For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

PRESCRIBING INFORMATION

Encorate 200
(Sodium Valproate Tablets BP)

COMPOSITION

Each enteric-coated tablet of Encorate contains
Sodium Valproate BP..... 200 mg

Excipients:

Sodium valproate, colloidal anhydrous silica, Microcrystalline cellulose, starch, polyvinyl pyrrolidone, calcium silicate, magnesium stearate, purified talc, sodium starch glycolate, colloidal silicon dioxide, Hypromellose 2910, Dibutyl Phthalate, Methacrylic acid copolymer, Titanium dioxide, sunset yellow FCF lake, Ponceau 4R Lake, Isopropyl Alcohol, Acetone, Purified water.

DESCRIPTION

A pink coloured, circular, biconvex, enteric –coated tablet, plain on both sides.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES [1]

Pharmacodynamic

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AG01

The most likely mode of action for sodium 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 was reported that Sodium Valproate could stimulate HIV replication but studies on peripheral blood mononuclear cells from HIV infected subjects show that sodium valproate does not have a mitogen-like effect on inducing HIV replication. Indeed the effect of sodium valproate on HIV replication exvivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

Pharmacokinetics

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.

Distribution

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 sodium valproate may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Placental transfer (see section Fertility, pregnancy and lactation)

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 is usually reported to be within the range 8 – 20 hours. It is usually shorter in children.
In patients with severe renal insufficiency it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

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.

INDICATIONS

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

- Absence
- Myoclonic
- Tonic-clonic
- Atonic
- Mixed

As well as, for partial epilepsy:

- Simple or complex seizures
- Secondary generalized seizures
- Specific syndromes (West, Lennox-Gastaut)

Treatment and prevention of mania associated with bipolar disorder.

DOSE AND METHOD OF ADMINISTRATION

Encorate are for oral administration. Daily dosage requirements vary according to age and body weight General dosage recommendations have been mentioned below.

Sodium valproate tablets may be given twice daily. Tablets should be swallowed whole and not crushed or chewed. In patients where adequate control has been achieved sodium valproate formulations are interchangeable with other sodium valproate conventional or prolonged release formulations on an equivalent daily dosage basis.

Dosage

Usual requirements are as follows:

Treatment of epilepsy

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 mg to 2000 mg per day, ie 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 20kg

An alternative formulation of sodium valproate should be used in this group of patients, due to the tablet size and need for dose titration. Sodium valproate syrup is an alternative.

20mg/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 40mg/kg/day, clinical chemistry and haematological parameters should be monitored.

In the treatment and prevention of mania associated with bipolar disorders

Adults

The recommended initial dose is 1000mg/day. The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose, which produces the desired clinical effects. The recommended maintenance dosage for the treatment of bipolar disorder is between 1000mg and 2000mg daily. In exceptional cases, the dose may be increased to not more than 3000mg daily. Doses should be adjusted according to individual clinical response. Prophylactic treatment should be established individually with the lowest effective dose.

Children and adolescents

The efficacy of **Encorate** for the treatment of manic episodes in bipolar disorder has not been established in patients aged less than 18 years. (see also **Warnings and Precautions** and **Undesirable Effects**).

Special populations

Use in the elderly

Although the pharmacokinetics of sodium 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.

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 (see **Pharmacokinetics**).

In patients with hepatic insufficiency

Salicylates should not be used concomitantly with sodium valproate since they employ the same metabolic pathway (see also **Warnings and Precautions** and **Undesirable Effects**).

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in patients whose treatment included valproic acid (see **Contraindications** and **Warnings and Precautions**).

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

Female children, women of childbearing potential and pregnant women

Encorate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Sodium valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Sections Contraindications, Warnings/ Precautions and Pregnancy). Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Program (PPP Section Warnings/Precautions). In the exceptional circumstance when valproate is the only treatment option during pregnancy in women with epilepsy, **Encorate** should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose of non-prolonged release formulations should be divided into at least two single doses during pregnancy (see Section Pregnancy).

Estrogen-containing products

Valproate does not reduce efficacy of hormonal contraceptives.

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

Combined therapy

When starting sodium valproate in patients already on other anticonvulsants, these should be tapered slowly: initiation of sodium 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 anticonvulsants 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 sodium valproate. 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 (see **Pharmacokinetics**).

Method of administration

Oral.

CONTRAINDICATIONS

Sodium valproate is contraindicated in the following situations:

- **In epilepsy**
  - Sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment
  - Sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Warnings and precautions and Fertility, Pregnancy and Lactation section)

- **In bipolar disorder**
  - Sodium valproate is contraindicated in pregnancy.
  - Sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section)

- **All indications**
  - Personal or family history of severe hepatic dysfunction, especially drug related
  - Patients with known urea cycle disorders
  - Hypersensitivity to sodium valproate
  - Acute or chronic hepatitis
  - Hepatic porphyria
  - Patients with known systemic primary carnitine deficiency with uncorrected hypocarnitinemia (see **Section Warnings/Precautions** – Patients at risk of hypocarnitinemia)
  - 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 **Warnings and Precautions**).

