PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

VIMCOSA 50 mg (film coated tablet)

VIMCOSA 100 mg (film coated tablet)

VIMCOSA 150 mg (film coated tablet)

VIMCOSA 200 mg (film coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIMCOSA 50 mg: Each film coated tablet contains 50 mg **VIMCOSA**.

VIMCOSA 100 mg: Each film coated tablet contains 100 mg **VIMCOSA**.

VIMCOSA 150 mg: Each film coated tablet contains 150 mg **VIMCOSA**.

VIMCOSA 200 mg: Each film coated tablet contains 200 mg **VIMCOSA**.

Sugar-free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet

VIMCOSA 50 mg: Pink coloured, biconvex, oval shaped, film coated tablets debossed with “L50” on one side and plain on other side.

VIMCOSA 100 mg: Yellow coloured, biconvex, oval shaped, film coated tablets debossed with “L100” on one side and plain on other side.

VIMCOSA 150 mg: Salmon coloured, biconvex, oval shaped, film coated tablets debossed with “L150” on one side and plain on other side.

VIMCOSA 200 mg: Blue coloured, biconvex, oval shaped, film coated tablets debossed with “L200”

on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIMCOSA is indicated as monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

VIMCOSA is indicated as adjunctive therapy

• in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy.

• in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy.

4.2 Posology and method of administration

The physician should prescribe the most appropriate formulation and strength according to weight and dose.

Posology

The recommended posology for adults, adolescents and children from 2 years of age is summarised in the following table.

VIMCOSA must be taken twice a day, approximately 12 hours apart.

If a dose is missed, the patient should be instructed to take the missed dose immediately, and then to take the next dose of **VIMCOSA** at the regularly scheduled time. If the patient notices the missed dose within 6 hours of the next one, he/she should be instructed to wait to take the next dose of **VIMCOSA** at the regularly scheduled time. Patients should not take a double dose.

Adolescents, children and adults weighing 50 kg or more		
Starting dose	**Titration (Incremental steps)**	**Maximum recommended dose**
Monotherapy: 50 mg twice a day (100 mg/day) or 100 mg twice a day (200	50 mg twice a day (100 mg/day) at weekly intervals	**Monotherapy:** up to 300 mg twice a day (600 mg/day). **Adjunctive therapy:**

mg/day). **Adjunctive therapy:** 50 mg twice a day (100 mg/day)		up to 200 mg twice a day (400 mg/day)
Alternate initial dosage* (If applicable): 200 mg single loading dose followed by 100 mg twice a day (200 mg/day)		
*A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of **VIMCOSA** steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of serious cardiac arrhythmia and central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus.		

Children from 2 years of age and adolescents weighing less than 50 kg*

Starting dose	Titration (Incremental steps)	Maximum recommended dose
Monotherapy and Adjunctive therapy: 1 mg/kg twice a day (2 mg/kg/day)	1 mg/kg twice a day (2 mg/kg/day) at weekly intervals	**Monotherapy:** - up to 6 mg/kg twice a day (12 mg/kg/day) in patients ≥ 10 kg to < 40 kg - up to 5 mg/kg twice a day (10 mg/kg/day) in patients ≥ 40 kg to < 50 kg **Adjunctive therapy:** - up to 6 mg/kg twice a day (12 mg/kg/day) in patients ≥ 10 kg to < 20 kg - up to 5 mg/kg twice a day (10 mg/kg/day) in patients ≥ 20 kg to < 30 kg - up to 4 mg/kg twice a day (8 mg/kg/day) in patients ≥ 30 kg to < 50 kg

Adolescents and children weighing 50 kg or more, and adults

Monotherapy (in the treatment of partial-onset seizures)

The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/day) after one week.

VIMCOSA can also be initiated at the dose of 100 mg twice a day (200 mg/day) based on the physician's assessment of required seizure reduction versus potential side effects.

Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 300 mg twice a day (600 mg/day).

In patients having reached a dose greater than 200 mg twice a day (400 mg/day) and who need an additional antiepileptic medicinal product, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy (in the treatment of partial-onset seizures or in the treatment of primary generalised tonic-clonic seizures)

The recommended starting dose is 50 mg twice a day (100 mg/day) which should be increased to an initial therapeutic dose of 100 mg twice a day (200 mg/day) after one week.

Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended daily dose of 200 mg twice a day (400 mg/day).

Children from 2 years of age and adolescents weighing less than 50 kg

The dose is determined based on body weight.

