1.3 Product Information

1.3.1 Summary of Product Characteristics

Summary of product characteristic is attached.

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of medicinal product

VALCONTIN 500
(Controlled Release Tablets of Sodium Valproate and Valproic Acid)

2. Qualitative and Quantitative composition

Unit Composition:

Name of ingredients	Quantity (mg/tablet)	Active/ Inactive	Pharmacopoeial Reference	Function
Valproic Acid	145.00	Active	USP	Anti-epileptic
Sodium Valproate	333.00	Active	BP	Anti-epileptic
Avicel PH 102 (MCC)	50.00	Inactive	IH	Diluent
Cetostearyl Alcohol	80.00	Inactive	BP	Retarding agent
Magnesium Stearate	45.00	Inactive	BP	Lubricant
Microcrystalline Cellulose	60.00	Inactive	BP	Diluent
Hydroxy Ethyl Cellulose	60.00	Inactive	BP	Release retardant polymer
Talc	12.00	Inactive	BP	Lubricant
Colloidal Silicon Dioxide	50.00	Inactive	USP	Lubricant
Purified water*	0.070ml	Inactive	BP	Solvent

*Not present in final weight

Coating Composition:

Name of ingredients	Quantity (mg/tablet)	Active/ Inactive	Pharmacopoeial Reference	Function
Diethyl Phthalate	3.64	Inactive	USP	Plasticizer
Insta moistshield IC – MS – 2673 White	31.36	Inactive	IH	Coating agent
Isopropyl Alcohol*	258.00	Inactive	BP	Solvent
Methylene Chloride*	512.00	Inactive	BP	Solvent

*Not present in final weight

3. Pharmaceutical form

Controlled release tablets

4. Clinical particulars

4.1 Therapeutic indications

In the treatment of generalized seizures, notably tonic – clonic, absence and myoclonic seizures and also for partial seizures (simple and complex).

4.2 Posology and method of administration

For Seizure Control

Daily dosage should be established according to age and body weight; nevertheless the wide individual sensitivity to valproate should also be considered. A good correlation has not been established between daily dose, serum concentration and therapeutic effect and optimum dosage should be determined essentially according to the clinical response; the determination of Valproic Acid plasma levels may be considered in addition to clinical monitoring when adequate seizure control is not achieved or when adverse effects are suspected. The reported effective range is usually between 40-100 mg/l (300-700 μmol/l).

Initiation of Valcontin therapy

In patients not receiving other anti-epileptic drugs, the dosage should be preferably increased by successive dose levels at 2-3 day intervals in order to reach the optimum dosage in about 1 week.
In patients previously receiving anti-epileptic agents, substitution with Valcontin should be progressive, the optimum dosage being reached in about 2 weeks and other treatments being tapered and then stopped.
Addition of an other anti-epileptic agent should be done progressively where it is necessary.

Dosage

Initial daily dosage is usually 10-15 mg/kg, then doses are titrated upto the optimum dosage. This is generally within the range of 20 to 30 mg/kg/day. Nevertheless, where seizure control is not achieved within this range, the dose may be further increased adequately; patients should be carefully monitored when receiving daily doses higher than 50 mg/kg.
In adults, the usual dosage is within the range of 20-30 mg/kg/day. Valcontin may be used in children provided that they are able to take such a form. The usual dosage is about 30 mg/kg per day. Valcontin tablet is for twice daily administration. It is to be swallowed whole and not crushed or chewed.

4.3 Contraindications

- Acute hepatitis
- Chronic hepatitis
- Personal or family history of severe hepatitis, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

4.4 Warnings and Precautions

Warnings

Liver dysfunction

Conditions of occurrence
Severe liver damage resulting sometimes in fatalities have been exceptionally 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 with severe seizure disorders, particularly those with brain damage, mental retardation and (or) congenital metabolic or degenerative disease. After the age of 3, the incidence of occurrence is significantly reduced and progressively 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. Non-specific symptoms, usually of sudden onset, such as asthenia, anorexia, lethargy, drowsiness, which are sometimes associated with repeated vomiting and abdominal pain. in patients with epilepsy, recurrence of seizures. Patients (or their family or 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 performed before and then periodically monitored during the first 6 months of therapy. 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 Valcontin 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.

