

Approved Professional Information for Medicines for Human Use

EMBivil MR has a high teratogenic potential and when used in pregnancy, may cause various major and minor congenital abnormalities of body organs and/or body structures as well as may harm the developing brain of the foetus resulting in negative effects in childhood which may include neurodevelopmental disorders such as late walking and talking, poor language skills, memory problems, lower intellectual abilities.

Exposure to EMBivil MR *in utero* is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention deficit hyperactivity disorder (ADHD).

EMBivil MR treatment must be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy or bipolar disorder or migraines and EMBivil MR must not be prescribed if the relevant risk minimisation measures/Pregnancy Prevention Programme, cannot be implemented and supervised and patients are not committed to adhere to these measures.

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

EMBivil MR 250 mg gastro-resistant tablets

EMBivil MR 500 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet of EMBivil MR 250 mg contains 269,1 mg of valproate semisodium, equivalent to 250 mg of valproic acid.

Sugar free.

Excipient with known effect:

Sunset yellow (E110) – 0,2 mg

Each gastro-resistant tablet of EMBivil MR 500 mg contains 538,2 mg of valproate semisodium, equivalent to 500 mg of valproic acid.

Sugar free.

Excipient(s) with known effect:

Carmoisine (E122) – 0,104 mg

Ponceau 4R (E124) – 0,091 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

EMBivil MR 250 mg gastro-resistant tablets

Peach oblong tablet without inscriptions.

EMBivil MR 500 mg gastro-resistant tablets

Pink oblong tablet without inscriptions.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For generalized seizures as well as for partial (focal) seizures, including complex partial seizures evolving to generalized seizures.

For the treatment of manic episode in bipolar disorder when lithium is contraindicated or not tolerated.

Continuation of treatment after manic episode could be considered in patients who have responded to EMBivil MR for acute mania.

Prophylaxis of treatment resistant migraine headaches.

4.2 Posology and method of administration

Patients who have previously received treatment with valproic acid should initiate therapy with the same daily dose and regimen. After stabilization of the patient with the new product, a daily scheme of 2 to 3 doses may be established.

The frequency of the side effects (mainly increased levels of liver enzymes) may be related to the dose. The benefit of a more effective seizure control with higher doses should be evaluated in terms of the possibility of a higher incidence of adverse reactions.

With the progressive increase of the dosage of the product, phenytoin concentrations in the blood can be affected (see section 4.4).

For patients with gastrointestinal irritation complaints, it is recommended to administer the EMBivil MR during meals and to progressively increase the dose starting off with a low initial dose.

Epilepsy

For adults and children for which 250/500 mg tablets may be appropriate: The recommended initial dose is 10-15 mg/kg/day administered in divided doses, increasing at one-week intervals by to 5-10 mg/kg/day until seizures are controlled or side effects preclude further increases.

The maximum recommended dosage is 60 mg/kg/day. If the total daily dosage exceeds 250 mg, it should be given in a divided regimen. A good correlation has not yet been established between daily dose, serum concentration and therapeutic effect. However, therapeutic valproate serum concentrations for most patients will range from 50 to 100 µg/mL.

In the case dosage is equal to or greater than 50 mg/kg/day, it is recommended to monitor blood levels.

Manic episodes in bipolar disorder

Adults

The daily dosage should be established and controlled individually by the treating medical practitioner.

The initial recommended daily dose is 750 mg. In addition, in clinical trials a starting dose of 20 mg/kg body weight of valproate semisodium has also shown an acceptable safety profile.

The dose should be increased as rapidly as possible to achieve the lowest therapeutic dose which produces the desired clinical effect. The daily dose should be adjusted to the clinical response to establish the lowest effective dose for the individual patient.

The mean daily dose usually ranges between 1000 and 2000 mg valproate semisodium. Patients receiving daily doses higher than 45 mg/kg body weight should be carefully monitored.

Continuation of treatment of manic episodes in bipolar disorder should be adapted individually using the lowest effective dose.

Children and adolescents

The safety and efficacy of EMBivil MR for the treatment of manic episodes in bipolar disorder have not been evaluated in patients aged less than 18 years.

Female children and women of childbearing potential

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

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 (see section 4.6).