WARNINGS AND PRECAUTIONS

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of sodium 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 sodium 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 anticonvulsant therapy, are infants and in particular young children under the age of 3 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, the incidence of occurrence is significantly reduced and progressively decreases with age. The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity. Additionally, salicylates should not be 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 sodium valproate, but the potential benefit of sodium valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy. In most cases, such liver damage has been 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'):

- nonspecific 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 sodium 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 antiepileptic 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:

CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.

Pregnancy Prevention Program:

Sodium valproate has a high teratogenic potential and children exposed in utero to sodium valproate have a high risk for congenital malformations and neurodevelopmental disorders (See Section Pregnancy).

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Sodium valproate is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment for epilepsy indication.
- In pregnancy for bipolar disorder indication.
- In women of childbearing potential unless below conditions are fulfilled.

Conditions of Pregnancy Prevention Programme:

The prescriber must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to sodium 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 sodium valproate.
- The patient understands the need for regular (at least annual) review of treatment by a prescriber 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 sodium valproate use (Annual Risk Acknowledgement Form).

In women planning to become pregnant, all efforts should be made to switch to approproate alternative treatment prior to conc eption, if possible (see Fertility, Pregnancy and Lactation sections). Sodium valproate therapy should only be continued after reasse ssment of the benefits and risks of the treatment with sodium valproate for the patient by a physician experienced in the management of epilepsy.

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 doctor once the female child using sodium valproate experiences menarche.
- The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformation andneurodevelopmental disorders including the magnitude of these risks for children exposed to sodium valproate in utero.

In patients who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium 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 prescriber to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with sodium valproate. Treatment with sodium 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 sodium valproate must use effective contraception without interruption during the entire duration of treatment with sodium valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Annual treatment reviews by the prescriber

The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber 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 prescriber experienced in the management of epilepsy must reassess sodium 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 sodium valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor top re-evaluate treatment with sodium valproate and consider alternative treatment options. The patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

- The Patient Card is provided with every sodium valproate dispensation and that patients understand its content.
- Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to sodium valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of sodium 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 sodium valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber, at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

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

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased sodium valproate efficacy (see **Drug Interactions**). Prescribers should monitor response (seizure control) when initiating, or discontinuing oestrogen- containing products. On the opposite, sodium valproate does not reduce efficacy of hormonal contraceptive.

Use in male patients of reproductive potential

A retrospective observational study indicates an increased risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam (see Pregnancy). Despite study limitations, by way of precautions, the prescriber should inform the male patients of this potential risk. The prescribers should discuss with the patient, the need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment. The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known. The male patient should be advised:

- not to donate sperm during treatment and for 3 months after stopping the treatment,
- of the need to consult his doctor to discuss alternative treatment options, as soon as he is planning to father a child, and before discontinuing contraception,
- that he and his female partner should contact their doctor for counseling in case of pregnancy if he used valproate within 3 months prior to conception.

The male patient should also be informed about the need for regular (at least annual) review of treatment by a specialist

experienced in the management of epilepsy or bipolar disorder. The specialist should at least annually review whether valproate is the most suitable treatment for the patient. During this review, the specialist should ensure the male patient has acknowledged the risk and understood the precautions needed with valproate use (Annual Risk Acknowledgement Form). Educational materials are available for healthcare professionals and male patients. A patient guide and a patient card should be provided to all men of reproductive potential using valproate.

Aggravated convulsions

As with other antiepileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of types of convulsions with sodium 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 small increased risk of suicidal ideation and behaviour have been reported with anti-epileptic drugs. The mechanism of this risk is not known and the reported data do not exclude the possibility of a 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.

Urea cycle disorders and risk of hyperammonemia:

When an urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with **Sodium Valproate tablets** (see Section Contrindications and Warnings/Precautions - Patients at risk of hypocarnitinemia and Severe liver damage).

Patients at risk of hypocarnitinemia

Valproate administration may trigger occurrence or worsening of hypocarnitinemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinemia or pre-existing hypocarnitinemia. Valproate may decrease carnitine blood and tissue levels and therefore impair mitochondrial metabolism including the mitochondrial urea cycle. Patients at increased risk for symptomatic hypocarnitinemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also Warnings on Patients with known or suspected mitochondrial disease and urea cycle disorders and risk of hyperammonemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics. Patients should be warned to report immediately any signs of hyperammonemia such as ataxia, impaired consciousness, vomiting for further investigation. Carnitine supplementation should be considered when symptoms of hypocarnitinemia are observed. Patients with known systemic primary carnitine deficiency and corrected for hypocarnitinemia should be treated with valproate only if the benefits of valproate treatment outweigh the risks in these patients and there is no suitable therapeutic alternative. In these patients, close monitoring for recurrence of hypocarnitinemia should be implemented.