Monotherapy (in the treatment of partial-onset seizures)

The recommended starting dose is 1 mg/kg twice a day (2 mg/kg/day) which should be increased to an initial therapeutic dose of 2 mg/kg twice a day (4 mg/kg/day) after one week.

Depending on response and tolerability, the maintenance dose can be further increased by 1 mg/kg twice a day (2 mg/kg/day) every week. The dose should be gradually increased until the optimum response is obtained.

The lowest effective dose should be used.

In children weighing from 10 kg to less than 40 kg, a maximum dose of up to 6 mg/kg twice a day (12 mg/kg/day) is recommended.

In children weighing from 40 to under 50 kg, a maximum dose of 5 mg/kg

twice a day (10 mg/kg/day) is recommended.

Adjunctive therapy (in the treatment of primary generalised tonic-clonic seizures from 4 years of age or in the treatment of partial-onset seizures from 2 years of age)

The recommended starting dose is 1 mg/kg twice a day (2 mg/kg/day) which should be increased to an initial therapeutic dose of 2 mg/kg twice a day (4 mg/kg/day) after one week.

Depending on response and tolerability, the maintenance dose can be further increased by 1 mg/kg twice a day (2 mg/kg/day) every week. The dose should be gradually adjusted until the optimum response is obtained.

The lowest effective dose should be used.

Due to an increased clearance compared to adults, in children weighing from 10 kg to less than 20 kg, a maximum dose of up to 6 mg/kg twice a day (12 mg/kg/day) is recommended. In children weighing from 20 to under 30 kg, a maximum dose of 5 mg/kg twice a day (10 mg/kg/day) is recommended and in children weighing from 30 to under 50 kg, a maximum dose of 4 mg/kg twice a day (8 mg/kg/day) is recommended, although in open-label studies (see sections 4.8 and 5.2), a dose up to 6 mg/kg twice a day (12 mg/kg/day) has been used by a small number of children from this latter group.

Initiation of VIMCOSA treatment with a loading dose (initial monotherapy or conversion to monotherapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of primary generalised tonic-clonic seizures).

In adolescents and children weighing 50 kg or more, and adults, **VIMCOSA** treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice a day (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of **VIMCOSA** steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of serious cardiac arrhythmia and central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus.

Discontinuation

If **VIMCOSA** has to be discontinued, it is recommended that the dose is reduced gradually in weekly decrements of 4 mg/kg/day (for patients with a body weight less than 50 kg) or 200 mg/day (for patients with a body weight of 50 kg or more) for patients who have achieved a dose of **VIMCOSA** ≥ 6 mg/kg/day or ≥ 300 mg/day, respectively. A slower taper in weekly decrements of 2 mg/kg/day or 100

mg/day can be considered, if medically necessary.

In patients who develop serious cardiac arrhythmia, clinical benefit/risk assessment should be performed and if needed **VIMCOSA** should be discontinued.

Special populations

Elderly (over 65 years of age)

No dose reduction is necessary in elderly patients. Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). There is limited clinical data in the elderly patients with epilepsy, particularly at doses greater than 400 mg/day (see sections 4.4,

4.8, and 5.1).

Renal impairment

No dose adjustment is necessary in mildly and moderately renally impaired adult and paediatric patients (CLCR > 30 ml/min). In paediatric patients weighing 50 kg or more and in adult patients with mild or moderate renal impairment a loading dose of 200 mg may be considered, but further dose titration (> 200 mg daily) should be performed with caution. In paediatric patients weighing 50 kg or more and in adult patients with severe renal impairment (CLCR ≤ 30 ml/min) or with end-stage renal disease, a maximum dose of 250 mg/day is recommended and the dose titration should be performed with caution. If a loading dose is indicated, an initial dose of 100 mg followed by a 50 mg twice daily regimen for the first week should be used. In paediatric patients weighing less than 50 kg with severe renal impairment (CLCR ≤ 30 ml/min) and in those with end-stage renal disease, a reduction of 25 % of the maximum dose is recommended. For all patients requiring haemodialysis a supplement of up to 50 % of the divided daily dose directly after the end of haemodialysis is recommended. Treatment of patients with end-stage renal disease should be made with caution as there is little clinical experience and accumulation of a metabolite (with no known pharmacological activity).

