PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SENCRESUS 25 (film-coated tablets)

SENCRESUS 50 (film-coated tablets)

SENCRESUS 100 (film-coated tablets)

SENCRESUS 200 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SENCRESUS 25: Each film-coated tablet contains 25 mg topiramate.

Sugar free.

SENCRESUS 50: Each film-coated tablet contains 50 mg topiramate.

Sugar free

SENCRESUS 100: Each film-coated tablet contains 100 mg topiramate.

Sugar free

SENCRESUS 200: Each film-coated tablet contains 200 mg topiramate.

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets (Tablets)

SENCRESUS 25: White, round, biconvex, film-coated tablets debossed with “G” on one side and “TO” over 25 on the other side.

SENCRESUS 50: Yellow, round, biconvex, film-coated tablets debossed with “G” on one side and “TO” over 50 on the other side.

SENCRESUS 100: Yellow, round, biconvex, film-coated tablets debossed with “G” on one side and “TO” over 100 on the other side.

SENCRESUS 200: Red, round, biconvex, film-coated tablets debossed with “G” on one side and “TO” over 200 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SENCRESUS is indicated as monotherapy in patients with newly diagnosed epilepsy or for conversion to monotherapy in patients with epilepsy.

SENCRESUS is indicated as adjunctive therapy for adults and children aged 12 years and above who are inadequately controlled on conventional first-line anti-epileptic medicines for:

- Partial onset seizures with or without secondary generalised seizures.
- Primary generalised tonic-clonic seizures.

4.2 Posology and method of administration

Posology

For optimal control in both adults and children, it is recommended that therapy be initiated at a low dose, followed by titration to an effective dose.

It is recommended that tablets not be broken and can be taken with or without meals.

MONOTHERAPY:

When concomitant anti-epileptic medicines (AEMs) are withdrawn to achieve monotherapy with **SENCRESUS**, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AEM, a gradual discontinuation at the rate of approximately one-third of the concomitant AEM dose every 2 weeks is recommended. When enzyme inducing medicines are withdrawn, topiramate levels will increase. A decrease in **SENCRESUS** dosage may be required if clinically indicated.

Adults:

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 to 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, small increments or longer intervals between increments can be used. Dose and titration rate should be guided by clinical outcome.

The recommended initial target dose for **SENCRESUS** monotherapy in adults is 100 mg/day and the maximum recommended daily dose is 400 mg. Some patients with refractory forms of epilepsy have tolerated **SENCRESUS** monotherapy at doses of 1 000 mg/day, administered in

two divided doses. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

Children:

Treatment of children aged 12 years and above should begin at 0,5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 0,5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Dose and dose titration should be guided by clinical outcome.

The recommended initial target dose range for **SENCRESUS** monotherapy in children aged twelve years and above is 3 to 6 mg/kg/day. Children with recently diagnosed partial onset seizures have received doses of up to 500 mg/day.

ADJUNCTIVE THERAPY:

Adults:

Therapy should begin at 25 - 50 mg nightly for one week. Subsequently, at weekly intervals, the dose should be increased by 25 – 50 mg/day and the dose should be taken in two divided doses. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials, 200 mg was effective and was the lowest dosage studied. This is therefore considered the minimal effective dose. The usual total daily dose is 200 mg to 400 mg in two divided doses. Some patients may

require doses up to 800 mg per day, which is the maximum dose. It is recommended that therapy be initiated at a low dose, followed by titration to an effective dose.

Since **SENCRESUS** is removed from plasma by haemodialysis, a supplemental dosage of **SENCRESUS** equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease. (See **Section 4.4**)

This formulation is not suitable for children younger than 12 years.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to any component in **SENCRESUS.**
- The safety and efficacy of topiramate in children under 2 years have not been established.
- Pregnancy and lactation, as topiramate is teratogenic in animals.
- In women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Acute myopia and secondary angle closure glaucoma:

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving **SENCRESUS.** Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperaemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating **SENCRESUS** therapy.

