SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

OXCARBAZEPINE 150 VIATRIS film-coated tablets

OXCARBAZEPINE 300 VIATRIS film-coated tablets

OXCARBAZEPINE 600 VIATRIS film-coated tablets

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each film-coated tablet contains 150 mg, 300 mg or 600 mg oxcarbazepine.

Contains sugar (lactose monohydrate 1,23 mg, 2,46 mg or 4,92 mg)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

OXCARBAZEPINE 150 VIATRIS: 5,5 mm x 11,0 mm oblong, normal convex, buff film-coated tablet debossed “OX I 150” on one side and “G I G” on the other side.

OXCARBAZEPINE 300 VIATRIS: 6,5 mm x 15,0 mm oblong, normal, convex, buff film-coated tablet debossed “OX I 300” on one side and “G I G” on the other side.

OXCARBAZEPINE 600 VIATRIS: 8,0 mm x 18, 5 mm oblong, normal, convex, buff film-coated tablet debossed “OX I 600” on one side and “G I G” on the other side.

Note: The tablets have a scoreline to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OXCARBAZEPINE VIATRIS is indicated for the treatment of partial seizures with or without secondary generalised seizures and generalised tonic-clonic seizures.

OXCARBAZEPINE VIATRIS is suitable both for use in monotherapy and for use in combination with other anti-epileptic medicines in adults and children from the age of 6 years and older.

4.2 Posology and method of administration

Posology

Both in mono- and combination therapy, the treatment with OXCARBAZEPINE VIATRIS is started with a clinically effective dose divided into two administrations.

The dose may be increased, depending on the patient's clinical response.

If other anti-epileptic medicines (AEMs) are replaced by OXCARBAZEPINE VIATRIS, the dose of the other anti-epileptic medicines should be reduced gradually while the therapy with OXCARBAZEPINE VIATRIS is being started. In cases of adjunct therapy, it may be necessary to lower the dose of the other anti-epileptic medicines and/or increase the dose of OXCARBAZEPINE VIATRIS more slowly on account of an increased total amount of anti-epileptic medicines (see section 4.5).

OXCARBAZEPINE VIATRIS can be taken with or without food.

Therapeutic drug monitoring

The therapeutic effect of oxcarbazepine is primarily exerted through the active metabolite 10-monohydroxy derivative (MHD) of oxcarbazepine (see section 5).

Plasma level monitoring of oxcarbazepine or MHD is not routinely warranted. However, may be useful in situations where an alteration in MHD clearance is to be expected (see section 4.4).

If any of these situations apply, the dose of OXCARBAZEPINE VIATRIS may be adjusted (based on plasma levels measured 2 - 4 hours post dose) to maintain peak MHD plasma levels < 35 mg/litre.

Adults:

Monotherapy

Recommended initial dose

OXCARBAZEPINE VIATRIS should be started with a dose of 600 mg/day (8 – 10 mg/kg/day) divided into 2 doses.

Maintenance dose

If clinically indicated, the dose may be increased from the initial dose in increments of a maximum of 600 mg/day at intervals of approximately a week until the desired clinical response is achieved. The therapeutic effects are achieved with doses between 600 mg/day and 2400 mg/day.

Maximum recommended dose

Under controlled hospitalised conditions, dose increases up to 2400 mg/day over 48 hours have taken place. Most adult patients are controlled on dosages of 900 - 1200 mg/day.

Adjunctive therapy:

Recommended initial dose

OXCARBAZEPINE VIATRIS should be started with a dose of 600 mg/day (8 – 10 mg/kg/day) divided into two doses.

Maintenance dose

If clinically indicated, the dose may be increased from the initial dose in increments of a maximum of 600 mg/day at intervals of approximately a week until the desired clinical

response is achieved. Therapeutic effects are achieved with doses between 600 mg/day and 2400 mg/day.

Maximum recommended dose

Daily doses of 600 to 2400 mg/day have been shown to be effective in studies with controlled adjunctive therapy, although most patients were not able to tolerate the dose of 2400 mg/day without a reduction of the other anti-epileptics. This is mainly due to the occurrence of adverse events affecting the central nervous system.

Daily doses above 2400 mg/day have not been studied systematically in clinical trials.

Elderly (65 years or above):

An adjustment of the dosage is recommended in elderly patients based on decreased renal function. Close monitoring of sodium levels is required in patients at risk of hyponatraemia (see section 4.4).

