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INSTRUCTION
for medical use

OXAPIN®

Composition:
active substance: oxcarbazepine;
1 tablet contains oxcarbazepine 300 mg;
excipients: microcrystalline cellulose, crospovidone, povidone, colloidal anhydrous silica, magnesium stearate, Opadry 04F82783 yellow coating: hypromellose, polyethylene glycol, titanium dioxide (E 171), iron oxide yellow (E 172).

Pharmaceutical form. Film coated tablets.
General physical-chemical properties: yellow, capsule-shaped, film coated tablets with a break-line on both sides.

Pharmacotherapeutic group.
Antiepileptic agents. ATC code: N03A F02.

Pharmacological properties.
Pharmacodynamics.
Oxcarbazepine pharmacological activity is primarily caused by the action of its metabolite – 10-monohydroxy derivative (MHD). Mechanism of action of oxcarbazepine and its MHD is mainly related to blockade of voltage-dependent sodium channels that leads to stabilization of over-excited nerve membranes, inhibition of repetitive neuronal discharges and reduction of synaptic conduction of impulses. Moreover, increased potassium ions conductivity and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects. No significant interactions with brain neurotransmitters or receptor modulator sites have been demonstrated.
Animal studies have shown that oxcarbazepine and its active metabolite (MHD) are potent and effective anticonvulsants.
They protected animals against generalized tonic-clonic seizures and, to a lesser extent, clonic seizures and abolished or reduced the frequency of chronically recurring focal seizures in animals with aluminum implants. No development of tolerance (i.e., attenuation of anticonvulsive activity) to tonic-clonic seizures was observed when animals were treated daily for 5 days or 4 weeks, respectively, with oxcarbazepine or MHD.
Clinical efficacy
Oxcarbazepine is used as an antiepileptic drug in both monotherapy and combination therapy and can replace other antiepileptic drugs that do not provide adequate seizure control.

Pharmacokinetics.

Absorption.

After oral use oxcarbazepine is completely absorbed and is largely metabolized forming a pharmacologically active metabolite (MHD).

After a single use of oxcarbazepine in a dose of 600 mg to healthy male volunteers under fasted condition, mean value of C_{max} of MHD was 34 μmol/L with corresponding median t_{max} of 4.5 hours.

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

Food has no effect on the rate and extent of absorption of oxcarbazepine. Therefore, Oxapin® can be taken regardless of food intake.

Distribution.

The apparent volume of distribution of MHD is 49 L.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. In the therapeutically relevant range, the degree of binding is independent of medicine concentration in blood serum. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Oxcarbazepine and MHD cross the placenta. In one case neonatal and maternal plasma MHD concentrations were similar.

Biotransformation.

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to pharmacologically active metabolite (MHD), which is primarily responsible for pharmacological effect of the drug. 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 cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Faecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%), whereas the inactive DHD accounts for approximately 3% and conjugates of oxcarbazepine account for 13% of the dose.

Oxcarbazepine is rapidly eliminated from the plasma with apparent half-life values between 1.3 and 2.3 hours. In contrast to oxcarbazepine, the apparent plasma half-life of MHD averaged 9.3±1.8 h.

Dose-proportionality.

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 pharmacokinetic of MHD is linear and show dose-proportionality across the dose range of 300 to 2400 mg/day.

Special populations.

Patients with hepatic impairment.

The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. Pharmacokinetics of 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, in renally impaired patients (creatinine clearance <30 ml/min) the elimination half-life of MHD is prolonged by 60–90% (16 to 19 hours) with a twofold increase in AUC compared to adults with normal renal function (10 hours).

Children.

The pharmacokinetics of oxcarbazepine was evaluated in paediatric patients taking it in the dose range 10–60 mg/kg/day. Weight-adjusted MHD clearance decreases as age and weight increase approaching that of adults. The mean weight clearance in children 1 month to 4 years of age is approximately 93%

higher than that of adults. Therefore, MHD exposure in these children is expected to be about twice more than that of adults when treated with a similar weight-adjusted dose.
The mean weight clearance in children 4 to 12 years of age is approximately 40% higher than that of adults. Therefore, MHD exposure in these children is expected to be about 2/3 that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients over 13 years of age, weight-adjusted MHD clearance is expected to reach that of adults.
Pregnancy.
Data from a limited number of women show a gradual decrease in plasma levels of MHD during pregnancy.
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). Comparisons of creatinine clearances values in young and elderly volunteers show 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.

Clinical particulars.
Indications.
Treatment of partial seizures with or without secondarily generalised tonic-clonic seizures as monotherapy or adjunctive therapy in adults and in children aged 6 years and above.

Contraindications.
Hypersensitivity to oxcarbazepine, eslicarbazepine or to any of the excipients.