Secondary angle closure glaucoma associated with **SENCRESUS** has been reported in paediatric patients as well as adults. Treatment includes discontinuation of **SENCRESUS** as rapidly as possible and appropriate measures applied to reduce intraocular pressure.

Oral contraceptives:

Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding (see **Section 4.5**).

Hepatic impairment:

In hepatically impaired patients, **SENCRESUS** should be administered with caution as the clearance of topiramate may be decreased.

Anti-epileptic medicines, including **SENCRESUS**, should be withdrawn gradually to minimise the potential of increased seizure frequency.

Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.

The titration schedule should be guided by clinical outcome (i.e. seizure control, avoidance of side-effects) with the knowledge that subjects with known renal impairment may require a longer time to reach steady-state at each dose.

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain.
Risk factors for nephrolithiasis include stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis may be at increased risk.

Adequate hydration while using **SENCRESUS** is very important. Hydration can reduce the risk of nephrolithiasis (renal stone formation). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse events.
In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Metabolic acidosis:

Hypocloraemic metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with **SENCRESUS** treatment. This decrease in serum bicarbonate is due to the inhibitory effect of **SENCRESUS** on renal carbonic anhydrase and consequently renal bicarbonate wasting.

Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate; however, patients have experienced decreases to values below 10 mmol/l. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or certain medicines) may be additive to the bicarbonate lowering effects of **SENCRESUS**.

Chronic metabolic acidosis can lead to nephrolithiasis and increased risk of fractures.

Appropriate evaluation of patients including serum bicarbonate levels is recommended with **SENCRESUS** therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing **SENCRESUS** (using dose tapering).

Pregnancy prevention programme

Topiramate can cause major congenital malformations and fetal growth restriction when administered to a pregnant woman.

Some data suggest an increased risk of neurodevelopmental disorders in children exposed to topiramate in utero, while other data do not suggest an increased risk (see **section 4.6**).

Topiramate is contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see **section 4.3 and 4.6**)

The conditions of the Pregnancy Prevention Programme are that the prescriber must ensure that:

- a pregnancy test before starting treatment;
- counselling about the risks of topiramate treatment and the need for highly effective contraception throughout treatment;
- a review of ongoing treatment at least annually by completion of a risk awareness form.
- To confirm that appropriate measures have been taken, patients and prescribers will go through this form at the beginning of treatment and at each annual review and if the patient is planning a pregnancy or has become pregnant. It should be ensured that the patient is fully informed and has understood the risks and measures to be taken.

Women of childbearing potential

Pregnancy testing should be performed before initiating treatment with topiramate in a woman of childbearing potential.

The patient must be fully informed and understand the risks related to the use of topiramate during pregnancy (see sections 4.3 and 4.6). This includes the need to consult her doctor if the woman is
planning a pregnancy to discuss switching to alternative treatments prior to discontinuation of contraception, and for prompt contact with a doctor if she becomes pregnant or thinks she may be pregnant.
This includes the need to consult her doctor as soon as she is planning for pregnancy, and for prompt contact with her doctor if she becomes pregnant or thinks she may be pregnant and is taking topiramate.

Oligohydrosis

Oligohydrosis (decreased sweating) has been reported in association with the use of topiramate.
Decreased sweating and hyperthermia (rise in body temperature) may occur especially in young children exposed to high ambient temperature.

Mood disturbances/depression

An increased incidence of mood disturbances and depression has been observed during topiramate treatment.

Hyperammonemia and encephalopathy

Hyperammonemia with or without encephalopathy has been reported with topiramate treatment (see **section 4.8**). The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid (see section 4.5).

In patients who develop unexplained lethargy or changes in mental status associated with topiramate
monotherapy or adjunctive therapy, it is recommended to consider hyperammonemic encephalopathy and measuring ammonia levels.

Nutritional supplementation

Some patients may experience weight loss whilst on treatment with topiramate. It is recommended that patients on topiramate treatment should be monitored for weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight while on topiramate.