Pancreatitis

Severe pancreatitis which may result in fatalities have been rarely reported. Young children are at particular risk. This risk decreases with increasing age. Severe seizures or neurological impairment may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.

Precautions

- Liver function tests should be carried out before therapy, and periodically during the first 6 months especially in patients at risk.

As with most anti-epileptic drugs, mild increased liver enzymes may be noted particularly at the beginning of therapy, they are transient and isolated, without clinical sign.

More extensive biological investigation (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.

- Monotherapy is recommended in children under the age of 3 years when prescribing Valcontin but the potential benefit of Valcontin should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy. The concomitant use of salicylates should be avoided in those children under 3 due to the risk of liver toxicity.

- Blood tests (blood cell count, 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.

- 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.

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

- Exceptional cases of pancreatitis have been reported, therefore patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, valproate should be interrupted.

- When an urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate

4.5 Interaction with other medicinal products and other forms of interactions

Effects of valproate on other drugs

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

- **Phenobarbital**

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

- **Primidone**

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

- **Phenytoin**

Valproate increases phenytoin total plasma concentration. Moreover, valproate increases 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 be evaluated.

- **Carbamazepine**

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

- **Lamotrigine**

Valproate may reduce lamotrigine metabolism and increase its mean half life; dosages should be adjusted (lamotrigine dosage decreased) when appropriate. There are suggestions, yet to be proven that the risk of rash may be increased by coadministration of lamotrigine with valproic acid.

- **Zidovudine**

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

Effects of other drugs on valproate

- Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbital, and carbamazepine) decrease valproate serum concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.
- On the other hand, combination of felbamate and valproate may increase valproate serum concentration. Valproate dosage should be monitored.
- Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy.
- In case of concomitant use of valproate and highly protein bound agents (aspirin), valproate free serum levels may be increased. Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent anticoagulant.
- Valproate serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.

- Carbapenem antibiotics like imipenem/meropenem: Decrease in valproate blood level sometimes associated with convulsions has been observed when panipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproate blood level is recommended.

Other interactions

- Valproate usually has no enzyme inducing effect as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

4.6 Pregnancy and lactation

Pregnancy

From experience in treated epileptic mothers, the risk associated with the use of valproate during pregnancy has been described as follows:

Risk associated with epilepsy and anti-epileptics

In offspring born to mothers with epilepsy receiving any antiepileptic treatment, the global rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3%) reported in the general population. Although an increased number of children with malformations has been reported in case of multiple drug therapy, the respective part of treatment and disease has not been formally established. Malformations most frequently encountered are labial clefts and cardiovascular malformations. Sudden discontinuation in the anti-epileptic therapy may be associated with a worsening of the disease in the mother and subsequent untoward effects in the foetus.

Risk associated with sodium valproate

In animals: Teratogenic effects have been demonstrated in the mouse, rat and rabbit. In humans: The global risk of malformations in women receiving valproate during the first trimester of pregnancy is not higher than the risk described with other anti-epileptics.
Cases of facial dysmorphia have been reported. A few cases of multiple malformations particularly of the limbs have been observed. The frequency of those effects has not been yet clearly established. Nevertheless valproate preferably induces neural tube defects: myelomeningocele, spina bifida. The frequency of this effect is estimated to be 1 to 2%.

In view of the above data

If a woman plans a pregnancy, it is an opportunity of reviewing the indication for anti-epileptic therapy; folate supplementation should be considered.

During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective. Monotherapy is to be recommended; the minimum effective daily dosage should be used, in several divided doses over the day. Nevertheless, specialised antenatal monitoring should be instituted in order to detect the possible occurrence of neural tube detect or any other malformation.