Hepatic impairment

A maximum dose of 300 mg/day is recommended for paediatric patients weighing 50 kg or more and for adult patients with mild to moderate hepatic impairment. The dose titration in these patients should be performed with caution considering co-existing renal impairment. In adolescents and adults weighing 50 kg or more, a loading dose of 200 mg may be considered, but further dose titration (> 200 mg daily) should be performed with caution. Based on data in adults, in paediatric patients

weighing less than 50 kg with mild to moderate hepatic impairment, a reduction of 25 % of the maximum dose should be applied. The pharmacokinetics of **VIMCOSA** has not been evaluated in severely hepatic impaired patients (see section 5.2).

VIMCOSA should be administered to adult and paediatric patients with severe hepatic impairment only when the expected therapeutic benefits are anticipated to outweigh the possible risks. The dose may need to be adjusted while carefully observing disease activity and potential side effects in the patient.

Paediatric population

VIMCOSA is not recommended for use in children below the age of 4 years in the treatment of primary generalized tonic-clonic seizures and below the age of 2 years in the treatment of partial-onset seizures as there is limited data on safety and efficacy in these age groups, respectively.

Loading dose

Administration of a loading dose has not been studied in children. Use of a loading dose is not recommended in adolescents and children weighing less than 50 kg.

Method of administration

For oral use.

VIMCOSA may be taken with or without food.

4.3 Contraindications

VIMCOSA is contraindicated:

- in patients with a history of hypersensitivity to the active substance or to any of the excipients listed in 6.1.
- Known second- or third-degree atrioventricular (AV) block.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicinal products in several indications. A meta-analysis of randomised placebo-controlled clinical studies of antiepileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the

possibility of an increased risk for **VIMCOSA**.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge (see section 4.8).

Cardiac rhythm and conduction

Dose-related prolongations in PR interval with **VIMCOSA** have been observed in clinical studies. **VIMCOSA** should be used with caution in patients with underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (e.g. myocardial ischaemia/ infarction, heart failure, structural heart disease or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blocking antiepileptic medicinal products (see section 4.5), as well as in elderly patients. In these patients it should be considered to perform an ECG before a **VIMCOSA** dose increase above 400 mg/day and after **VIMCOSA** is titrated to steady-state.

In the placebo-controlled clinical studies of **VIMCOSA** in epilepsy patients, atrial fibrillation or flutter were not reported; however, both have been reported in open-label epilepsy studies and in post-marketing experience.

In post-marketing experience, AV block (including second degree or higher AV block) has been reported. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been reported. In rare cases, these events have led to asystole, cardiac arrest and death in patients with underlying proarrhythmic conditions.

Patients should be made aware of the symptoms of cardiac arrhythmia (e.g. slow, rapid or irregular pulse, palpitations, shortness of breath, feeling lightheaded, fainting). Patients should be counselled to seek immediate medical advice if these symptoms occur.

Dizziness

Treatment with **VIMCOSA** has been associated with dizziness which could increase the occurrence of accidental injury or falls. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicine (see section 4.8).

Potential for new onset or worsening of myoclonic seizures

New onset or worsening of myoclonic seizures has been reported in both adult and paediatric patients with PGTCS, in particular during titration. In patients with more than one seizure type, the observed benefit of control for one seizure type should be weighed against any observed worsening in another seizure type.

Potential for electro-clinical worsening in specific paediatric epilepsy syndromes

The safety and efficacy of **VIMCOSA** in paediatric patients with epilepsy syndromes in which focal and generalised seizures may coexist have not been determined.

4.5 Interaction with other medicines and other forms of interaction

VIMCOSA should be used with caution in patients treated with medicines known to be associated with PR prolongation (including sodium channel blocking antiepileptic medicinal products) and in patients treated with antiarrhythmics. However, subgroup analysis in clinical studies did not identify an increased magnitude of PR prolongation in patients with concomitant administration of carbamazepine or lamotrigine.

***In vitro* data**

Data generally suggest that **VIMCOSA** has a low interaction potential. In vitro studies indicate that the enzymes CYP1A2, CYP2B6, and CYP2C9 are not induced and that CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP2E1 are not inhibited by **VIMCOSA** at plasma concentrations observed in clinical studies. An *in vitro* study indicated that **VIMCOSA** is not transported by P-glycoprotein in the intestine. *In vitro* data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite.

***In vivo* data**

VIMCOSA does not inhibit or induce CYP2C19 and CYP3A4 to a clinically relevant extent. **VIMCOSA** did not affect the AUC of midazolam (metabolised by CYP3A4, **VIMCOSA** given 200 mg twice a day), but C_{max} of midazolam was slightly increased (30 %). **VIMCOSA** did not affect the pharmacokinetics of omeprazole (metabolised by CYP2C19 and CYP3A4, **VIMCOSA** given 300 mg twice a day).