Excipients with known effect

SENCRESUS contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially sodium-free.

4.5 Interaction with other medicines and other forms of interaction

Effects of **SENCRESUS** on other anti-epileptic medicines:

The addition of **SENCRESUS** to other anti-epileptic agents (phenytoin,carbamazepine, valproic acid, phenobarbital, primodone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of **SENCRESUS** to phenytoin may

result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform ($CYP2C_{meph}$).

Consequently any patient on phenytoin should have phenytoin levels monitored.

A pharmacokinetic interaction study of patients with epilepsy indicated the addition of **SENCRESUS** to lamotrigine had no effect on steady state plasma concentration of lamotrigine at **SENCRESUS** doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of **SENCRESUS** during or after removal of lamotrigine.

However, the incidence of adverse effects was meaningfully increased with the combination.

Effects of other anti-epileptic medicines on **SENCRESUS:**

Phenytoin and carbamazepine decrease the plasma concentration of **SENCRESUS** The addition or withdrawal of phenytoin or carbamazepine to **SENCRESUS** therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes

in plasma concentrations of **SENCRESUS** and therefore, does not warrant dosage adjustment of **SENCRESUS.**

The above interactions are summarised in the following table:

AEM Co-administered	AEM Concentration	**SENCRESUS** Concentration
Phenytoin	↔**	↓
Carbamazepine (CBZ)	↔	↓
Valproic acid	↔	↔
Lamotrigine	↔	↔
Phenobarbital	↔	NS
Primidone	↔	NS

↔ = No effect on plasma concentration (< 15 % change)

** = Plasma concentrations increase in individual patients

↓ = Plasma concentrations decrease

NS = Not studied
AEM = Anti-epileptic medicine

Other medicine interactions:

Digoxin:

Concomitant administration has shown a decrease in serum digoxin. When **SENCRESUS** is added or withdrawn in patients on digoxin therapy, careful attention should be given to the monitoring of serum digoxin.

Oral contraceptives:

SENCRESUS increases plasma clearance of the oestrogenic component significantly and efficacy of the oral contraceptive may be compromised.

The possibility of increased breakthrough bleeding should be therefore considered in patients taking combination oral contraceptive products with **SENCRESUS.** Patients taking oestrogen-containing contraceptives should be asked to report any change in their bleeding patterns.

Patients should use an alternative non-hormonal method of contraception or patients should, bearing in mind the potential risk of teratogenicity, receive a preparation containing not less than 50 micrograms of oestrogen.

Hydrochlorothiazide (HCTZ):

The concomitant use of hydrochlorothiazide and **SENCRESUS** may increase the peak concentration and AUC of topiramate. Dosage reduction of **SENCRESUS** may be required.

Metformin:

The concomitant use of metformin and **SENCRESUS** may increase the peak concentration and AUC of metformin.

When **SENCRESUS** is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

Pioglitazone:

When **SENCRESUS** is added to pioglitazone therapy or pioglitazone is added to **SENCRESUS** therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

CNS depressants:

Concomitant use of **SENCRESUS** with alcohol or other central nervous system (CNS) depressant medicines should be avoided.

Additional pharmacokinetic medicine interaction studies:

Clinical studies have been conducted to assess the potential pharmacokinetic medicine interaction between topiramate and other agents. The changes in Cmax or AUC as a result of the interactions are summarised below. The second column (concomitant substance concentration) describes what happens to the concentration of the concomitant substance listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the co-administration of a substance listed in the first column modifies the concentration of topiramate.