Risk in the neonate

Exceptional cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenaemia; afibrinogenaemia has also been reported and may be fatal. This hypofibrinogenaemia is possibly associated with decrease of coagulation factors.
However, this syndrome has to be distinguished from the decrease of the vitamin K dependent factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Lactation

Excretion of valproate in breast milk is low, with a concentration between 1% to 10% of maternal serum levels; up to now breast fed children that have been monitored during the neonatal period have not experienced clinical effects.

4.7 Effects on ability to drive and use machines

Patient should be warned of the risk of somnolence especially in cases of anticonvulsant polytherapy or association with benzodiazepines

4.8 Side effects

Rare cases of liver dysfunction.
Teratogenic risk.

- Neurological disorders: confusion; a few cases of stupor or lethargy sometimes leading to transient coma (encephalopathy) have been described during sodium valproate therapy; these were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and these decreased on withdrawal of treatment or reduction of dosage. These cases have most often been reported during combined therapy (in particular with phenobarbital) or after a sudden increase in valproate doses. Very rare cases of reversible dementia associated with reversible cerebral atrophy have been reported. Isolated reversible parkinsonism have been reported.
- Digestive disorders (nausea, gastralgia) frequently occur in some patients at the start of treatment, but they usually disappear after a few days without discontinuing the treatment.
- Transient and (or) dose related undesirable effects have often been reported; hair loss, fine postural tremor and somnolence.
- Isolated reduction of fibrinogen or increase in bleeding 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)
- Hematologic side effects: frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia.
- Very rare cases of pancreatitis, sometimes lethal, have been reported .
- The occurrence of vasculitis has been reported. Allergic reactions have been reported.
- Cases of isolated and moderate hyperammonemia without change in liver function tests may frequently occur and should not cause treatment discontinuation. Hyperammonemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered.
- Increase in weight may occur; amenorrhea and irregular periods have also been reported.

- Hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has not been established.
- Cutaneous reactions may occur with valproate such as exanthematous rash. In exceptional cases, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme have been reported.
- There have been isolated reports of a reversible Fanconi's syndrome associated with valproate therapy but the mode of action is as yet unclear.

4.9 Overdose

Clinical signs of acute massive overdosage usually include coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions. 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. Hospital management of over dosage should include gastric lavage, that is useful up to 10 to 12 hours following ingestion, cardio-respiratory monitoring. Naloxone has been successfully used in a few isolated cases. Death have occurred following massive overdosage; nevertheless, a favourable outcome is usual.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

Broad spectrum anti-epileptic agent.- Sodium valproate exerts its effects mainly on central nervous system. Pharmacological studies in animalshave demonstrated that valproate has anti-convulsant properties in various models of experimental epilepsy (generalized and partial seizures). In humans, sodium valproate has demonstrated anti-epileptic activity in various types of epilepsy. - Its main mechanism of action seems to be related to a reinforcement of the GABAergic pathway.

5.2 Pharmacokinetic properties

- Sodium valproate bioavailability is close to 100% following oral administration.
- The volume of distribution is mainly limited to blood and extracellular fluid. Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentration in plasma (about 10% of the total concentration) Valproate is transferred through placenta. When given to breast feeding mothers, valproate is excreted in breast milk at low concentrations (between 1 to 10% of the total serum concen-tration).
- Steady state plasma concentration is reached rapidly (3 to 4 days) following oral administration.
- Valproate is highly bound to plasma proteins; protein binding is dose dependent and saturable.
- Valproate molecule can be dialysed but only the free form (approximately 10%) is excreted.

- Unlike other anti-epileptics, sodium valproate does not increase its own degradation, neither that of other agents such as oestroprogestatives. This is due to the absence of enzyme inducing effect involving cytochrome P450.
- Half life is approximately 8 to 20 hours. It is usually shorter in children.
- Sodium valproate is mainly excreted in urine following metabolization via glucuro conjugation and betaoxidation.

