1st Floor, Abimbola House, 24, Abimbola Street, Ilasamaja, Isolo, Lagos, Nigeria

8. MARKETING AUTHORISATION NUMBER

Encorate Chrono 200 - A4-0895 &
Encorate Chrono 500 - A4-0894

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

31/10/2007

10. DATE OF REVISION OF THE TEXT

March 2023

REFERENCES

- Summary of Product Characteristics of Epilim Chrono 200 mg, 300 mg and 500 mg Tablets, Aventis Pharma Limited, UK, August 2022.