Summary of results from additional clinical pharmacokinetic substance interaction studies:

Concomitant substance	Concomitant substance concentration[a]	Topiramate concentration[a]
Amitriptyline	↔ 20 % increase in C_{max} and AUC of nortriptyline metabolite	NS

Dihydroergotamine (Oral and subcutaneous)	↔	↔
Haloperidol	↔ 31 % increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17 % increase in C_{max} for 4-OH propranolol (TPM 50 mg q12h)	16 % increase in C_{max} 17 % increase in AUC (80 mg propranolol q12h)
Sumatriptan (Oral and subcutaneous)	↔	NS
Pizotifen	↔	↔

a % values are the changes in treatment mean Cmax or AUC with respect to monotherapy

↔ = No effect on Cmax and AUC (≤15 % change) of the parent compound

NS = No studies

Other interactions:

St John's Wort (Hypericum perforatum):

A risk of decreased plasma concentrations resulting in a loss of efficacy could be observed with co-administration of **SENCRESUS** and St John's Wort.

Lithium:

There was an observed reduction in systemic exposure for lithium during concomitant administration with **SENCRESUS.**

Lithium levels should be monitored when co-administered with **SENCRESUS.**

Risperidone:

When administered concomitantly with ~~**MYLAN TOPIRAMATE**~~ **SENCRESUS** there was a reduction in risperidone.

Glyburide:

When topiramate is added to glyburide therapy or glyburide is added to **SENCRESUS** therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Agents predisposing to nephrolithiasis:

Concomitant use of **SENCRESUS** with agents predisposing to nephrolithiasis (renal stone formation) should be avoided.

Valproic acid:

Concomitant administration of **SENCRESUS** and valproic acid has been associated with hyperammonaemia with or without encephalopathy in patients who had tolerated either medicinal product alone.

Warfarin

Decreased Prothrombin Time/International Normalized Ratio (PT/INR) has been reported in patients treated with topiramate in combination with warfarin. Therefore, INR should be carefully monitored in patients concomitantly treated with topiramate and warfarin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and anti-epileptic drugs (AEDs) in general

Specialist advice regarding the potential risks to a fetus caused by both seizures and antiepileptic treatment should be given to women of childbearing potential, and especially to women planning for pregnancy and women who are pregnant. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the fetus. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Risk related to topiramate

Topiramate is teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.

In humans, topiramate crosses the placenta and similar concentrations have been reported in the umbilical cord and maternal blood.

Cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.

It is recommended that women of child bearing potential use adequate contraception.

Topiramate is contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see section 4.3 and 4.4 ~~4.6~~)

Alternative therapeutic options should be considered in women of childbearing potential.

Pregnancy testing should be performed before initiating treatment with topiramate in a woman of childbearing potential.

Breastfeeding

Animal studies have shown the excretion of topiramate in milk.

Limited observations in patients suggest an extensive excretion of topiramate into breast milk.

Effects that have been observed in breastfed newborns/infants of treated mothers, include diarrhea, drowsiness, irritability and inadequate weight gain. Therefore, a decision must be made whether to suspend breast-feeding or to discontinue/ abstain from topiramate therapy taking into account the benefit of breastfeeding for the child and the benefit of topiramate therapy for the women.

Safety has not been demonstrated (see **section 4.3**).

Fertility

Animal studies did not reveal impairment of fertility by topiramate. The effect of topiramate on human fertility has not been established.

4.7 Effects on ability to drive and use machines

SENCRESUS may produce central nervous system related events such as: drowsiness, dizziness or other related symptoms. Caution is advised when driving or operating machinery.

SENCRESUS may be more sedating than other anti-epileptic medicines.

4.8 Undesirable effects

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Neutropenia, thromboembolic events, leucopenia, thrombocytopenia, Eosinophilia
	Frequent	Anaemia, purpura
Immune system disorders	Frequent	Hypersensitivity