5.3 Preclinical safety data

Not Applicable

6.0 Pharmaceutical Particulars

6.1 List of Excipients

S. No.	Name of the Excipient
1.	Microcrystalline Cellulose
2.	Cetostearyl Alcohol
3.	Magnesium Stearate
4.	Hydroxy ethyl cellulose
5.	Purified Talc
6.	Colloidal Silicon Dioxide
7.	Diethyl Phthalate
8.	Insta moistshield IC – MS – 2673 White
9.	Isopropyl Alcohol
10.	Methylene Chloride

6.2 Incompatibilities

None of the incompatibilities has been reported.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25^{o} C in dry place, protected from light

6.5 Nature and content of container

Valcontin 500 mg Tablets are packed in Aluminum strips made up of printed aluminum foil (201mm × 0.04 mm) and plain aluminum foil (201mm × 0.04 mm). Ten strips having 10 tablets each are placed in a carton with a package insert.

6.6 Instructions for use/handling

Keep out of reach of children.
The tablets should be swallowed whole and not chewed.

7.0 Marketing authorization holder

Modi-Mundipharma Private Limited
1400, Modi Tower, 98 Nehru Place,
New Delhi – 110019, India
Phone: +91-11-42504969
Fax: +91-11-26451659
E-mail: mithu.sen@winmedicare.com

8. Marketing authorization number

A4-5954

9. Date of first authorization/renewal of the authorization

09/05/2011

10. Date of revision of the text

02/01/2022

1.3.2 Labelling (outer & inner labels)

Artwork of Valcontin 500 is attached.

℞

VALCONTIN™ 500

CONTINUS™ controlled release system

Controlled Release Tablets of
Sodium Valproate and Valproic Acid

Manufactured by
MODI-MUNDIPHARMA PVT. LTD.
Mfd. at : Modipuram - 250 110, U.P., India
Office : 1400, Modi Tower,
98, Nehru Place, New Delhi - 110 019, India

8 901814 002254

NAFDAC Reg. No. : A4-5954
Mfg. Lic. No. 29/92

Imported and Distributed by:
Phillips Pharmaceuticals (Nigeria) Limited.
122-132, Afprint Industrial Estate,
Apapa-Oshodi Expressway,
Iyana-Isolo, Lagos, Nigeria.

VLC2-CTM1-E01/0520-NIG

℞

VALCONTIN™ 500

CONTINUS™ controlled release system

Controlled Release Tablets of
Sodium Valproate and Valproic Acid

℞ 500 mg 100 Tablets

VALCONTIN™ 500

CONTINUS™ controlled release system

Controlled Release Tablets of
Sodium Valproate and Valproic Acid

℞

VALCONTIN™ 500

CONTINUS™ controlled release system

Controlled Release Tablets of
Sodium Valproate and Valproic Acid

Each film-coated tablet contains
Sodium Valproate BP : 333 mg

(Both together correspond to sodium valproate
500 mg in a controlled release system)
Colour : Titanium dioxide
Dosage : As directed by the physician.

These tablets should be swallowed whole and not chewed.

For full prescribing information, please consult the package insert.

Warning : To be sold by retail on the prescription of a Registered Medical Practitioner only.

Store at or below 30° C, in a dry place, protected from light.

Keep out of reach of children.