Children:

Recommended initial dose

In mono- and adjunctive therapy OXCARBAZEPINE VIATRIS should be started with a dose of 8 – 10 mg/kg/day divided into 2 doses.

Maintenance dose

The target maintenance dose of OXCARBAZEPINE VIATRIS for adjunctive therapy is 30 - 46 mg/kg/day and should be achieved over two weeks.

Therapeutic effects are seen with a median maintenance dose of approximately 30 mg/kg/day.

Maximum recommended dose

If clinically indicated, the dose may be increased from the initial dose in increments of a maximum of 10 mg/kg/day at intervals of approximately a week up to a maximum dose of 46 mg/kg/day in order to achieve the desired clinical response.

Safety of OXCARBAZEPINE VIATRIS has not been established in children below 6 years of age.

Patients with hepatic impairment:

In patients with mild to moderate hepatic impairment an adjustment of the dose is not necessary. OXCARBAZEPINE VIATRIS has not been studied in patients with severe hepatic impairment; caution should therefore be exercised in patients with severe impairment of liver function (see section 5.2).

Patients with renal impairment:

In patients with impaired renal function (creatinine clearance less than 30 ml/min), the therapy with OXCARBAZEPINE VIATRIS should be initiated with half the normal starting dose (300 mg/day). This dose should be increased slowly at intervals of at least a week until the desired clinical response is achieved (see section 5.2).
It may be necessary to monitor the increase in dosage more carefully in patients with renal impairment.

Method of administration

OXCARBAZEPINE VIATRIS must only be used in children who are able to swallow tablets. If they are unable to swallow tablets an oral suspension must be used.

4.3 Contraindications

Known hypersensitivity to oxcarbazepine or eslicarbazepine or to any of the excipients.

4.4 Special warnings and precautions for use

Hypersensitivity:

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been reported. Cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of OXCARBAZEPINE VIATRIS. If a patient develops these reactions after treatment with OXCARBAZEPINE VIATRIS, the medicine should be discontinued and an alternative treatment started.

Patients who develop hypersensitivity reactions to carbamazepine should be informed that they have an approximately 25 - 30 % chance of hypersensitivity reactions (e.g. severe skin reactions) with OXCARBAZEPINE VIATRIS (see section 4.8).

Hypersensitivity reactions, including multi-organ hypersensitivity reactions, may also occur in patients without a history of hypersensitivity to carbamazepine. Such reactions can affect the skin, liver, blood and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see section 4.8).
If signs and symptoms suggestive of hypersensitivity reactions (e.g. severe skin reactions) occur, the administration of OXCARBAZEPINE VIATRIS should be withdrawn immediately.

Dermatological effects:

Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome) and erythema multiforme, have been reported in association with the use of OXCARBAZEPINE VIATRIS. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and very rarely be

fatal. OXCARBAZEPINE VIATRIS associated cases occurred in both children and adults. The median time to onset was 19 days. Several isolated cases of recurrence of the serious skin reaction when rechallenged with OXCARBAZEPINE VIATRIS were reported.
Should a patient develop a skin reaction with OXCARBAZEPINE VIATRIS, consideration should be given to discontinuing OXCARBAZEPINE VIATRIS and prescribing another anti-epileptic medicine.

Patients should be made aware of early toxic signs of the above-mentioned reactions, e.g. fever, rash, lesions in the mouth, bruising, purpura. They should be advised to contact their doctor immediately if such a reaction appears.

Risk of seizure aggravation:
Risk of seizure aggravation has been reported with OXCARBAZEPINE VIATRIS. The risk of seizure aggravation is seen especially in children but may also occur in adults. In case of seizure aggravation, OXCARBAZEPINE VIATRIS should be discontinued.

Hyponatraemia:
Serum sodium concentrations below 125 mmol/l, which are mostly asymptomatic and do not require an adjustment of the therapy, have been confirmed in 2,7 % of the patients who were treated with oxcarbazepine. Experience with clinical trials shows that the sodium level recovered after the oxcarbazepine dose was reduced, was stopped, or after the patient was treated conservatively (e.g. restricted fluid intake). It is recommended that the sodium level in the serum be monitored before the beginning of treatment and during treatment in the following cases: patients with pre-existing renal abnormalities associated with a low sodium value, patients receiving concomitant treatment with sodium-lowering medicines (e.g. diuretics, desmopressin) and NSAIDs (e.g indomethacin). The sodium level in the serum

should be measured after about two weeks, and subsequently at monthly intervals during the first three months of treatment, or otherwise in accordance with clinical need.
These risk factors can apply particularly for older patients. For patients who are stabilised on OXCARBAZEPINE VIATRIS and begin with sodium-lowering medicines, the same approach for measurement of the sodium value may be followed. In general, if clinical symptoms occur that may indicate hyponatraemia during treatment with OXCARBAZEPINE VIATRIS, measurement of the serum sodium level may be considered. In other patients the serum sodium level may be measured as part of the routine laboratory tests.