Metabolism and nutrition disorders	Frequent	Weight loss, Anorexia Decreased appetite
	Less frequent	Metabolic acidosis, Hypokalaemia, Increased appetite, hyperammonemic, hyperchloraemic
Psychiatric disorders	Frequent	Confusion and psychomotor slowing, depression, concentration disturbances, anxiety, apathy, euphoria, emotional lability, agitation, cognitive problems, decreased libido, aggressive reactions, personality disorders
	Less frequent	Hallucinations, suicidal ideation, suicidal attempts, suicide,

		psychosis or psychotic symptoms, Mania, Panic disorder,
Nervous system disorders	Frequent	Ataxia, paraesthesia, speech disorders, aphasia, tremor, asthenia, fatigue, dizziness, headache, somnolence, insomnia, Difficulty with memory
	Less frequent	Hypokinesia, hyperkinesias, stupor, co-ordination problems, abnormal gait
Eye disorders	Frequent	Diplopia, abnormal vision, nystagmus
	Less frequent	Acute myopia and secondary angle closure glaucoma, conjunctivitis, eye pain, blurred vision, Visual acuity, reduced, Scotoma, Dry eye, Photophobia, Blepharospasm, Lacrimation increased,

		Photopsia, Mydriasis, Presbyopia, Accommodation disorder, Blindness unilateral
Ear and labyrinth disorders	Frequent	Tinnitus, Ear pain, Vertigo
	Less frequent	Deafness, Deafness unilateral, Deafness neurosensory, Ear discomfort, Hearing impaired
Cardiac disorders	Less frequent	Bradycardia, Sinus bradycardia, Palpitations
Vascular disorders	Less frequent	Hypotension, postural hypotension, Flushing, Hot flush, Raynaud's phenomenon
Respiratory thoracic and mediastinal disorders	Frequent	Epistaxis, rhinitis, pharyngitis, pneumonia, Rhinorrhoea
	Less frequent	Dyspnoea, Hypersecretion, Dysphonia
	Frequency unknown	Cough

Gastrointestinal disorders	Frequent	Constipation, nausea, abdominal pain, dyspepsia, increased saliva, taste perversion
	Less frequent	Diarrhoea, vomiting and dry mouth, pancreatitis, Flatulence, Gastrooesophageal reflux disease, Hypoaesthesia oral, Gingival bleeding, Abdominal distention, Epigastric discomfort, Abdominal tenderness, Salivary hypersecretion, Oral pain, Breath odour, Glossodynia
Hepato-biliary disorders	Less frequent	Hepatitis, hepatic failure
Skin and subcutaneous tissue disorders	Frequent	Alopecia, increased sweating, Rash, Pruritus
	Less frequent	Folliculitis, pruritus, decreased sweating, bullous skin and mucosal reactions (including

		erythema multiforme, pemphigus, Stevens-Johnson syndrome and toxic epidermal necrolysis), Anhidrosis, Hypoaesthesia facial, Urticaria, Skin discolouration, Dermatitis allergic, Swelling face
Musculoskeletal and connective tissue disorders	Frequent	Skeletal pain, Muscle spasms, Myalgia, Muscle twitching, Muscular weakness, Musculoskeletal chest pain
	Less frequent	Musculoskeletal stiffness, Flank pain, Muscle fatigue
Renal and urinary disorders	Frequent	Urinary frequency, urinary incontinence, dysuria, haematuria, renal failure, Pollakiuria
	Less frequent	Nephrolithiasis, Calculus urinary,

Reproductive system and breast disorders	Frequent	Menstrual disturbances, impotence
General disorders and administration site conditions	Frequent	Allergic reaction, Hyperthermia, Thirst, Sluggishness
	Less frequent	Malaise, Feeling abnormal

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Signs and symptoms:

Convulsions, drowsiness, speech disturbances, blurred vision, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression.

Treatment:

In acute **SENCRESUS** overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis.

Activated charcoal has been shown to absorb topiramate in vitro. Treatment should be appropriately supportive. Hemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A.2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: antiepileptics, other antiepileptics.

ATC Code: N03AX11

Topiramate is an anti-epileptic agent. Topiramate is classified as a sulfamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsive activity:

- Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.
- Topiramate enhances the activity of GABA at some types of GABA receptors.
- Topiramate weakly antagonises the excitatory activity of kainite/AMPA (2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl)propanoic acid) subtype of glutamate receptor but has no

apparent effect on the activity of N-methyl-D-asparate (NMDA) at the NMDA receptor subtype.