Drug interactions and other types of interactions.
Enzyme induction.
Oxcarbazepine and its pharmacologically active metabolite (10-monohydroxy derivative, MHD) are weak inducers *in vitro* and *in vivo* of the cytochrome P450 enzymes CYP3A4 and CYP3A5 responsible for the metabolism of a very large number of medicines, in particular, dihydropyridine calcium antagonists (e.g. felodipine), immunosuppressants (e.g. cyclosporin, tacrolimus), oral contraceptives (see below), and some other antiepileptic medicinal products (e.g. carbamazepine) resulting in a lower plasma concentrations of these medicinal products (in table 1 see summarizing results with other antiepileptic medicinal products).
Oxcarbazepine and MHD *in vitro* are weak inducers of UDP-glucuronyl transferases (effects on specific enzymes in this family are not known). Therefore, *in vivo* they may have a small inducing effect on the metabolism of medicinal products which are mainly eliminated by conjugation through the UDP-glucuronyl transferases. When initiating treatment with oxcarbazepine or changing the dose, it may take 2 to 3 weeks to reach the new level of induction.
In case of discontinuation of oxcarbazepine therapy, a dose reduction of the concomitant medications may be necessary and should be decided upon by clinical and/or plasma level monitoring. The induction is likely to gradually decrease over 2 to 3 weeks after therapy discontinuation.
Hormonal contraceptives.
Oxcarbazepine was shown to have an influence on two components of oral contraceptives, ethinyloestradiol and levonorgestrel. The mean AUC values of ethinyloestradiol and levonorgestrel were decreased by 48–52% and 32–52%, respectively. Other hormonal contraceptives have not been studied. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives ineffective. Another reliable contraceptive method should be used.
Enzyme inhibition.

Oxcarbazepine and MHD inhibit CYP2C19. Therefore, interactions could arise when co-administering high doses of oxcarbazepine with medicinal products that are mainly metabolised by CYP2C19 (e.g. phenytoin). Phenytoin plasma levels increased by up to 40% when oxcarbazepine was given at doses above 1200 mg/day (in table 1 see summarizing results with other anticonvulsants). In this case, a reduction of co-administered phenytoin may be required.

Antiepileptic medicinal products.

Potential interactions between oxcarbazepine and other antiepileptic medicinal products were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarised in the table 1.

Table 1.

Information on antiepileptic medicinal product interactions with oxcarbazepine.

Antiepileptic medicinal product	Influence of oxcarbazepine on antiepileptic medicinal product, C_{min}	Influence of antiepileptic medicinal product on MHD** AUC
Co-administration	Concentration	Concentration
Carbamazepine	0–22% decrease (30% increase of carbamazepine-epoxide level)	40% decrease
Clobazam	Not studied	No influence
Felbamate	Not studied	No influence
Lamotrigine	No influence*	No influence
Phenobarbiton	14–15% increase	30–31% decrease
Phenytoin	0–40% increase	29–35% decrease
Valproic acid	No influence	0–18% decrease

* Does not affect C_{min}, AUC or C_{max}.

** MHD: monohydroxy derivative (pharmacologically active metabolite of oxcarbazepine).

Strong inducers of cytochrome P450 enzymes (i.e. carbamazepine, rifampicin, phenytoin and phenobarbitone) have been shown to decrease the plasma levels of MHD (29–40%) in adults.

Therefore, monitoring of plasma levels and/or dose adjustment is required if one or more of these drugs are co-administered with oxcarbazepine.

In children 4 to 12 years of age, MHD clearance increased by approximately 35% when given one of the three enzyme-inducing antiepileptic medicinal products compared to monotherapy. Concomitant therapy of oxcarbazepine and lamotrigine has been associated with an increased risk of adverse events (nausea, somnolence, dizziness, and headache).

When one or several antiepileptic medicinal products are concurrently administered with oxcarbazepine, the possibility of adjusting the dose of antiepileptic drugs and/or a careful dose adjustment may be considered. This applies especially to paediatric patients treated concomitantly with lamotrigine.

No self-induction of enzymes has been observed with oxcarbazepine.

Interactions with other medicinal products.

Cimetidine, erythromycin, viloxazine, warfarin and dextropropoxyphene had no effect on the pharmacokinetics of MHD.

The interaction between oxcarbazepine and MAOIs is theoretically possible based on a structural relationship of oxcarbazepine to tricyclic antidepressants.

Tricyclic antidepressants.

No clinically significant interactions were observed in clinical trials.
Pharmacodynamic interactions.
The combination of lithium and oxcarbazepine might cause enhanced neurotoxicity.

No clinically significant interactions were observed in clinical trials.
Pharmacodynamic interactions.
The combination of lithium and oxcarbazepine might cause enhanced neurotoxicity.