All patients with cardiac insufficiency and secondary heart failure should have regular weight measurements to determine occurrence of fluid retention. In case of fluid retention or worsening of the cardiac condition, serum sodium levels should be checked. If hyponatraemia is observed, water restriction is an important counter-measurement. As OXCARBAZEPINE VIATRIS may, less frequently, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. atrioventricular-block, arrhythmia) should be followed carefully.

Hypothyroidism:
Hypothyroidism is an adverse reaction (with “less frequent” frequency, see section 4.8). Considering the importance of thyroid hormones in children's development after birth, thyroid function monitoring is recommended in the paediatric age group while on OXCARBAZEPINE VIATRIS therapy.

Hepatic function:
Cases of hepatitis have been reported less frequently, which in most of the cases resolved favourably. When a hepatic event is suspected, liver function should be evaluated and

discontinuation of OXCARBAZEPINE VIATRIS should be considered. Caution should be exercised when treating patients with severe hepatic impairment (see section 4.2 and 5.2).

Renal function:

In patients with impaired renal function (creatinine clearance less than 30 ml/min), caution should be exercised during OXCARBAZEPINE VIATRIS treatment especially with regard to the starting dose and up titration of the dose. Plasma level monitoring of MHD may be considered (see section 4.2 and 5.2).

Haematological effects:

Agranulocytosis, aplastic anaemia and pancytopenia have been seen in patients treated with OXCARBAZEPINE VIATRIS (see section 4.8). However, due to the very low incidence of these conditions and confounding factors (e.g. underlying disease, concomitant medication), causality cannot be established.

If during treatment, low or decreased white blood cell or platelet counts are observed, the patient and the complete blood count should be monitored closely. OXCARBAZEPINE VIATRIS should be discontinued if any evidence of significant bone-marrow depression appears.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicines, including OXCARBAZEPINE VIATRIS, has shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.

Therefore, patients should be monitored for signs of suicidal ideation and behaviour 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.

Hormonal contraceptives:

Female patients of childbearing age should be warned that the concurrent use of OXCARBAZEPINE VIATRIS and hormonal contraceptives may render the latter ineffective (see section 4.5). Additional non-hormonal forms of contraception are recommended when OXCARBAZEPINE VIATRIS is used.

Alcohol:

Patients treated with OXCARBAZEPINE VIATRIS should abstain from alcohol on account of a possible additive sedative effect.

Withdrawal:

OXCARBAZEPINE VIATRIS should be withdrawn gradually to minimise the potential of increased seizure frequency. If OXCARBAZEPINE VIATRIS has to be discontinued abruptly, e.g. owing to severe adverse reactions, the change-over to another anti-epileptic preparation should be affected under cover of suitable medication (e.g. diazepam i.v., rectal; phenytoin i.v.) and under close supervision.

OXCARBAZEPINE VIATRIS should be given only under medical supervision.

Monitoring of plasma levels

Although correlations between dosage and plasma levels of oxcarbazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following situations in order to rule out noncompliance or in situations where an alteration in MHD clearance is to be expected, including:

• changes in renal function (see renal impairment in section 4.2).

• pregnancy (see sections 4.6).

• concomitant use of liver enzyme-inducing medicines (see section 4.5).

Elderly patients should be carefully monitored as they are at higher risk of adverse reactions (see section 5.2).

4.5 Interaction with other medicines and other forms of Interaction

Enzyme inhibition:

Oxcarbazepine, as OXCARBAZEPINE VIATRIS, has been studied in human liver microsomes in order to determine its capacity to inhibit the major P450 cytochromes, which are responsible for the metabolism of other medicines.