In addition, topiramate also inhibits some isoenzymes of carbonic anhydrase. This is not thought to be a major component of the anti-epileptic activity of topiramate.

5.2 Pharmacokinetic properties

Topiramate is well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (Cmax) of 1,5 µg/ml is achieved within 2 to 3 hours (Tmax). Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of 14C-topiramate was at least 81 %. Bioavailability of topiramate is not affected by food.

Generally, 13 to 17 % of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/ml has been observed.

The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0,55 - 0,81 l/kg for a single dose range of 100 to 1 200 mg. An effect of gender on the volume of distribution was detected with values for females which was approximately 50 % of those in males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

Topiramate is not extensively metabolised (> 20 %) in healthy volunteers. Its metabolism may increase up to 50 % in patients receiving concomitant

anti-epileptic therapy with known inducers of substance metabolising enzymes.

The major route of elimination of unchanged topiramate and its metabolites is the urine. Overall, plasma clearance is approximately 20 to 30 ml/min in humans following oral administration.

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. In healthy subjects, pharmacokinetics of topiramate is linear over a single oral dose range of 100 to 400 mg. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. Following administration of multiple doses of 50 mg and 100 mg of topiramate twice a day, the mean plasma elimination half-life was approximately 21 hours.

Concomitant multi-dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

Special population groups (children, elderly, renal and hepatic impairment):

Renal impairment:

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function, and the plasma clearance is decreased in patients with end-stage renal disease. Topiramate is effectively removed from plasma by haemodialysis. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

Hepatic impairment:

Plasma clearance is decreased in patients with moderate to severe impaired hepatic function.

Children and the elderly:

The pharmacokinetics of topiramate in children (4 – 16 years), as in adults receiving add-on therapy; are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose.

Children, however, have a higher clearance, and consequently shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing anti-epileptic medicines decrease the steady state plasma concentration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SENCRESUS 25:

Uncoated tablet:

Microcrystalline cellulose

Povidone

Colloidal silicon dioxide

Sodium starch glycollate

Magnesium stearate

Film-coating:

Opadry white (YS-1-7003)

Purified water

SENCRESUS 50:

Uncoated tablet:

Microcrystalline cellulose

Povidone

Colloidal silicon dioxide

Sodium starch glycollate

Magnesium stearate

Film-coating:

Opadry yellow (03B92164)

Purified water

SENCRESUS 100:

Uncoated tablet:

Microcrystalline cellulose

Povidone

Colloidal silicon dioxide

Sodium starch glycollate

Magnesium stearate

Film-coating:

Opadry yellow (03819280)

Purified water

SENCRESUS 200:

Uncoated tablet:

Microcrystalline cellulose

Povidone

Colloidal silicon dioxide

Sodium starch glycollate

Magnesium stearate

Film-coating:

Opadry maroon (05B16131)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 º C in a dry place.

Protect from moisture

6.5 Nature and contents of container

SENCRESUS 25 is packed in cold forming aluminium blister pack, shiny on one side and dull (matte) on the other side, packed in an outer carton in pack sizes of 28 or 60 tablets.

SENCRESUS 50 is packed in cold forming aluminium blister pack, shiny on one side and dull (matte) on the other side, packed in an outer carton in pack sizes of 28 or 60 tablets.

SENCRESUS 100 is packed in cold forming aluminium blister pack, shiny on one side and dull (matte) on the other side, packed in an outer carton in pack sizes of 28 or 60 tablets.

SENCRESUS 200 is packed in cold forming aluminium blister pack, shiny on one side and dull (matte) on the other side, packed in an outer carton in pack sizes of 28 or 60 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

TRINITY PHARMA (PTY) LTD

106 16th Road, Building 2

Midrand

1686

Contact number: +27 (0)10 594 5610

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8. REGISTRATION NUMBER(S)

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