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking valproate. Carnitine supplementation should be considered in these patients. (See also Sections Interactions, Adverse Reactions and Overdose.)

Carbapenem agents:

The concomitant use of sodium valproate and carbapenem agents is not recommended.

Patients with known or suspected mitochondrial disease:

Sodium 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, sodium valproate- induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neuro-metabolic 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 Contraindications).

Estrogen-containing products

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

Liver function tests

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

Precautions

Haematological: 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 Undesirable Effects).

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 **Dose and Method of Administration** and **Pharmacokinetics**).

Systemic lupus erythematosus: Although immune disorders have only rarely been reported during the use of sodium valproate, the potential benefit of sodium valproate should be weighed against its potential risk inpatients with systemic lupus erythematosus (see **Undesirable Effects**).

Hyperammonaemia: When a urea cycle enzymatic deficiency is suspected, metabolic investigations shouldbe performed prior to treatment because of the risk of hyperammonaemia with sodium valproate.

Weight gain: Sodium 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 **Undesirable Effects**).

Diabetic patients: Sodium valproate 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 sodium valproate.

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

***Children*:** Monotherapy is recommended in children under the age of 3 years when prescribing **Encorate** but the potential benefit of **the** tablets should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy (see Section Warnings/Precautions and see also Section Interactions). The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity.

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

Effects on ability to drive and use machines

Use of sodium 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 anticonvulsantpolytherapy or association with benzodiazepines (see **Drug Interactions**).

DRUG INTERACTIONS

Effects of sodium valproate on other drugs

- ***Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines***

Sodium 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 other psychotropics should be adjusted when appropriate.In particular, as per the reported data adding olanzapine to sodium 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***

Sodium valproate has no effect on serum lithium levels

- Olanzapine

Valproic acid may decrease the olanzapine plasma concentration.

- ***Phenobarbital***

Sodium valproate has been reported to increase 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 phenobarbitaldoses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- ***Primidone***

Sodium valproate has been reported to increase primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long term treatment. Clinical monitoring is recommendedespecially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Phenytoin***

Sodium valproate has been reported to decrease phenytoin total plasma concentration. Moreover, sodium valproate has been reported to increase phenytoin free form with possible overdosage symptoms (valproic acid displaces phenytoin from

its plasma protein binding sites and reduces its hepatic catabolism). Therefore clinical monitoring is recommended; when phenytoin plasma levels are determined, the free form should beevaluated.

- ***Carbamazepine***

Clinical toxicity has been reported when sodium valproate was administered with carbamazepine as sodium valproate may potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

- ***Lamotrigine***

Sodium valproate has been reported to reduce the metabolism of lamotrigine and increase 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 sodium valproate, a reduction of the dose of propofol should be considered.

- ***Zidovudine***

Sodium 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.

- ***Vitamin K-dependent 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.

- ***Temozolomide***

Co-administration of temozolomide and sodium 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***

Antiepileptics 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 sodium valproate has been reported to decrease valproic acid acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Sodium 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 sodium valproate tablets may need adjustment.

- ***Highly protein bound agents***

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

- ***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 (see **Warnings and Precautions**). If treatment with these antibiotics cannot be avoided close monitoring of valproic acid blood levels should be performed.

- ***Protease inhibitors***

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

- ***Cholestyramine***

Colestyramine may decrease the absorption of sodium valproate.

- Rifampicin

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

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives

Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in sodium valproate glucuronidation and may increase the clearance of sodium valproate, which would result in decreased serum concentration of sodium valproate and potentially decreased sodium valproate efficacy. Consider monitoring of sodium valproate serum levels. On the opposite, sodium valproate has no enzyme inducing effect; as a consequence, sodium valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

Other interactions

Risk of liver damage

The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see Section Warnings/Precautions - “Severe liver damage” and “children”). Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see Section Warnings/Precautions - “Severe liver damage” and “children”). In patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, clinical trials have

reported ALT increases greater than 3 times the upper limit of normal in 19% of patients. Appropriate liver monitoring should be exercised when valproate is used concomitantly with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see Section Warnings/Precautions).