The results show that oxcarbazepine and its pharmacologically active metabolite (the monohydroxy derivative, MHD) inhibit CYP2C19. Therefore, interactions may occur if high doses of OXCARBAZEPINE VIATRIS are administered concomitantly with medicines that are metabolised by CYP2C19 (e.g. phenobarbitone, phenytoin, see below). In some patients treated with OXCARBAZEPINE VIATRIS and medicines that are metabolised by CYP219 a reduction of the co-administered medicine may be necessary. In human liver microsomes oxcarbazepine and MHD have little or no capacity to function as inhibitors of the following enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11.

Enzyme induction:

Oxcarbazepine and MHD induce *in vitro* and *in vivo* the cytochromes CYP3A4 and CYP3A5, which are responsible for the metabolism of dihydropyridine calcium antagonists, oral contraceptives and anti-epileptics (e.g. carbamazepine). This can result in lowered plasma concentration of these medicines (see below). Such level of decrease in plasma concentrations may also be observed in other medicines mainly metabolised by CYP3A4 and CYP3A5, for example immunosuppressants (e.g. ciclosporin).

In vitro, MHD is a weak inducer of UDP-glucuronyl transferase. As a result, it is unlikely *in vivo* that it has an effect on medicines that are mainly excreted by conjugation via UDP-glucuronyl transferases (e.g valproic acid, lamotrigine). Even in view of the weak induction potential of OXCARBAZEPINE VIATRIS and MHD, a higher dose of concomitantly used medicines which are metabolised via CYP3A4 or via conjugation (UDPGT) may be necessary. In the event of discontinuation of the OXCARBAZEPINE VIATRIS therapy a reduction in the dose of the co-medication may be necessary.

In induction studies carried out with human hepatocytes it was confirmed that oxcarbazepine and MHD are weak inducers of isoenzymes of the 2B and 3A4 CYP. The ability of oxcarbazepine/MHD to induce other isoenzymes is not known.

Anti-epileptic medicines:

Possible interactions between OXCARBAZEPINE VIATRIS and other anti-epileptic medicines (AEMs) have been studied in clinical trials. The effect of these interactions on the mean AUCs and C_{min} are summarised in the following table:

Summary of interactions between OXCARBAZEPINE VIATRIS and anti-epileptic medicines

Co-administered anti-epileptic medicine	Influence of OXCARBAZEPINE VIATRIS on the concentration of the AEM	Influence of AEM on the MHD concentration
Carbamazepine	0 – 22 % reduction (30 % increase of carbamazepine-epoxide)	40 % reduction
Clobazam	Not studied	No influence

Felbamate	Not studied	No influence
Phenobarbitone	14 – 15 % increase	30 – 31 % reduction
Phenytoin	0 – 40 % increase	29 – 35 % reduction
Valproic acid	No influence	0 – 18 % reduction

In vivo the plasma levels of phenytoin increased by up to 40 % when OXCARBAZEPINE VIATRIS was given in doses higher than 1200 mg/day. It may therefore be necessary during adjunctive therapy with OXCARBAZEPINE VIATRIS doses higher than 1200 mg/day to reduce the phenytoin dose.

The increase in the level of phenobarbitone is limited (15 %) when this medicine is given in combination with OXCARBAZEPINE VIATRIS.

Strong inducers of cytochrome P450 enzymes and/or UGT (such as rifampicin, carbamazepine, phenytoin and phenobarbitone) have led to reduced plasma concentrations of MHD (29 – 40 %).

No auto-induction has been observed with OXCARBAZEPINE VIATRIS.

Hormonal contraceptives:

OXCARBAZEPINE VIATRIS has been shown to influence two components of oral contraceptives: ethinyloestradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE and LNG were reduced by 48 – 52 % and 32 – 52 % respectively. No studies have been carried out with other oral or implantation contraceptives. Therefore, the concomitant use of OXCARBAZEPINE VIATRIS and hormonal contraceptives may render the latter ineffective (see section 4.4).

Calcium antagonists:

After repeated concomitant use with OXCARBAZEPINE VIATRIS the AUC values of felodipine were reduced by 28 %. Despite this, the plasma concentration remained within the recommended therapeutic range.

Verapamil lowered the plasma concentration of MHD by 20 %. This reduction of the plasma MHD was not considered clinically relevant.

Other medicine interactions:

Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD, while viloxazine caused a slight alteration in the plasma concentration of MHD (approximately 10 % higher after repeated concomitant administration). The results with warfarin provide no evidence of interactions with single or repeated doses of OXCARBAZEPINE VIATRIS.