Prophylactic treatment of headache

Adults

The minimum effective dose is 250 mg twice daily and treatment should last at least 3 months. Some patients may benefit from doses up to 1,000 mg/day. In the clinical trials, there was no evidence that higher doses led to greater efficacy. EMBivil MR should only be initiated and

Austell Pharmaceuticals (Pty) Ltd, 55/2.5/0504-05, EMBivil MR, Gastro-resistant tablets, 250 mg & 500 mg supervised by a medical practitioner experienced in the management of migraine. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews.

Children and adolescents

The safety and efficacy of EMBivil MR for the prophylaxis of migraine have not been evaluated in patients aged less than 18 years.

Method of administration

The tablets are administered orally. The tablets should be swallowed whole with a drink of water, and not crushed or chewed.

4.3 Contraindications

EMBivil MR is contraindicated in the following situations

- Hypersensitivity to the active substance, valproate semisodium or to any of the excipients of EMBivil MR listed in section 6.1.
- Pregnancy and lactation (see section 4.4 and 4.6)
 - Treatment of epilepsy
 - in pregnancy unless there is no suitable alternative treatment
 - in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled
 - Treatment of bipolar disorder and prophylaxis of migraine attacks
 - in pregnancy
 - in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see section 4.4 and 4.6).
- Active liver disease, including the following
 - acute hepatitis
 - chronic hepatitis

- Personal or family history of severe hepatitis, especially if medicine-related
- Hepatic porphyria
- Women of childbearing potential who are not using effective methods of contraception during treatment with valproate semisodium (see sections 4.4 and 4.6). Pregnancy must be excluded before start of treatment with valproate.
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).
- Patients with known urea cycle disorders (see section 4.4)

4.4 Special warnings and precautions for use

Treatment initiation and supervision

Treatment with EMBivil MR must be initiated and supervised by a medical practitioner experienced in the management of epilepsy, migraine or bipolar disorders.

Female children, women of childbearing potential and pregnant women

Pregnancy Prevention Programme

EMBivil MR has a high teratogenic potential and children exposed *in utero* to EMBivil MR have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

EMBivil MR is contraindicated in the following situations:

- Treatment of epilepsy
 - in pregnancy unless there is no suitable alternative treatment (see section 4.3 and 4.6).
 - in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see section 4.3 and 4.6).
- Treatment of bipolar disorder and prophylaxis of migraine attacks
 - in pregnancy (see section 4.3 and 4.6).

- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see section 4.3 and 4.6).

Conditions of the Pregnancy Prevention Programme

The medical practitioner must ensure that

- individual circumstances are 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 EMBivil MR *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 (refer to Contraception in this section), without interruption during the entire duration of treatment with EMBivil MR
- the patient understands the need for regular (at least annual) review of treatment by a medical practitioner experienced in the management of epilepsy, or bipolar disorder or migraine
- the patient understands the need to consult her medical practitioner as soon as she is planning pregnancy to ensure timeous discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued
- the patient understands the need to urgently consult her medical practitioner 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 EMBivil MR use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the medical practitioner considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Pharmacists or healthcare professionals must ensure that

- the patient card is provided with every EMBivil MR dispensing and that the patients understand its content
- patients are advised not to stop their EMBivil MR medication and to immediately contact a medical practitioner in case of planned or suspected pregnancy.

Female children

- The medical practitioner must ensure that parents/caregivers of female children understand the need to contact the medical practitioner once the female child using EMBivil MR experiences menarche (see section 4.3)
- The medical practitioner must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for infants exposed to EMBivil MR *in utero* (see section 4.3)
- In patients who experienced menarche, the medical practitioner must reassess the need for EMBivil MR therapy annually and consider alternative treatment options. If EMBivil MR is the only suitable treatment, the need for using effective contraception and all other conditions of the Pregnancy Prevention Programme must be discussed. Every effort should be made by the medical practitioner to switch female children on EMBivil MR to alternative treatment before they reach adulthood (see section 4.3).

Pregnancy test

Pregnancy must be excluded before start of treatment with EMBivil MR. Treatment with EMBivil MR must not be initiated in women of childbearing potential without a negative pregnancy test (plasma

Austell Pharmaceuticals (Pty) Ltd, 55/2.5/0504-05, EMBivil MR, Gastro-resistant tablets, 250 mg & 500 mg pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed EMBivil MR must use effective contraception without interruption during the entire duration of treatment with EMBivil MR. 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, which includes a barrier method, should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method, and involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhoea, she must follow all the advice on effective contraception (see section 4.3).