Topiramate and acetazolamide

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

Pivalate-conjugated medicines

Concomitant administration of valproate and pivalate-conjugated medicines that decrease carnitine levels (such as cefditoren pivoxil, adefovir dipivoxil, pivmecillinam and pivampicillin) may trigger occurrence of hypocarnitinemia (see Section 5 Patients at risk of hypocarnitinemia). Concomitant administration of these medicines with valproate is not recommended. Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinemia.

Quetiapine

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

UNDESIRABLE EFFECTS

Congenital malformations and developmental disorders: *(see* **Warnings and Precautions** *and* **Fertility, pregnancy and lactation sections***)*

Hepato-biliary disorders:

Common: liver injury *(see* **Warnings and Precautions***).* Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see **Dose and Method of Administration***,* **Contraindications** and **Warnings and Precautions**). Increased liver enzymes are common, particularly early in treatment, and may be transient (see **Warnings and Precautions**).

Gastrointestinal disorders:

Very common: nausea

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

The above adverse events have been reported to occur frequently at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking sodium valproate with or after food or by using enteric coated sodium valproate. *Uncommon*: pancreatitis, sometimes lethal (see **Warnings and Precautions**).

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, paresthesia, aggravated convulsions.

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 has been reported 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 anticonvulsants, notably phenobarbital or topiramate. They have usually been reported to be 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 reported in the paediatric population.

Metabolism and nutrition disorders:

Common: hyponatraemia, weight increased*

Rare: hyperammonaemia* (see **Warnings and Precautions**)

*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 sodium valproate should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported *(see* **Warnings and Precautions**). 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 **Fertility, pregnancy and lactation sections**)

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia, (see **Warnings and Precautions**).

Uncommon: pancytopenia, leucopenia

The blood picture was reported to return to normal when the drug on discontinuation of drug.

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

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 (Sodium 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 also **Fertility, pregnancy and lactation sections**).

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)

Hirsutism and acne have been very rarely reported.

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 (see **Warnings and Precautions; Fertility, pregnancy and lactation sections**).
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 sodium valproate therapy, but the mode of action is as yet unclear.

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

Musculoskeletal and connective tissue disorders:

Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long- term therapy with sodium valproate. The mechanism by which sodium valproate affects bone metabolism has not been reported.

Rare: systemic lupus erythematosus, rhabdomyolysis (see **Warnings and Precautions**)

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.

FERTILITY, PREGNANCY AND LACTATION [1, 2, 3]

- Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.
- Sodium valproate is contraindicated as treatment for bipolar disorder during pregnancy
- Sodium valproate is contraindicated for use in women of childbearing potential unless the above mentioned conditions of Pregnancy Prevention Programme are fulfilled (see **Contraindications and Warnings and Precautions section).**

Pregnancy Exposure Risk related to sodium valproate

Both sodium valproate monotherapy and sodium valproate polytherapy are associated with abnormal pregnancy outcomes. Available reported data suggest that antiepileptic polytherapy including sodium valproate is associated with a greater risk of congenital malformations than sodium valproate monotherapy. Sodium valproate has been reported to cross the placental barrier both in animal species and in humans.

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 sodium 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.

In utero exposure to sodium 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. Reported 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). These have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

Developmental disorders

Data have shown that exposure to sodium 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 sodium 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 sodium 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 sodium 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 sodium 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 sodium valproate in utero may be more likely to deveolop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see Contraindications and Warnings and Precautions Sections)

If a Woman plans a Pregnancy

If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium 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 sodium valproate for the unborn child to support her informed decision-making regarding family planning.

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

Pregnant women
Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor 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 sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy.

It is recommended to:
- Use the lowest effective dose and divide the daily dose sodium 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 to avoid high peak plasma concentrations.

All patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor 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 sodium valproate exposure.

Risk in the neonate
- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken sodium 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 sodium valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken sodium 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 sodium valproate during the last trimester of their pregnancy.

Breastfeeding
Sodium valproate has been reported to excrete in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Haematological disorders have been reported in breastfed newborns/infants of treated women (see Undesirable Effects). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sodium 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 sodium valproate (see **Undesirable Effects**). Sodium valproate administration may also impair fertility in men (see **Undesirable Effects**). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

OVERDOSE
Cases of accidental and deliberate sodiu valproate overdosage 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 massive overdose, i.e. plasma concentration 10 to 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 **Pharmacokinetics**). Cases of intracranial hypertension related to cerebral oedema have been reported. The presence of sodium content in the sodium valproate formulations may lead to hypernatraemia when taken in overdose.

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

Haemodialysis and haemoperfusion have been used successfully.

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 used successfully.

STORAGE
Store below 30°C in dry place, protected from light.

SUPPLY
Encorate is available in strips of 10x10s.

INCOMPATIBILITIES
NA

SHELF LIFE
3 Years

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Revision date: January 2025