The use of OXCARBAZEPINE VIATRIS in combination with monoamine oxidase inhibitors (MAOIs) is not recommended. Before administering OXCARBAZEPINE VIATRIS, MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits.

The combination of lithium and OXCARBAZEPINE VIATRIS might cause enhanced neurotoxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy has not been established.

Data from a limited number of pregnancies indicate that OXCARBAZEPINE VIATRIS can cause serious congenital malformations (e.g. cleft palate) when it is used during pregnancy.

In animal studies, increased embryo mortality, delayed growth and malformations were observed.

Taking these data into consideration:

- If women being treated with OXCARBAZEPINE VIATRIS become pregnant, plan to become pregnant or if starting treatment with OXCARBAZEPINE VIATRIS during pregnancy is considered necessary, the possible benefits of the medicine must be carefully weighed against the possible risk of foetal malformations (e.g. cleft palate). This is particularly important during the first three months of pregnancy.
- Minimum effective doses should be given.
- In women of childbearing age OXCARBAZEPINE VIATRIS should be administered as monotherapy if possible. Patients should be informed of the possibility of an increased risk of malformations, and they must be offered the chance of antenatal screening.
- During pregnancy, anti-epileptic treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention:

Anti-epileptic medicines such as OXCARBAZEPINE VIATRIS may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy.

Due to physiological changes during pregnancy, plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxyderivative (MHD), may gradually decrease throughout pregnancy. It is recommended that clinical response should be monitored carefully in women receiving OXCARBAZEPINE VIATRIS treatment during pregnancy and determination of changes in MHD plasma concentrations should be considered to ensure that adequate seizure control is maintained throughout pregnancy. Postpartum MHD plasma levels may

also be considered for monitoring especially in the event that medication was increased during pregnancy.

In the newborn child:

Abnormal bleeding caused by anti-epileptic substances such as OXCARBAZEPINE VIATRIS has been reported in neonates. As a precaution, vitamin K1 should be administered in the last few weeks of pregnancy and to the neonate.

OXCARBAZEPINE VIATRIS and its active metabolite MHD cross the placenta. Neonatal and maternal plasma MHD concentrations were comparable in one case.

Lactation:

Oxcarbazepine and its active metabolite MHD pass into breast milk. The ratio of the concentrations in milk and plasma is 0,5 for the two compounds. The effect on the infant exposed to OXCARBAZEPINE VIATRIS in this way is unknown. Therefore OXCARBAZEPINE VIATRIS should not be given during breastfeeding.

Infertility:

There are no human data on fertility.

In rats, fertility in both sexes was unaffected by oxcarbazepine or MHD at oral doses up to 150 and 450 mg/kg/day, respectively. However, disruption of oestrous cyclicity and reduced numbers of corpora lutea, implantations and live embryos were observed in female animals at the highest dose of MHD.

4.7 Effects on ability to drive and use machines

The use of OXCARBAZEPINE VIATRIS is associated with adverse events such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatraemia and depressed level of consciousness were reported with OXCARBAZEPINE VIATRIS (for the

complete list of Undesirable effects, see section 4.8), especially at the start of treatment or in connection with dose adjustments (more frequently during the up-titration phase). Patients should therefore be informed that their physical and mental abilities required for operating machinery or driving a vehicle might be impaired.

4.8 Undesirable effects

The most commonly reported adverse reactions are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue occurring in more than 10 % of patients. In clinical trials, adverse events (AEs) were generally mild to moderate in severity, of transient nature and occurred predominantly at the start of treatment.

The safety profile is based on adverse events (AEs) from clinical trials assessed as related to oxcarbazepine. In addition, clinically meaningful reports on adverse experiences from named patient programs and post-marketing experience were taken into account.

Blood and lymphatic system disorders	
Less frequent	Leucopenia, bone marrow depression, aplastic anaemia, agranulocytosis, pancytopenia, thrombocytopenia, neutropenia.
Immune system disorders	
Less frequent	Anaphylactic reactions, hypersensitivity.[#]
Endocrine disorders	
Frequent	Weight increased.
Less frequent	Hypothyroidism.
Metabolism and nutrition disorders	
Frequent	Hyponatraemia.[†]