TM : Trade Mark

℞ 500 mg 100 Tablets

VALCONTIN™ 500

CONTINUS™ controlled release system

Controlled Release Tablets of
Sodium Valproate and Valproic Acid

Artwork of **Valcontin 500 Sale Pack (Nigeria)**, Carton Size - 233 x 70 x 70 mm, 65% Reduced Print
Pantone - 2425C, 25-05-2020, **Dynamic Design** (OD0520)

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VALCONTIN™ 500

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Controlled Release Tablets of
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Each film-coated tablet contains
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Valproic Acid USP : 145 mg
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VLC2-FTM1-E01/0520-NIG
Mfg. Lic. No. 29/92
NAFDAC Reg. No. : A4-5954
TM : Trade Mark

VALCONTIN™ 500 VALCONTIN™ 500 VALCONTIN™ 500

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VALCONTIN™ 500

CONTINUS™ controlled release system

Controlled Release Tablets of
Sodium Valproate and Valproic Acid

Each film-coated tablet contains
Sodium Valproate BP : 333 mg
Valproic Acid USP : 145 mg
(Both together correspond to sodium valproate 500 mg in a controlled release system)
Colour : Titanium dioxide

Dosage : As directed by the physician.

These tablets should be swallowed whole and not chewed

Store at or below 30° C, in a dry place, protected from light.

Keep out of reach of children.

Warning : To be sold by retail on the prescription of a Registered Medical Practitioner only.

Manufactured by :
MODI-MUNDIPHARMA PVT. LTD.
Mfd. at : Modipuram - 250 110, U.P., India
Office : 1400, Modi Tower, 98, Nehru Place, New Delhi-110019, India

Imported and Distributed by:
Phillips Pharmaceuticals (Nigeria) Limited.
122-132, Afprint Industrial Estate, Apapa-Oshodi Expressway, Iyana-Isolo, Lagos, Nigeria.

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Controlled Release Tablets of

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CONTINUS™ controlled release system

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VALCONTIN™ 5

Artwork of **Valcontin 500 Foil** (Nigeria)
Strip Size - 67 x 230 mm, Repeat 70 mm, 90% Reduced Print
Foil width 201 mm
25.05.2020, **Dynamic Design** (OD0520)

1.3.3 Packaging Insert (also known as patient information PIL)

Pack insert of Valcontin 500 mg is enclosed.

without change in liver function tests may frequently occur and should not cause treatment discontinuation. Hyperammonemia associated with neurological symptoms has also been reported. In such cases further investigations should be considered (see **Precautions**).

- Increase in weight may occur, amenorrhea and irregular periods have also been reported.
- Hearing loss, either reversible or irreversible, has been reported rarely; however a cause and effect relationship has not been established.
- Cutaneous reactions may occur with valproate such as exanthematous rash. In exceptional cases, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme have been reported.
- There have been isolated reports of a reversible Fanconi's syndrome associated with valproate therapy but the mode of action is as yet unclear.

Overdose & Its Treatment

Clinical signs of acute massive overdosage usually include coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory functions.

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. Hospital management of over dosage should include gastric lavage, that is useful up to 10 to 12 hours following ingestion, cardio-respiratory monitoring. Naloxone has been successfully used in a few isolated cases.

Death have occurred following massive overdosage; nevertheless, a favourable outcome is usual.

Pharmaceutical Particulars

Incompatibilities : None reported

Shelf Life : 24 months from the date of manufacturing.

Storage precautions : Store at or below 30° C, in a dry place, protected from light.

Keep out of reach of children.

Presentation : Box of 100 tablets (10 x 10's Aluminium strip)

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NAFDAC Reg. No.
Valcontin 500 : A4-5954
Valcontin 200 : A4-5955
TM : Trade Mark

VLC1-PTM1-E03/0722-NIG

70 x 210 mm

70 x 210 mm

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

Rx

VALCONTIN™ 200/500

CONTINUS™ controlled release system

Controlled Release Tablets of
Sodium Valproate and Valproic Acid

Description

Valcontin™ 200

White to off white, round, biconvex, plain film-coated tablets:
Sodium Valproate BP : 133.5 mg
Valproic acid USP : 58 mg
(Both together correspond to sodium valproate 200 mg in a Continus™ controlled release system)

Valcontin™ 500

White to off white, caplet shaped, biconvex, plain film-coated tablets:
Sodium Valproate BP : 333 mg
Valproic acid USP : 145 mg
(Both together correspond to sodium valproate 500 mg in a Continus™ controlled release system)

Indications

In the treatment of generalized seizures, notably tonic-clonic, absence and myoclonic seizures and also for partial seizures (simple and complex).