Estrogen-containing products

EMBivil MR 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 EMBivil MR efficacy. Medical practitioners should monitor clinical response (seizure control or mood control) when initiating, or discontinuing estrogen-containing products. Consider monitoring of valproate serum levels (see section 4.5).

Annual treatment reviews by a medical practitioner

The medical practitioner must at least annually review whether EMBivil MR is the most suitable treatment for the patient. The medical practitioner should discuss the annual risk acknowledgement form, at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning

For the indication of epilepsy, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess EMBivil MR therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.6: Pregnancy).

If switching is not possible, the woman should receive further counselling regarding the EMBivil MR risks for the unborn child, to support her informed decision-making regarding family planning (see section 4.3).

For the indication of bipolar disorder or prophylaxis of treatment resistant migraine attacks, if a woman is planning to become pregnant a medical practitioner experienced in the management of bipolar disorder or migraine must be consulted and treatment with EMBivil MR should be discontinued and, if needed, switched to an alternative treatment prior to conception and before contraception is discontinued (see section 4.3).

In case of pregnancy

If a woman using EMBivil MR becomes pregnant, she must be immediately referred to a medical practitioner to re-evaluate treatment with EMBivil MR and consider alternative options. Patients with an EMBivil MR -exposed pregnancy and their partners should be referred to a medical practitioner experienced in teratology/pre-natal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.3 and 4.6: Pregnancy).

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to EMBivil MR during pregnancy, educational materials are provided to reinforce the warnings and to provide guidance regarding use of EMBivil MR in women of childbearing potential and includes the details of the

Pregnancy Prevention Programme. A patient guide and patient card should be provided to all women of childbearing potential using EMBivil MR (see section 4.3).

An annual risk acknowledgement form needs to be completed at time of treatment initiation and during each annual review of EMBivil MR treatment by the medical practitioner.

Children (male and female) less than 18 years of age

Epilepsy

Some psychiatric disorders, including aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder, may be observed in paediatric patients receiving EMBivil MR. Current evidence is inconclusive as to the possibility of harm to reproductive organs, skeletal system growth or developing brain of patients less than 18 years of age.

In male children less than 18 years of age, EMBivil MR should be used with caution and in alignment with guidelines on the use of antiepileptics.

EMBivil MR can be used in female children less than 18 years of age only if there is no suitable safer alternative therapy or alternate therapy have failed to control the epilepsy. In addition, for female children, ensure that the conditions of the Pregnancy Prevention Programme are met (see section 4.4 and 4.6: Pregnancy).

Bipolar disorder

EMBivil MR is not indicated for the treatment of manic episodes in bipolar disorder in children (see section 4.1).

Migraine

EMBivil MR is not indicated for the prophylaxis of migraine in children (see section 4.1).

Adult males intending procreation

EMBivil MR has been associated with male fertility dysfunction that may not always be reversible after treatment discontinuation (see section 4.6 and 4.8). The medical practitioner should discuss with adult males their intent to procreate, when prescribing EMBivil MR. If procreation is intended, EMBivil MR should be used only if alternative treatment options are not suitable.

Severe liver damage

Conditions of occurrence

Cases of severe liver damage, which may result in fatalities, have been reported.

Experience in epilepsy has indicated that patients most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children under the age of 3 years with severe seizure disorders, particularly those with brain damage, mental retardation and/or congenital metabolic or degenerative disease.

After the age of 3 years, the incidence of occurrence is reduced and decreases with age.

In most cases, such liver damage occurred during the first 6 months of therapy.

Suggestive signs

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

Conditions of occurrence):

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

Patients (or their family in the case of children) should be instructed to report immediately any such signs to a medical practitioner should they occur. Investigations including clinical examination and laboratory assessment of liver function should be undertaken immediately.

Detection

Liver function tests should be performed before therapy is initiated and then periodically monitored during the first 6 months of therapy (see section 4.5).

Increased liver enzymes may be noted, particularly at the beginning of therapy. More extensive biological investigations (including prothrombin index/prothrombin time [INR/PT]) are recommended in patients developing increased liver enzymes.

An adjustment of dosage (decrease) may be needed when appropriate and tests should be repeated as necessary.