Less frequent	Inappropriate ADH secretion like syndrome with signs and symptoms of lethargy, nausea, dizziness, decrease in serum (blood) osmolality, vomiting, headache, confusional state or other neurological signs and symptoms.
Psychiatric disorders	
Frequent	Agitation (e.g. nervousness), affect lability, confusional state, depression, apathy.
Nervous system disorders	
Frequent	Somnolence, headache, dizziness, ataxia, tremor, nystagmus, disturbance in attention, amnesia. Speech disorders (including dysarthria); more frequent during up titration of OXCARBAZEPINE VIATRIS dose.
Eye disorders	
Frequent	Diplopia, vision blurred, visual disturbance.
Ear and labyrinth disorders	
Frequent	Vertigo.
Cardiac disorders	
Less frequent	Atrioventricular block, arrhythmia.
Vascular disorders	
Less frequent	Hypertension.
Gastrointestinal disorders	
Frequent	Vomiting, nausea, diarrhoea, abdominal pain, constipation.
Less frequent	Pancreatitis and/or lipase and/or amylase increase.
Hepatobiliary disorders	
Less frequent	Hepatitis.

Skin and subcutaneous tissue disorders	
Frequent	Rash, alopecia, acne.
Less frequent	Urticaria, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP).
	Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioedema, erythema multiforme (see section 4.4).
Musculoskeletal, connective tissue and bone disorders	
Less frequent	There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with OXCARBAZEPINE VIATRIS. The mechanism by which OXCARBAZEPINE VIATRIS affects bone metabolism has not been identified.
	Systemic lupus erythematosus
General disorders and administrative site conditions	
Frequent	Fatigue, asthenia.
Investigations	
Less frequent	Hepatic enzymes increased, blood alkaline phosphatase increased, decrease in T4 (with unclear clinical significance).
Injury, poisoning and procedural complications	
Less frequent	Fall.

[#]Hypersensitivity (including multi-organ hypersensitivity) characterised by features such as rash, fever. Other organs or systems may be affected such as blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leucopenia, lymphadenopathy, splenomegaly); liver (e.g. hepatitis, abnormal liver function tests); muscle and joints (e.g. joint swelling, myalgia, arthralgia); nervous system (e.g. hepatic encephalopathy); kidney (e.g. renal failure, nephritis

interstitial, proteinurea); lungs (e.g. pulmonary oedema, asthma, bronchospasms, interstitial lung disease, dyspnoea); angioedema.

† Serum sodium levels below 125 mmol/l have been observed in up to 2,7 % of oxcarbazepine treated patients with frequency common (see section 4.4). In most cases, the hyponatriaemia is asymptomatic and does not require adjustment of therapy.

Less frequently, the hyponatraemia is associated with signs and symptoms such as seizures, encephalopathy, confusion, depressed level of consciousness, confusion (see also Nervous system disorders for further undesirable effects), vision disorders (e.g. blurred vision), hypothyroidism, vomiting and nausea.

Low serum sodium levels generally occurred during the first 3 months of treatment with OXCARBAZEPINE VIATRIS, although there were patients who first developed a serum sodium levels < 125 mmol/l more than 1 year after initiation of therapy (see section 4.4).

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

The symptoms of overdose are somnolence, dizziness, nausea, vomiting, hyperkinesias, hyponatraemia, ataxia and nystagmus. There is no specific antidote. The treatment should be symptomatic and supportive. Removal of the medicine by gastric lavage and/or inactivation by administering activated charcoal should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.5 Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group: Anti-epileptics, ATC code: N03A F 02

The pharmacological activity of oxcarbazepine is primarily exerted through the active metabolite, 10-monohydroxy derivative (MHD). Oxcarbazepine and MHD are anticonvulsants. The mechanism of action of oxcarbazepine and MHD is thought to be mainly based on the blockade of voltage-sensitive sodium channels, thus resulting in stabilisation of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminishment of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects.

No significant interactions with brain neurotransmitters or modulator receptors were found.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration of OXCARBAZEPINE VIATRIS, oxcarbazepine is completely absorbed and extensively metabolised to its pharmacologically active metabolite MHD.

After a single dose administration of 600 mg oxcarbazepine to healthy male volunteers under fasted conditions, the mean C_{max} value of MHD was 34 mmol/l, with a corresponding median t_{max} of 4,5 hours.

Steady-state plasma concentrations of MHD are reached within 2 – 3 days in patients when oxcarbazepine is given twice a day. At steady-state, the pharmacokinetics of MHD are linear and show dose proportionality across the dose range of 300 to 2400 mg/day.