Special warnings and precautions for use.
Hypersensitivity.
Hypersensitivity reactions, including class I reactions and other hypersensitivity reactions have been registered during the treatment with oxcarbazepine. If a patient develops these symptoms, the administration of Oxapin® should be discontinued and an alternative treatment with antiepileptic drug should be started.
Immediate (class I) hypersensitivity reactions including rash, oedema, pruritus, urticaria, dyspnoea, bronchospasm, angioneurotic oedema and 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. If a patient develops these reactions after treatment with oxcarbazepine, it should be discontinued and an alternative treatment started.
Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25–30% of these patients may experience hypersensitivity reactions (e.g. severe skin reactions) with oxcarbazepine. For this reason, patients should be asked about prior carbamazepine treatment before starting Oxapin® therapy. Patients with a history of hypersensitivity to carbamazepine may generally use Oxapin® only if the expected benefit justifies the potential risk. Hypersensitivity reactions, including multiorgan hypersensitivity reactions, have been observed in both adults and children in close temporal association (preferably within the first 3 weeks, maybe even later) with the start of treatment. They are also possible in patients without a history of hypersensitivity to carbamazepine. The symptoms varied greatly. Such reactions can be manifested not only by fever and rash, but also spread to the skin, liver, circulatory and lymphatic systems and other organs, either individually or together as a systemic reaction. In general, Oxapin® should be discontinued immediately if signs and symptoms suggestive of hypersensitivity reactions occur.
There have been reports of asthenia, itching, arthralgia, joint swelling, lymphadenopathy, splenomegaly, hematologic abnormalities (e.g. eosinophilia, thrombocytopenia, neutropenia), pulmonary oedema, interstitial lung changes, abnormal liver function tests, hepatitis, proteinuria, oliguria, interstitial nephritis, renal failure and hepatorenal syndrome. Symptoms can occur in other organs as well. Some cases have resulted in hospitalization, some are considered life-threatening.
Dermatological effects.
Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema multiform, have been reported very rarely in association with oxcarbazepine use. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and very rarely be fatal. Oxcarbazepine-associated cases of severe skin adverse reactions 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 rechallenge with oxcarbazepine were reported. Patients who develop skin reaction with oxcarbazepine should be promptly evaluated and Oxapin® withdrawn immediately unless the rash is clearly not related to drug administration. In case of oxcarbazepine withdrawal, consideration should be given to replacing it with other antiepileptic drug therapy to avoid seizures. Oxcarbazepine should not be restarted in patients who discontinued oxcarbazepine treatment due to hypersensitivity reactions. There is growing evidence that different HLA alleles play a role in adverse immune and skin reactions in predisposed patients.
Association with HLA-B*1502 allele
Human leukocyte antigen (HLA)-B*1502 in individuals of Han Chinese and Thai origin has been shown

to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) when treated with carbamazepine. The chemical structure of oxcarbazepine is similar to that of carbamazepine, and it is possible that patients who are positive for HLA-B*1502 may also be at risk for SJS/TEN after treatment with oxcarbazepine. There are some data that suggest that such an association exists for oxcarbazepine. The prevalence of HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine or a chemically-related active substance. If patients of these origins are tested positive for HLA-B*1502 allele, the use of oxcarbazepine may be considered if the benefits are thought to exceed risks.
Because of the prevalence of this allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered. The prevalence of the HLA-B*1502 allele is negligible (<1%) in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans.
Allele frequencies refer to the percentage of chromosomes in the population that carry a given allele. Since a person carries two copies of each chromosome, but even one copy of the HLA-B*1502 allele may be enough to increase the risk of SJS, the percentage of patients who may be at risk is nearly twice the allele frequency.

Association with HLA-A*3101 allele

Human leukocyte antigen (HLA)-A*3101 may be a risk factor for adverse skin reactions such as SJS/TEN, rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and maculopapular rash. In particular, there are some data that suggest these reactions occurred after the use of carbamazepine. Patients at increased risk of adverse reactions due to their origin should be screened before starting treatment with oxcarbazepine to determine if they are carriers of the HLA-A*3101 allele. Screening for HLA-A*3101 is not recommended in low-prevalence populations. Similarly, screening is not appropriate for patients who have used oxcarbazepine for a long time because SJS/TEN, DRESS, AGEP, and maculopapular rash are usually seen only in the first few months of therapy. Carriers of the HLA-A*3101 allele can be treated with oxcarbazepine, provided that the benefits outweigh the risks.
The results of genetic screening do not substitute proper monitoring of the patient's condition, especially if the risk of serious skin reactions may be increased due to the influence of other factors (such as comorbidities).

Risk of seizure aggravation.