Clinical Pharmacology

Pharmacodynamics

- Broad spectrum anti-epileptic agent.
- Sodium valproate exerts its effects mainly on central nervous system. Pharmacological studies in animals have demonstrated that valproate has anti-convulsant properties in various models of experimental epilepsy (generalized and partial seizures). In humans, sodium valproate has demonstrated anti-epileptic activity in various types of epilepsy.
- Its main mechanism of action seems to be related to a reinforcement of the GABAergic pathway.

Pharmacokinetics

- Sodium valproate bioavailability is close to 100% following oral administration.
- The volume of distribution is mainly limited to blood and extracellular fluid. Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of the total concentration) Valproate is transferred through placenta. When given to breast feeding mothers, valproate is excreted in breast milk at low concentrations (between 1 to 10% of the total serum concentration).
- Steady state plasma concentration is reached rapidly (3 to 4 days) following oral administration.
- Valproate is highly bound to plasma proteins; protein binding is dose dependent and saturable.
- Valproate molecule can be dialysed but only the free form (approximately 10%) is excreted.
- Unlike other anti-epileptics, sodium valproate does not increase its own degradation, neither that of other agents such as oestroprogestatives. This is due to the absence of enzyme inducing effect involving cytochrome P450.
- Half life is approximately 8 to 20 hours. It is usually shorter in children.
- Sodium valproate is mainly excreted in urine following metabolization via glucuro-conjugation and beta-oxidation.

Dosage and Administration

For Seizure Control

Daily dosage should be established according to age and body weight; nevertheless the wide individual sensitivity to valproate should also be considered.

A good correlation has not been established between daily dose, serum concentration and therapeutic effect and optimum dosage should be determined essentially according to the clinical response; the determination of valproic acid plasma levels may be considered in addition to clinical monitoring when adequate seizure control is not achieved or when adverse effects are suspected. The reported effective range is usually between 40-100 mg/l (300-700 µmol/l).

Initiation of Valcontin™ therapy

- In patients not receiving other anti-epileptic drugs, the dosage should be preferably increased by successive dose levels at 2-3 day intervals in order to reach the optimum dosage in about 1 week.
- In patients previously receiving anti-epileptic agents, substitution with Valcontin™ should be progressive, the optimum dosage being reached in about 2 weeks and other treatments being tapered and then stopped.
- Addition of an other anti-epileptic agent should be done progressively where it is necessary (see **Drug Interactions**).

Dosage

Initial daily dosage is usually 10-15 mg/kg, then doses are titrated upto the optimum dosage *(See initiation of Valcontin™ therapy)*. This is generally within the range of 20 to 30 mg/kg/day. Nevertheless, where seizure control is not achieved within this range, the dose may be further increased adequately; patients should be carefully monitored when receiving daily doses higher than 50 mg/kg (see **Precautions**).

In adults, the usual dosage is within the range of 20-30 mg/kg/day.

Valcontin™ may be used in children provided that they are able to take such a form. The usual dosage is about 30 mg/kg per day.

Valcontin™ tablet is for twice daily administration. It is to be swallowed whole and not crushed or chewed.

Contraindications

- Acute hepatitis
- Chronic hepatitis
- Personal or family history of severe hepatitis, especially drug related
- Hypersensitivity to sodium valproate
- Porphyria

Warnings

Liver dysfunction

Conditions of occurrence

Severe liver damage resulting sometimes in fatalities have been exceptionally 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 with severe seizure disorders, particularly those with brain damage, mental retardation and (or) congenital metabolic or degenerative disease. After the age of 3, the incidence of occurrence is significantly reduced and progressively 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 Conditions of occurrence):*

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70 x 210 mm

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

Patients (or their family or 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 performed before and then periodically monitored during the first 6 months of therapy. 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 Valcontin™ 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.