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

The concomitant use of salicylates should be avoided in children due to the risk of liver toxicity.

Pancreatitis

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

Suicidal ideation and behaviour

Suicidal behaviour and ideation and have been reported in patients treated with antiepileptic medicines, including EMBivil MR, in several indications. A meta-analysis of randomized placebo-controlled trials of antiepileptic medicines has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.

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

Carbapenem antibiotics

The concomitant use of EMBivil MR and carbapenem antibiotics is not recommended (see section 4.5).

Patients with known or suspected mitochondrial disease

Valproate, such as in EMBivil MR, may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, acute liver failure and liver-related deaths have been associated with EMBivil MR treatment 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 (see section 4.3).

Aggravated convulsions

Some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with EMBivil MR. In case of aggravated convulsions, the patients should be advised to consult their medical practitioner immediately.

Haematological tests

Considering previously described cases of thrombocytopenia, inhibition of secondary phase of platelet aggregation and abnormal coagulation parameters, laboratory blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended before initiating treatment and at periodic intervals, especially prior to surgery, and in case of spontaneous bruising or bleeding.

In case of appearance of bruising, bleeding or other changes in haemostasis/coagulation, the dose should be reduced, or the treatment discontinued.

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 section 4.2 and 5.2).

Systemic lupus erythematosus

New development and exacerbation of systemic lupus erythematosus (SLE) may occur. The potential benefit of EMBivil MR should be weighed against its potential risk in patients with systemic lupus erythematosus.

Hyperammoniaemia

Hyperammoniaemia with or without lethargy or coma has been reported with EMBivil MR and may be present in the absence of abnormal liver function tests.

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with EMBivil MR (see section 4.3).

Weight gain

Patients should be warned of the considerable risk of weight gain at the initiation of therapy, and

appropriate strategies should be adopted to minimise this (see section 4.8).

Carnitine palmitoyltransferase (CPT) type II deficiency patients:

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when taking EMBivil MR.

Alcohol use during treatment with EMBivil MR

Alcohol intake is not recommended during treatment with EMBivil MR.

Other antiepileptics

Since valproate may react with concomitantly administered antiepileptic medicines, periodic plasma concentration determinations of the other administered medicines should be performed on a regular basis, especially during the early course of therapy (see section 4.5).

Laboratory Tests

Valproate is partially eliminated in the urine, as a keto metabolite, which may lead to false positives in the analysis of urine for determination of ketone bodies.

There have been reports of altered thyroid function tests associated with valproate administration, although its clinical significance is unknown.

Excipients

EMBivil MR 250 mg gastro-resistant tablets contain sunset yellow (E110) and EMBivil MR 500 mg gastro-resistant tablets contain carmoisine (E122) and ponceau 4R (E124) that may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Alcohol

Valproate may potentiate the CNS depressant action of alcohol.

Medicines highly bound to plasma proteins

The concomitant administration of valproate with other medicines that bind extensively to plasma proteins (e.g. acetylsalicylic acid (aspirin), carbamazepine, dicumarol and phenytoin) may result in alteration of serum medicine concentrations.

Barbiturates

There is evidence that valproate can cause an increase in serum phenobarbital concentrations by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproate and phenobarbital has also been reported to produce CNS depression but however without significant elevations of barbiturate or valproate serum concentrations.

All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity, reducing the dosage of the barbiturate as needed. Primidone is metabolized to a barbiturate and, therefore, may also be involved in a similar or identical interaction.

Phenytoin

Changes of phenytoin serum concentrations have been reported, when administered concomitantly. However there have also been reports of both increasing and lowering phenytoin concentrations with further increase. In addition, a decrease in total serum phenytoin with an increase in the free versus protein-bound phenytoin concentrations has been observed. The dosage of phenytoin should be readjusted as required by the clinical situation.

Clonazepam

The concomitant use of valproate and clonazepam may produce absence seizures.

Ethosuximide

There is inconclusive evidence regarding the effect of valproate on serum ethosuximide concentrations. Patients receiving treatment with valproate and ethosuximide, concomitantly with other anticonvulsants, should be carefully monitored for alterations in serum concentrations of both medicines.

Medicines affecting coagulation

Caution is recommended when valproate is administered concomitantly with medicines affecting coagulation (e.g, acetylsalicylic acid and warfarin). (See section 4.8).