The CYP2C19 inhibitor omeprazole (40 mg once daily) did not give rise to a clinically significant change in **VIMCOSA** exposure. Thus, moderate inhibitors of CYP2C19 are unlikely to affect systemic

VIMCOSA exposure to a clinically relevant extent.

Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (e.g. fluconazole) and CYP3A4 (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead to increased systemic exposure of **VIMCOSA**. Such interactions have not been established *in vivo*, but are possible based on *in vitro* data.

Strong enzyme inducers such as rifampicin or St John's wort (*Hypericum perforatum*) may moderately reduce the systemic exposure of **VIMCOSA**. Therefore, starting or ending treatment with these enzyme inducers should be done with caution.

Antiepileptic medicines

In interaction studies **VIMCOSA** did not significantly affect the plasma concentrations of carbamazepine and valproic acid. **VIMCOSA** plasma concentrations were not affected by carbamazepine and by valproic acid. Population pharmacokinetic analyses in different age groups estimated that concomitant treatment with other antiepileptic medicinal products known to be enzyme inducers (carbamazepine, phenytoin, phenobarbital, in various doses) decreased the overall systemic exposure of **VIMCOSA** by 25 % in adults and 17 % in paediatric patients.

Oral contraceptives

In an interaction study there was no clinically relevant interaction between **VIMCOSA** and the oral contraceptives ethinylestradiol and levonorgestrel. Progesterone concentrations were not affected when the medicinal products were co-administered.

Others

Interaction studies showed that **VIMCOSA** had no effect on the pharmacokinetics of digoxin. There was no clinically relevant interaction between **VIMCOSA** and metformin.

Co-administration of warfarin with **VIMCOSA** does not result in a clinically relevant change in the pharmacokinetics and pharmacodynamics of warfarin.

Although no pharmacokinetic data on the interaction of **VIMCOSA** with alcohol are available, a pharmacodynamic effect cannot be excluded.

VIMCOSA has a low protein binding of less than 15 %. Therefore, clinically relevant interactions with other medicines through competition for protein binding sites are considered unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

VIMCOSA should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding

VIMCOSA is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. It is recommended that breast-feeding should be discontinued during treatment with **VIMCOSA**.

Fertility

No adverse reactions on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the maximum recommended human dose (MHRD).

4.7 Effects on ability to drive and use machines

VIMCOSA has minor to moderate influence on the ability to drive and use machines. **VIMCOSA** treatment has been associated with dizziness or blurred vision. Accordingly, patients should be advised not to drive or to operate other potentially hazardous machinery until they are familiar with the effects of **VIMCOSA** on their ability to perform such activities.

4.8 Undesirable effects

Summary of the safety profile

Based on the analysis of pooled placebo-controlled clinical studies in adjunctive therapy in 1,308 patients with partial-onset seizures, a total of 61.9 % of patients randomised to **VIMCOSA** and 35.2 % of patients randomised to placebo reported at least 1 adverse reaction. The most frequently reported adverse reactions (≥ 10 %) with **VIMCOSA** treatment were dizziness, headache, nausea and diplopia. They were usually mild to moderate in intensity. Some were dose related and could be alleviated by reducing the dose. Incidence and severity of central nervous system (CNS) and gastrointestinal (GI) adverse reactions usually decreased over time.

Tabulated summary of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Blood and lymphatic system disorders			Agranulocytosis
Immune system disorders		Drug hypersensitivity	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Psychiatric disorders	Depression, confusional state, insomnia	Aggression, agitation, euphoric mood, psychotic disorder, suicide attempt, suicidal ideation, hallucination	

Nervous system disorders	Dizziness, headache, myoclonic seizures, Ataxia, Balance disorder, memory impairment, cognitive disorder, somnolence, tremor, nystagmus, hypoesthesia, dysarthria, disturbance in attention, paraesthesia	Syncope, co-ordination abnormal, dyskinesia	convulsion
Eye disorders	Diplopia, Vision blurred		
Ear and labyrinth disorders	Vertigo, tinnitus		
Cardiac disorders		Atrioventricular block, bradycardia, atrial fibrillation, atrial flutter	Ventricular tachyarrhythmia

Gastrointestinal disorders	Nausea, vomiting, constipation, flatulence, dyspepsia, dry mouth, diarrhoea		
Hepatobiliaryd isorders		Liver function test abnormal, hepatic enzyme increased (> 2x ULN)	
Skin and subcutaneous tissue disorders	Pruritis, rash	Angioedema, urticaria	Steven's Johnson syndrome, Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Muscle spasms		
General disorders and administration site conditions	Gait disturbance, asthenia, fatigue, irritability, feeling drunk		
Injury, poisoning and procedural	Fall, skin laceration, confusion		

complications			

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

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

4.9 Overdose

Symptoms:

Symptoms observed after an accidental or intentional overdose of **VIMCOSA** are primarily associated with CNS and gastrointestinal system.