Pancreatitis

Severe pancreatitis which may result in fatalities have been rarely reported. Young children are at particular risk. This risk decreases with increasing age. Severe seizures or neurological impairment may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.

Precautions

- Liver function tests should be carried out before therapy (see **Contraindications**), and periodically during the first 6 months especially in patients at risk (see **Warnings**).
  As with most anti-epileptic drugs, mild increased liver enzymes may be noted particularly at the beginning of therapy, they are transient and isolated, without clinical sign.
  More extensive biological investigation (including prothrombin rate) are recommended in those patients; an adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.
- Monotherapy is recommended in children under the age of 3 years when prescribing Valcontin™ but the potential benefit of Valcontin™ should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy *(see Warnings)*. The concomitant use of salicylates should be avoided in those children under 3 due to the risk of liver toxicity.
- Blood tests (blood cell count, 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 **Side Effects**).
- 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 **Pharmacokinetics**).
- Although immune disorders have been only exceptionally noted during the use of valproate, the potential benefit of valproate should be weighed against its potential risk in patients with systemic lupus erythematosus.
- Exceptional cases of pancreatitis have been reported, therefore patients experiencing acute abdominal pain should have a prompt medical evaluation. In case of pancreatitis, valproate should be interrupted.
- When an urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonemia with valproate.

Effect on ability to drive and use machines

Patient should be warned of the risk of somnolence especially in cases of anticonvulsant polytherapy or association with benzodiazepines (See **Drug Interactions**).

Pregnancy

From experience in treated epileptic mothers, the risk associated with the use of valproate during pregnancy has been described as follows:

Risk associated with epilepsy and anti-epileptics

In offspring born to mothers with epilepsy receiving any anti-epileptic treatment, the global rate of malformations has been demonstrated to be 2 to 3 times higher than the rate (approximately 3%) reported in the general population. Although an increased number of children with malformations has been reported in case of multiple drug therapy, the respective part of treatment and disease has not been formally established. Malformations most frequently encountered are labial clefts and cardiovascular malformations.

Sudden discontinuation in the anti-epileptic therapy may be associated with a worsening of the disease in the mother and subsequent untoward effects in the foetus.

Risk associated with sodium valproate

In animals: Teratogenic effects have been demonstrated in the mouse, rat and rabbit.

In humans: The global risk of malformations in women receiving valproate during the first trimester of pregnancy is not higher than the risk described with other anti-epileptics. Cases of facial dysmorphia have been reported. A few cases of multiple malformations particularly of the limbs have been observed. The frequency of those effects has not been yet clearly established. Nevertheless valproate preferably induces neural tube defects: myelomeningocele, spina bifida. The frequency of this effect is estimated to be 1 to 2% .

In view of the above data

- If a woman plans a pregnancy, it is an opportunity of reviewing the indication for anti-epileptic therapy; folate supplementation should be considered.
- During pregnancy, valproate anti-epileptic treatment should not be discontinued if it has been effective. Monotherapy is to be recommended; the minimum effective daily dosage should be used, in several divided doses over the day. Nevertheless, specialised antenatal monitoring should be instituted in order to detect the possible occurrence of neural tube detect or any other malformation.

Risk in the neonate

Exceptional cases of haemorrhagic syndrome have been reported in neonates whose mothers have taken sodium valproate during pregnancy. This haemorrhagic syndrome is related to hypofibrinogenaemia; afibrinogenaemia has also been reported and may be fatal. This hypofibrinogenaemia is possibly associated with decrease of coagulation factors. However, this syndrome has to be distinguished from the decrease of the vitamin K dependent factors induced by phenobarbital and enzymatic inducers.

Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Lactation

Excretion of valproate in breast milk is low, with a concentration between 1% to 10% of maternal serum levels; up to now breast fed children that have been monitored during the neonatal period have not experienced clinical effects.