In a mass balance study in man, only 2 % of total radioactivity in plasma was due to unchanged oxcarbazepine, approximately 70 % was due to MHD, and the remainder attributable to minor secondary metabolites which were rapidly eliminated.

Food has no effect on the rate and extent of absorption of oxcarbazepine, therefore, oxcarbazepine can be taken with or without food.

Distribution:

The apparent volume of distribution of MHD is 49 litres.

Approximately 40 % of the active metabolite MHD is bound to plasma proteins, predominantly to albumin. Protein binding was independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoproteins.

Biotransformation:

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. MHD is metabolised further by conjugation with glucuronic acid. Minor amounts (4 % of the dose) are oxidised to the pharmacologically inactive metabolite (10, 11-dihydroxy derivative, DHD).

Elimination:

Oxcarbazepine is excreted from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95 % of the dose is excreted via the urine, with less than 1 % as unchanged oxcarbazepine. Less than 4 % of the administered dose is excreted via the faeces. Approximately 80 % of the dose is excreted in the urine either as

glucuronides of MHD (49 %) or as unchanged MHD (27 %). Approximately 3 % of the dose is excreted as the inactive DHD, and 13 % is excreted as conjugated oxcarbazepine.

Oxcarbazepine is rapidly eliminated from the plasma with a half-life of approximately 1,3 and 2,3 hours. In contrast, the plasma half-life of MHD averages 9,3 ± 1,8 hours.

Upon repeated oral dosing of oxcarbazepine, the pharmacokinetics of the unchanged medicine and its active metabolite do not change, indicating absence of auto-induction and accumulation characteristics.

Special populations:

Patients with hepatic impairment:

The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and in patients with hepatic impairment after a single oral dose of 900 mg. Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. Oxcarbazepine has not been studied in patients with severe hepatic impairment.

Patients with renal impairment:

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose to patients with renal impairment (creatinine clearance < 30 ml/min) the plasma half-life of MHD is prolonged by 60 – 90 % (16 – 19 hours) with a two-fold increase in AUC compared to adults with normal renal function (10 hours).

Children:

After a single dose administration of 5 or 15 mg/kg of oxcarbazepine, the (dose-adjusted) AUC values of MHD were 30 % lower in children aged 2 – 5 years than in older children aged

6 – 12 years. In general, in children with normal renal function, renal clearance of MHD normalised for bodyweight is higher than in adults.
In children a 10 to 50 % reduction of the MHD elimination half-life (5 to 9 hours) was observed compared to adults (10 hours).

Elderly:

Following administration of single (300 mg) and multiple doses (600 mg/day) of oxcarbazepine in elderly volunteers (60 – 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30 % - 60 % higher than in younger volunteers (18 – 32 years of age). Comparison of creatinine clearances in young and elderly volunteers indicates that the difference was due to age-related reductions in creatinine clearance. No special dose recommendations are necessary because therapeutic doses are individually adjusted.

Gender:

No gender related pharmacokinetic differences have been observed in children, adults or the elderly.

Pregnancy:

Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

crospovidone

hypromellose

microcrystalline cellulose

colloidal anhydrous silica

magnesium stearate

The tablet coating contains iron oxides (E172), hypromellose, lactose monohydrate, polyethylene glycol and titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 ˚C and protect from moisture.

6.5 Nature and contents of container

MYLAN OXCARBAZEPINE VIATRIS 150, 300 and 600 are supplied in

- PVDC coated PVC blister strips and aluminium foil lidding in packs of 10, 20, 30, 50, 100 or 200 tablets or,
- polypropylene containers with polyethylene caps and an optional polyethylene ullage filler in packs of 100, 200 and 500 tablets.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

1.3.1.1.1 Professional Information for medicines for human use

Viatris South Africa (Pty) Ltd

4 Brewery Street,

Isando, Johannesburg,

Gauteng, 1609

8 REGISTRATION NUMBER(S)

OXCARBAZEPINE 150 VIATRIS: 42/2.5/0354

OXCARBAZEPINE 300 VIATRIS: 42/2.5/0355

OXCARBAZEPINE 600 VIATRIS: 41/2.5/1106

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

OXCARBAZEPINE 150 VIATRIS: 02 March 2012

OXCARBAZEPINE 300 VIATRIS: 02 March 2012

OXCARBAZEPINE 600 VIATRIS: 29 October 2009

10 DATE OF REVISION OF TEXT

9 April 2024