Oral contraceptive medicines

In some cases, it was found that there is an association between the use of certain antiepileptics and the ineffectiveness of oral contraceptives. One explanation for this interaction is because most of antiepileptics are enzyme inducers and therefore reduce plasma concentrations of steroid hormones, which consequently results in inefficient inhibition of ovulation. Valproate is not an enzyme inducer and so it does not cause a decrease in concentrations of steroid hormones. Comparative clinical studies have shown that valproate is the only antiepileptic that does not interfere with the efficacy of oral contraceptive medicines.

Carbapenem antibiotics

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem antibiotics resulting in a 60 - 100 % decrease in valproic acid levels within two days. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem antibiotics in patients stabilized on valproic acid is not considered to be manageable and therefore should be avoided (see section 4.4).

4.6 Fertility, pregnancy and lactation

EMBivil MR is contraindicated in pregnancy and lactation (see section 4.3):

- Treatment of epilepsy
 - in pregnancy unless there is no suitable alternative treatment
- Treatment of bipolar disorder and prophylaxis of migraine attacks
 - EMBivil MR should not be used in pregnancy for the treatment of bipolar disorder and prophylaxis of migraine attacks

EMBivil MR is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled.

Pregnancy Exposure Risk related to EMBivil MR

Both EMBivil MR monotherapy and EMBivil MR polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including EMBivil MR is associated with a greater risk of congenital malformations than EMBivil MR monotherapy.

EMBivil MR was shown to cross the placental barrier both in animal species and in humans (see section 5.2).

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

Congenital malformations

A meta-analysis (including registries and cohort studies) showed that 10,73 % of children born to epileptic women exposed to EMBivil MR monotherapy during pregnancy suffered 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, craniosynostosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

In utero exposure to EMBivil MR may also result in hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function.

Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases had not resolved.

Monitoring of signs and symptoms of ototoxicity is recommended.

Developmental/neurodevelopmental disorders

Data have shown that exposure to EMBivil MR in uterus 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 uterus to EMBivil MR 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 uterus was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

Available data from a population-based study show that children exposed to EMBivil MR in uterus are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the unexposed population in the study.

Available data from a population-based study suggests that children exposed to EMBivil MR in uterus are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1,5-fold) compared to the unexposed population in the study.

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

In view of the above data, the following recommendations should be taken into consideration

If a woman plans a pregnancy

For the indication epilepsy, if a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision-making regarding family planning.

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

Pregnant women

EMBivil MR as treatment for bipolar disorder and prophylaxis of migraine attacks is contraindicated for use during pregnancy. EMBivil MR as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).

If a woman using EMBivil MR becomes pregnant, she must be immediately referred to a medical practitioner to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of EMBivil MR in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive EMBivil MR for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of EMBivil MR into several small doses to be taken throughout the day. The use of a prolonged release formulation may be

Austell Pharmaceuticals (Pty) Ltd, 55/2.5/0504-05, EMBivil MR, Gastro-resistant tablets, 250 mg & 500 mg
preferable to other treatment formulations in order to avoid high peak plasma concentrations
(see section 4.2).

- All patients with a EMBivil MR exposed pregnancy and their partners should be referred to a medical practitioner *experienced in in teratology/pre-natal medicine* for evaluation and counselling regarding the exposed pregnancy. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations.
- If appropriate, folate supplementation should be started before pregnancy and at relevant dosage (5 mg daily) as it may reduce the risk of neural tube defects. However, available evidence does not suggest this prevents the birth defects or malformations due to EMBivil MR exposure.

Risk in the neonate

- Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken EMBivil MR 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 (phenobarbitone) 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 EMBivil MR during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken EMBivil MR during pregnancy.
- 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 EMBivil MR during the last trimester of their pregnancy.

Breastfeeding

Valproate is excreted in human milk.

Mothers on EMBivil MR should not breastfeed their infants (see section 4.3).

Cases of haematological changes and somnolence have been reported in infants of mothers taking EMBivil MR, when breastfeeding their infants.

Fertility

Amenorrhoea, menstrual disorders, polycystic ovaries, increased testosterone levels and impairment of ovarian function and of fertility have been reported in women using EMBivil MR (see section 4.8). EMBivil MR administration may also impair fertility in male patients (see section 4.8 and 4.4).