General

Hepatic impairment: Hepatic dysfunction, including hepatic failure resulting in fatal outcomes, has occurred in patients whose treatment included valproic acid or sodium valproate (see **Precautions**).

Impaired renal function: Lower doses may be required since free drug levels may be high owing to lowered serum albumin and poor urinary excretion of free drug metabolites (see **Precautions**).

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

Drug Interactions

Effects of valproate on other drugs

- *Neuroleptics, MAO inhibitors, antidepressants and benzodiazepines.*
  Valproate may potentiate the effect of other psychotropics such as neuroleptics, MAO inhibitors, antidepressants and benzodiazepines, therefore clinical monitoring is advised and dosage should be adjusted when appropriate.
- *Phenobarbital*
  Valproate increases phenobarbital plasma concentrations (due to inhibition of hepatic catabolism) and sedation may occur, particularly in children. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.
- *Primidone*
  Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.
- *Phenytoin*
  Valproate increases phenytoin total plasma concentration. Moreover, valproate increases 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 be evaluated.
- *Carbamazepine*
  Clinical toxicity has been reported when valproate was administered with carbamazepine as valproate may potentiate toxic effect of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.
- *Lamotrigine*
  Valproate may reduce lamotrigine metabolism and increase its mean half life; dosages should be adjusted (lamotrigine dosage decreased) when appropriate. There are suggestions, yet to be proven that the risk of rash may be increased by coadministration of lamotrigine with valproic acid.
- *Zidovudine*
  Valproate may raise zidovudine plasma concentration leading to increased zidovudine toxicity.

Effects of other drugs on valproate

- Anti-epileptics with enzyme inducing effect (including phenytoin, phenobarbital, carbamazepine) decrease valproate serum concentrations. Dosages should be adjusted according to blood levels in case of combined therapy.
- On the other hand, combination of felbamate and valproate may increase valproate serum concentration. Valproate dosage should be monitored.
- Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore epileptic seizures may occur in cases of combined therapy.
- In case of concomitant use of valproate and highly protein bound agents (aspirin), valproate free serum levels may be increased. Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent anticoagulant.
- Valproate serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.
- Carbapenem antibiotics like imipenem/meropenem: Decrease in valproate blood level sometimes associated with convulsions has been observed when panipenem or meropenem were combined. If these antibiotics have to be administered, close monitoring of valproate blood level is recommended.

Other interactions

- Valproate usually has no enzyme inducing effect as a consequence, valproate does not reduce efficacy of oestroprogestative agents in women receiving hormonal contraception.

Side Effects

- Rare cases of liver dysfunction (see **Warnings**)
- Teratogenic risk (see **Pregnancy**)
- Neurological disorders: confusion; a few cases of stupor or lethargy sometimes leading to transient coma (encephalopathy) have been described during sodium valproate therapy; these were isolated or associated with an increase in the occurrence of convulsions whilst on therapy, and these decreased on withdrawal of treatment or reduction of dosage. These cases have most often been reported during combined therapy (in particular with phenobarbital) or after a sudden increase in valproate doses. Very rare cases of reversible dementia associated with reversible cerebral atrophy have been reported. Isolated reversible parkinsonism have been reported.
- Digestive disorders (nausea, gastralgia) frequently occur in some patients at the start of treatment, but they usually disappear after a few days without discontinuing the treatment.
- Transient and (or) dose related undesirable effects have often been reported; hair loss, fine postural tremor and somnolence.
- Isolated reduction of fibrinogen or increase in bleeding 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; see **Pregnancy**)
- Hematologic side effects: frequent occurrence of thrombocytopenia, rare cases of anaemia, leucopenia or pancytopenia.
- Very rare cases of pancreatitis, sometimes lethal, have been reported (see **Warnings and Precautions**).
- The occurrence of vasculitis has been reported. Allergic reactions have been reported.
- Cases of isolated and moderate hyperammonemia

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