▪ The types of adverse reactions experienced by patients exposed to doses above 400 mg up to 800 mg were not clinically different from those of patients administered recommended doses of **VIMCOSA.**

▪ Reactions reported after an intake of more than 800 mg are dizziness, nausea, vomiting, seizures (generalised tonic clonic seizures, status epilepticus). Cardiac conduction disorders, shock and coma have also been observed. Fatalities have been reported in patients following an intake of acute single overdose of several grams of **VIMCOSA.**

Management

There is no specific antidote for overdose with **VIMCOSA**. Treatment of **VIMCOSA** overdose should include general supportive measures and may include haemodialysis if necessary (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: antiepileptics, other antiepileptics,

ATC code: N03AX18

Mechanism of action

The active substance, **VIMCOSA** (R-2-acetamido-N-benzyl-3-methoxypropionamide) is a functionalised amino acid.

The precise mechanism by which **VIMCOSA** exerts its antiepileptic effect in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that **VIMCOSA** selectively enhances slow inactivation of voltage- gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Pharmacodynamic effects

VIMCOSA protected against seizures in a broad range of animal models of partial and primary generalised seizures and delayed kindling development. In non-clinical experiments VIMCOSA in combination with levetiracetam, carbamazepine, phenytoin, valproate, lamotrigine, topiramate or gabapentin showed synergistic or additive anticonvulsant effects.

5.2 Pharmacokinetic properties

Absorption

VIMCOSA is rapidly and completely absorbed after oral administration. The oral bioavailability of **VIMCOSA** tablets is approximately 100 %. Following oral administration, the plasma concentration of unchanged **VIMCOSA** increases rapidly and reaches Cmax about 0.5 to 4 hours post-dose. Vimpat tablets and oral syrup are bioequivalent. Food does not affect the rate and extent of absorption.

Distribution

The volume of distribution is approximately 0.6 L/kg**. VIMCOSA** is less than 15 % bound to plasma proteins.

Biotransformation

95 % of the dose is excreted in the urine as **VIMCOSA** and metabolites. The metabolism of **VIMCOSA** has not been completely characterised.

The major compounds excreted in urine are unchanged **VIMCOSA** (approximately 40 % of the dose) and its Odesmethyl metabolite less than 30 %.

A polar fraction proposed to be serine derivatives accounted for approximately 20 % in urine, but was detected only in small amounts (0-2 %) in human plasma of some subjects. Small amounts (0.5-2 %) of additional metabolites were found in the urine.

In vitro data show that CYP2C9, CYP2C19 and CYP3A4 are capable of catalysing the formation of the O-desmethyl metabolite but the main contributing isoenzyme has not been confirmed *in vivo*. No clinically relevant difference in **VIMCOSA** exposure was observed comparing its pharmacokinetics in extensive metabolisers (EMs, with a functional

CYP2C19) and poor metabolisers (PMs, lacking a functional CYP2C19).

Furthermore, an interaction study with omeprazole (CYP2C19-inhibitor) demonstrated no clinically relevant changes in **VIMCOSA** plasma concentrations indicating that the importance of this pathway is minor. The plasma concentration of O-desmethyl-**VIMCOSA** is approximately 15 % of the concentration of **VIMCOSA** in plasma. This major metabolite has no known pharmacological activity.

Elimination:

VIMCOSA is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of radiolabeled **VIMCOSA**, approximately 95 % of radioactivity administered was recovered in the urine and less than 0.5 % in the faeces. The elimination half-life of **VIMCOSA** is approximately 13 hours. The pharmacokinetics is dose-proportional and constant over time, with low intra- and inter-subject variability. Following twice daily dosing, steady state plasma concentrations are achieved after a 3 day period. The plasma concentration increases with an accumulation factor of approximately 2.

A single loading dose of 200 mg approximates steady-state concentrations comparable to 100 mg twice daily oral administration.

Gender:

Clinical studies indicate that gender does not have a clinically significant influence on the plasma concentrations of **VIMCOSA.**

Renal impairment:

The AUC of **VIMCOSA** was increased by approximately 30 % in mildly and moderately and 60 % in

severely renal impaired patients and patients with end-stage renal disease requiring haemodialysis compared to healthy subjects, whereas Cmax was unaffected.