Fertility dysfunctions may not always be reversible after treatment discontinuation.

Very low concentrations of valproate have been detected in semen of males on treatment with EMBivil MR.

It is not known with certainty if fertility would be affected by EMBivil MR treatment in children less than 18 years of age, as valproate may interact with sex hormones.

4.7 Effects on ability to drive and use machines

Since valproate semisodium may have a depressant effect on the central nervous system, especially when taken with alcohol or other CNS depressant medicines, patients are advised not to take part in hazardous work, such as operating machines or driving, until they are certain that the medication does not cause drowsiness to them.

4.8 Undesirable effects

a. Summary of the safety profile

Since valproate semisodium is frequently administered concomitantly with other antiepileptics, in most of the cases it is not possible to determine whether the following adverse reactions can be ascribed to valproate semisodium alone or to the combination of medicines.

The most commonly reported side effects at initiation of therapy are: nausea, vomiting and indigestion. These effects are usually transient and rarely require suspension of therapy.

The administration of delayed-release valproate semisodium generally results in reduction of gastrointestinal side effects.

b. Tabulated list of adverse reactions

System organ class	Frequency		
	Common	Rare	Frequency not known
Blood and lymphatic system disorders		Lymphocytosis, hyperfibrinogenaemia, leukopenia, eosinophilia, anaemia and bone marrow suppression	Thrombocytopenia and inhibition of secondary phase of platelet aggregation, which may be reflected in altered bleeding time, petechiae, bruising, hematoma formations and frank haemorrhage (see section 4.4)
Endocrine disorders			Abnormal thyroid function tests (see section 4.4)
Metabolism and nutrition disorders		Obesity	Hyperammonaemia (see section 4.4), hyperglycaemia, anorexia with immediate weight loss, increased appetite with weight gain

Psychiatric disorders			Emotional disorder, depression, psychosis, aggression, hyperactivity, dementia
Nervous system disorders		Coma	Sedation, ataxia, headache, confusion, asterixis, dysarthria, dizziness and incoordination, extrapyramidal disorders
Eye disorders		Diplopia	Nystagmus, “visual spots”
Gastrointestinal disorders	Nausea, vomiting, indigestion		Diarrhoea, abdominal cramps, constipation
Hepato-biliary disorders	Small increases in the level of transaminases (SGOT and SGPT) and LDH (appears to be dose dependent)	Acute pancreatitis (including fatal cases)	Increase in serum bilirubin and abnormal changes in other liver function. In this case, the results may reflect a potential severe liver toxicity (see section 4.4)
Skin and subcutaneous tissue disorders	Nail and nail bed disorders		Transient alopecia, rash, photosensitivity, generalized pruritus,

			erythema multiform, epidermal necrolysis
Musculoskeletal and connective tissue disorders			General weakness, decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy
Reproductive system and breast disorders			Irregular menstruation and secondary amenorrhoea, breast enlargement, galactorrhoea
Congenital, familial, and genetic disorders			Congenital malformations and developmental disorders (see section 4.4 and section 4.6)
General disorders and administration site conditions			Oedema of the extremities

c. Description of selected adverse reactions

Nervous system disorders

In some cases, sedative effects have occurred in patients receiving monotherapy, but such effects occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication.

Rare cases of diplopia and coma have been reported in patients receiving valproate semisodium as monotherapy or in combination with phenobarbital.

Skin and subcutaneous tissue disorders

A case of fatal epidermal necrolysis has been reported in a six month old child taking valproate concomitantly with and other medicines.

Musculoskeletal and connective tissue disorders

The mechanism by which valproate semisodium affects bone metabolism has not been identified.

Metabolism and nutrition disorders

Hyperglycaemia has occurred and was associated with a fatal outcome in a patient with pre-existent non-ketotic hyperglycinaemia.

d. Paediatric population

The safety profile of EMBivil MR in the paediatric population is comparable to adults, but some adverse reactions are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/Publications/Index/8>

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

The clinical condition of an overdose of valproate may lead to somnolence, hyponatraemia, heart block or deep coma. Induction of vomiting will depend on the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output. It has been observed that naloxone has the ability to reverse the depressant effects of valproate on the CNS. However, naloxone should be used with caution because it could theoretically also reverse the antiepileptic effects of valproate.

