

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



1. NAME OF THE MEDICINAL PRODUCT

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)

Strength : 200 mg

Pharmaceutical Form : Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RACEX (GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)

Each enteric coated tablet contains:

- Sodium Valproate BP (200 mg)
- Approved colour used.(-)
- Excipients : (0 QS)

Batch Size: 100,000 Tablets

Sr. No.	Ingredients	Quality standard	Overages (%)	Unit composition (mg)	Reason for inclusion
Active					
1	Sodium Valproate	BP	0%	200.00	Active
Ingredients					
2	Colloidal Silicon Dioxide	BP	0%	30.00	Diluents
3	Lactose	BP	0%	67.00	Diluents
4	Microcrystalline Cellulose	BP	0%	40.00	Diluents
5	Maize Starch	BP	8%	67.391	Diluents
6	P.V.P. K30	BP	0%	13.00	Binder
7	Methylene Chloride	BP	0%	----	Solvent
Lubrication					
8	Purified Talc	BP	0%	20.00	Lubricant
9	Magnesium Stearate	BP	0%	6.00	Lubricant
10	Colloidal Silicon Dioxide	BP	0%	20.00	Disintegrant
Coating					
11	Ethyl Cellulose	BP	20%	0.036	Coating material
12	Methylene Chloride	BP	20%	----	Solvent
13	Acetone	BP	20%	----	Solvent
14	Cellulose acetate phthalate	BP	20%	0.52	Enteric coating material
15	Purified Talc	BP	20%	0.025	Filler
16	Titanium Dioxide	BP	20%	0.008	colour
17	Diethyl phthalate	BP	20%	0.100	Plastisizer
18	Colour Carmosine Lake	IHS	20%	6.00	colour

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



8% Maize Starch Should be taken extra to compensate loss on drying.
20% material taken extra to compensate loss on spraying
BP = British Pharmacopoeia
IHS = In-House Specification

3. PHARMACEUTICAL FORM

Orange coloured, circular, biconvex, enteric coated tablets having break line on one side of each tablets.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For oral administration in the treatment of generalised, partial or other epilepsy.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration

Sodium Valproate 200mg Gastro-Resistant Tablets are for oral administration.

Daily dosage requirements vary according to age and body weight.

Tablets may be given twice daily.

Tablets should be swallowed whole and not crushed or chewed.

Posology

Usual requirements are as follows:

Adults:

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

Children over 20kg:

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

Children under 20kg:

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.

Use in the elderly:

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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.

In patients with hepatic insufficiency

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

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

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

Female children and women of childbearing potential

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

Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme.

The benefits and risks should be carefully reconsidered at regular treatment reviews.

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

Combined Therapy:

When starting 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 10mg/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 40mg/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.

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



4.3 CONTRAINDICATIONS

Sodium Valproate 200mg Gastro-Resistant Tablets are contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment.
- In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.
- Active liver disease
- Personal or family history of severe hepatic dysfunction, especially drug related
- Patients with known urea cycle disorders
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Porphyria
- Valproate is contraindicated in patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome and in children under two years of age who are suspected of having a POLG-related disorder.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of valproate, discontinuation should normally only be done under the supervision of a specialist in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that switching between different manufacturer's 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 significantly reduced and progressively decreases with age.

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

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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 occurred during the first 6 months of therapy, the period of maximum risk being 2-12 weeks.

Suggestive signs:

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

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

These are an indication for immediate withdrawal of the drug.

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

Detection:

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

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of 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 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.

Suicidal ideation and behaviour:

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

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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, ophthalmoplegia or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders.

Precautions

Haematological tests:

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding.

Renal insufficiency:

In patients with renal insufficiency, it may be necessary to decrease dosage.

As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring.

Patients with systemic lupus erythematosus:

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

Urea cycle disorders:

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

Diabetic patients:

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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 valproate.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of sodium valproate on other drugs

- Antipsychotics, 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 the other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to valproate or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

- **Lithium**

Sodium valproate has no effect on serum lithium levels.

- **Olanzapine**

Valproic acid may decrease the olanzapine plasma concentration.

- **Phenobarbital**

Sodium valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

- **Primidone**

Sodium 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**

Sodium valproate decreases phenytoin total plasma concentration. Moreover sodium 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.

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



• **Carbamazepine**

Clinical toxicity has been reported when sodium 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**

Sodium 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**

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.

• **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

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 sodium valproate decreases valproic acid clearance by 22% to 50% and consequently increase the valproic acid plasma concentrations. Sodium valproate dosage should be monitored.

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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 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.