VIMCOSA is effectively removed from plasma by haemodialysis. Following a 4-hour haemodialysis treatment, AUC of **VIMCOSA** is reduced by approximately 50 %. Therefore, dosage supplementation following haemodialysis is recommended (see section 4.2). The exposure of the O-desmethyl metabolite was several-fold increased in patients with moderate and severe renal impairment. In absence of haemodialysis in patients with end-stage renal disease, the levels were increased and continuously rising during the 24-hour sampling. It is unknown whether the increased metabolite exposure in end-stage renal disease subjects could give rise to adverse effects but no pharmacological activity of the metabolite has been identified.

Hepatic impairment:

Subjects with moderate hepatic impairment (Child-Pugh B) showed higher plasma concentrations of **VIMCOSA** (approximately 50 % higher AUCnorm). The higher exposure was partly due to a reduced renal function in the studied subjects. The decrease in non-renal clearance in the patients of the study was estimated to give a 20 % increase in the AUC of **VIMCOSA.** The pharmacokinetics of **VIMCOSA** has not been evaluated in severe hepatic impairment (see section 4.2).

Elderly (over 65 years of age):

In a study in elderly men and women including 4 patients > 75 years of age, AUC was about 30 and 50 % increased compared to young men, respectively. This is partly related to lower body weight. The body weight normalized difference is 26 and 23 %, respectively. An increased variability in exposure was also observed. The renal clearance of **VIMCOSA** was only slightly reduced in elderly subjects in this study.

A general dose reduction is not considered to be necessary unless indicated due to reduced renal function (see section 4.2).

Paediatric population:

The paediatric pharmacokinetic profile of **VIMCOSA** was determined in a population pharmacokinetic analysis using sparse plasma concentration data obtained in six placebo-controlled randomised clinical studies and five open-label studies in 1655 adult and paediatric patients with epilepsy aged 1 month to

17 years. Three of these studies were performed in adults, 7 in pediatric patients, and 1 in a mixed population. The administered **VIMCOSA** doses ranged from 2 to 17.8 mg/kg/day in twice daily intake, not to exceed 600 mg/day.

The typical plasma clearance was estimated to be 0.46 L/h, 0.81 L/h, 1.03 L/h and 1.34 L/h for paediatric patients weighing 10 kg, 20 kg, 30 kg and 50 kg respectively. In comparison, plasma clearance was estimated at 1.74 L/h in adults (70 kg body weight).

Population pharmacokinetic analysis using sparse pharmacokinetic samples from PGTCS study showed a similar exposure in patients with PGTCS and in patients with partial-onset seizures.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Crospovidone Type A

Colloidal silicon dioxide

Low substituted hydroxypropyl cellulose

Hydroxy propyl cellulose

Magnesium stearate

Tablet coat

Opadry II Pink, Opadry II Yellow, Opadry II Beige, Opadry II Blue

Film-coat: HPMC 2910/Hypromellose (6mPas) (E 464), HPMC 2910/Hypromellose (15mPas) (E 464), polyvinyl alcohol – part hydrolyzed, talc (E 553b), titanium dioxide (E171), Macrogol/PEG (MW 3350, Macrogol 4000), Lecithin (Soya)

Colourants*

*** The colourants are:**

50 mg tablet: red iron oxide (E172), black iron oxide (E172),

100 mg tablet: yellow iron oxide (E172).

150 mg tablet: yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172).

200 mg tablet: indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years for blister pack.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Do not store in a refrigerator.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Packs of 14, 28, 30, 56, 98 and 168 film-coated tablets in PVC/PVDC blister sealed with an aluminium foil.

Packs of 14 x 1 and 56 x 1 film-coated tablets in PVC/PVDC perforated unit dose blisters sealed with an aluminium foil.

Packs of 60 film-coated tablets in HDPE bottle with a child-resistant closure.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE, BASSONIA ROCK EXT 12

ALBERTON, SOUTH AFRICA

8. REGISTRATION NUMBERS

VIMCOSA 50 mg: 57/2.5 /0717.713

VIMCOSA 100 mg: 57/2.5 /0718.714

VIMCOSA 150 mg: 57/2.5 /0719.715

VIMCOSA 200 mg: 57/2.5 /0720.716

9. DATE OF FIRST AUTHORISATION

To be inserted

10. DATE OF REVISION OF THE TEXT

To be advised