In cases of massive overdose, haemodialysis and haemoperfusion have been used successfully to remove unbound drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 2.5 Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group: 2.6 - Central nervous system. Antiepileptic and anticonvulsant

ATC code: N03 AG01

Mechanism of action

Valproate semisodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

5.2 Pharmacokinetic properties

Absorption

Equivalent oral doses of valproate semisodium and valproic acid deliver equivalent quantities of valproate ion systemically. However, the rate of valproate ion absorption may vary with the conditions of use (e.g. fasting or postprandial).

When patients are in a fasting stage, peak plasma concentrations of valproate ion are observed after 3 to 4 hours following administration of the medicine. Clinical studies indicate that food can influence the absorption rate of valproate.

While absorption rate from the gastrointestinal tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate in chronic use is not affected.

Distribution

The plasma half-life of valproate is typically in the range of 6 to 16 hours. Half-lives in the lower part of the above range are usually found in patients taking other antiepileptic medicines capable of enzyme induction.

The therapeutic range is believed to be from 50 to 100 µg/mL of total valproate, although some patients may be controlled with plasma concentrations lower or higher than this range. Valproate is highly bound (90 %) to plasma proteins in the therapeutic range. However, protein binding is concentration-dependent and decreases at high valproate concentrations. The binding is variable among patients but can be influenced by fatty acids or by highly bound medicines such as salicylate.

Some clinicians advise monitoring free valproate concentrations, which may more accurately reflect CNS penetration of valproate. Yet, a consensus on the therapeutic range of free concentrations has not yet been established. However, monitoring total and free valproate may be informative when there are changes in clinical status, concomitant medication, or valproate dosage.

Biotransformation

Valproate is primarily metabolized in the liver. The major metabolic routes are: glucuronidation, mitochondrial β -oxidation and microsomal oxidation.

The major metabolites formed are the glucuronide conjugate, 2-propyl-3-keto-pentanoic acid and 2-propyl-hydroxypentanoic acid. Other unsaturated metabolites have been observed.

Elimination

The major route of elimination of these metabolites is in the urine.

Patients on monotherapy have generally longer half-life times and higher concentrations of valproate at a given dosage than patients receiving polytherapy. This is primarily due to enzyme induction caused by other antiepileptics, which results in enhanced clearance of valproate by glucuronidation and microsomal oxidation.

Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.

5.3 Preclinical safety data

Carcinogenicity studies revealed a statistically significant increase in the incidence of subcutaneous fibrosarcomas in male rats and a significant trend to dose-dependent appearance of lung adenomas and carcinomas in male mice treated with valproic acid. The clinical relevance of these findings is unknown.

Valproate revealed no evidence of genotoxic potential *in vitro* and *in vivo* studies.

Toxicity studies in the reproduction and development revealed teratogenic effects in the mouse, rat and dog. Chronic toxicity studies in rats and young and adult dogs showed a decrease of spermatogenesis and testicular atrophy. The clinical relevance of these findings, with regard to fertility in man, is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EMBivil MR 250 mg gastro-resistant tablets

Tablet core

Povidone

Pregelatinized starch

Silicon dioxide

Tablet coat

Talc

Titanium dioxide (E171)

Povidone

Hypromellose phthalate

Acetylated distilled monoglycerides

Yellow Aluminium Lake (Sunset yellow (E110))

Vanillin

EMBivil 500 mg gastro-resistant tablets

Tablet core

Silicon dioxide

Pregelatinized starch

Povidone

Tablet coat

Talc

Titanium dioxide (E171)

Povidone

Hypromellose phthalate

Acetylated distilled monoglycerides

Carmoisine lake (Carmoisine (E122) and Aluminium)

Ponceau 4R lake (Ponceau 4R (E124) and Aluminium)

Vanillin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister packs in the outer carton to protect from light and moisture.

6.5 Nature and contents of container

Gastro-resistant tablets 250 mg and 500 mg are packed in Aluminium/PVDC+PVC/PE/PVDC blisters.

The blisters are packed into cartons in pack sizes of 20 or 60 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBERS

EMBivil MR 250 mg gastro-resistant tablets: 55/2.5/0504

EMBivil MR 500 mg gastro-resistant tablets: 55/2.5/0505

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 October 2023

10. DATE OF REVISION OF THE TEXT