Vitamin K-dependent factor anticoagulants

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

Cimetidine or erythromycin

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

Carbapenem antibiotics (such as panipenem, imipenem and meropenem)

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60%-100% decrease in valproic acid levels within two days, sometimes associated with convulsions. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem agents in patients stabilised on valproic acid should be avoided. If treatment with these antibiotics cannot be avoided, close monitoring of valproic acid blood levels should be performed.

Rifampicin

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

Protease inhibitors

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

Cholestyramine

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

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives

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

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

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



4.6 PREGNANCY AND LACTATION

Pregnancy Exposure Risk related to valproate

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

Teratogenicity and developmental effects

Congenital malformations

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

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

Developmental disorders

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

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

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

There are limited data on the long term outcomes.

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

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

Female children and woman of childbearing potential

Oestrogen-containing products

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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

If a woman plans a pregnancy

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

Pregnant women

Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for 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 of valproate into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation 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 therefore 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.

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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

Breast-feeding

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

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from 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. Valproate administration may also impair fertility in men. Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Use of 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 anticonvulsant polytherapy or association with benzodiazepines.

4.8 UNDESIRABLE EFFECTS

The following CIOMS frequency rating is used, when applicable:

Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$);

Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$);

Very rare ($< 1/10,000$), not known (cannot be estimated from available data).

Congenital, familial and genetic disorders:

Congenital malformations and developmental disorders

Hepatobiliary disorders:

Common: liver injury.

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

Gastrointestinal disorders:

Very common: nausea

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

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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

Uncommon: pancreatitis, sometimes lethal.

Nervous system disorders:

Very common: tremor

Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus

Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paresthesia, aggravated convulsions.

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

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

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

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

Psychiatric disorders:

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

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

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:

Common: hyponatraemia, weight increased*.

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

Rare: obesity, hyperammonaemia*

*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. In such cases further investigations should be considered.

Endocrine disorders:

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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

Rare: hypothyroidism

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia.

Uncommon: pancytopenia, leucopenia.

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

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.

Skin and subcutaneous tissue disorders:

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

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

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme,

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Reproductive system and breast disorders:

Common: dysmenorrhea

Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:

Common: haemorrhage.

Uncommon: vasculitis

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.

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi 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 peripheral oedema.

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 identified.

Rare: systemic lupus erythematosus, rhabdomyolysis

Respiratory, thoracic and mediastinal disorders:

Uncommon: pleural effusion

Investigations:

Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged).

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

Rare: myelodysplastic syndrome

4.9 OVERDOSE

Cases of accidental and deliberate sodium valproate overdose have been reported.

At plasma concentrations of up to 5 to 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 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 occurred following massive overdose.

Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported.

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

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

Haemodialysis and haemoperfusion have been used successfully.

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

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS

Pharmacotherapeutic group: Anti-epileptics, ATC Code: N03AG01

The most likely mode of action for sodium valproate is potentiation of the inhibitory action of gamma aminobutyric 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 ex-vivo is highly variable, modest in quantity, appears to be unrelated to the dose and has not been documented in man.

5.2 PHARMACOKINETIC PROPERTIES

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

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

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

Metabolism

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

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

Interaction with oestrogen-containing products

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

5.3 PRECLINICAL SAFETY DATA

There are no additional preclinical data of relevance to the prescriber that have not been included in the main body of the text.

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sr. No.	Excipients	Quality standard	Overages (%)
1.	Colloidal Silicon Dioxide	BP	0%
2.	Lactose	BP	0%
3.	Microcrystalline Cellulose	BP	0%
4.	Maize Starch	BP	8%
5.	P.V.P. K30	BP	0%
6.	Methylene Chloride	BP	0%
7.	Purified Talc	BP	0%
8.	Magnesium Stearate	BP	0%
9.	Colloidal Silicon Dioxide	BP	0%
10.	Ethyl Cellulose	BP	20%
11.	Methylene Chloride	BP	20%
12.	Acetone	BP	20%
13.	Cellulose acetate phthalate	BP	20%
14.	Purified Talc	BP	20%
15.	Titanium Dioxide	BP	20%
16.	Diethyl phthalate	BP	20%
17.	Colour Carmosine Lake	IHS	20%

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

3 Years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Strip pack of 10 Tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Not Applicable

7. APPLICANT/MANUFACTURER

MEDICO REMEDIES LTD.

Address: 8 & 9, Dewan & Sons Udyog Nagar,
Palghar, Dist. Thane, Maharashtra.

RACEX
(GASTRO RESISTANT SODIUM VALPROATE TABLETS BP 200 MG)



Country: INDIA
Tel.: +91 2525255287/256381
Fax: +91 2525255287
Email: medicoremedies@yahoo.com