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

Hyponatraemia.

Serum sodium levels below 125 mmol/L, usually asymptomatic and not requiring adjustment of therapy, have been observed in 2.7% of oxcarbazepine-treated patients. Experience from clinical trials shows that serum sodium levels returned towards normal when the oxcarbazepine dosage was reduced, discontinued or the patient was treated conservatively (e.g. restricted fluid intake). In patients with pre-existing renal conditions associated with low sodium level (e.g. inappropriate ADH secretion syndrome) or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, desmopressin) as well as NSAIDs (e.g. indomethacin), serum sodium levels should be measured prior to initiating oxcarbazepine therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then once monthly for the first three months during therapy, or according to clinical need. Hyponatraemia risk factors may apply especially to elderly patients. For patients, receiving oxcarbazepine therapy when starting on sodium-lowering medicinal products, the same approach for sodium evaluation in blood serum should be followed. In general, serum sodium should be monitored in patients with clinical manifestations of hyponatraemia associated with oxcarbazepine therapy. Other patients may have serum sodium assessed as part of their routine laboratory studies.
Very rarely, clinically significant hyponatraemia (Na <125 mmol/L) may develop with oxcarbazepine

therapy. This usually occurred during the first three months of treatment, although there were patients who first developed a serum sodium level <125 mmol/L more than 1 year after initiation of therapy. Cases of seizures, disorientation, depressed consciousness, encephalopathy, visual disturbances (e.g. blurred vision), vomiting, nausea and folic acid deficiency have also been reported.
In some cases, inappropriate ADH secretion syndrome (SIADH) may occur during oxcarbazepine therapy.

Existing heart failure

All patients with cardiac insufficiency 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 may, very rarely, lead to impairment of cardiac conduction, patients with pre-existing conduction disturbances (e.g. atrioventricular-block, arrhythmia) should be followed carefully.

Hypothyroidism.

Hypothyroidism is a very rare side effect of oxcarbazepine. Due to the importance of thyroid hormones for postpartum development, it is advisable to test for thyroid function before starting treatment with oxcarbazepine in the paediatric population, especially in children over 2 years of age. In children, it is also recommended to monitor thyroid function during oxcarbazepine therapy. In patients with hypothyroidism, monitoring of thyroid function is recommended to determine the dose for hormone replacement therapy.

Hepatic function.

Very rare cases of hepatitis have been reported, which in most of the cases resolved favourably. When a hepatic event is suspected, liver function should be evaluated, and discontinuation of oxcarbazepine should be considered. Caution should be exercised when treating patients with severe hepatic impairment.

Renal function.

In patients with impaired renal function (creatinine clearance less than 30 ml/min), oxcarbazepine therapy is recommended with caution, especially at the beginning of treatment and during dose titration. Plasma MHD monitoring may be required.

Bone metabolism.

There have been reports of decreased bone mineral density to overt osteoporosis with fractures on long-term therapy with oxcarbazepine. The exact mechanism by which oxcarbazepine affects bone metabolism has not been studied.

Haematological effects.

Very rare reports of agranulocytosis, aplastic anaemia and pancytopenia have been seen in patients treated with oxcarbazepine. Discontinuation of the medicinal product should be considered if any evidence of significant bone marrow depression develops.

Suicidal behaviour.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. Meta-analysis of randomized placebo-controlled trials of antiepileptic drugs also demonstrated a small increase in the 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 oxcarbazepine intake. Therefore, during oxcarbazepine therapy, patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers) should be advised to seek medical advice in case of signs of suicidal ideation or behaviour.

Hormonal contraceptives.

Female patients of reproductive age should be warned that the concurrent use of oxcarbazepine with hormonal contraceptives may render this type of contraceptive ineffective. Other forms of contraception are recommended when using oxcarbazepine.

Vitamin B_{12} deficiency.

Vitamin B_{12} deficiency should be excluded or treated.

Alcohol.

Alcohol intake in combination with oxcarbazepine therapy may lead to a possible cumulative sedative effect.

Drug withdrawal.

As with all antiepileptic drugs, Oxapin® should be discontinued gradually to minimize the risk of increased seizure frequency or status epilepticus. If abrupt withdrawal of oxcarbazepine is imminent, in particular due to severe adverse effects, a suitable drug should be administered (e.g. intravenously or rectally diazepam, phenytoin) during the transition period to another antiepileptic drug; the patient's condition should be carefully monitored.

Oxcarbazepine has a weaker enzyme-inducing effect than carbamazepine. The dose of other combined antiepileptic drugs may be reduced.

Fertility.

There are no data on the effect on fertility in humans. Animal studies have not shown impaired fertility, but have shown a negative effect on the parameters of reproductive function in women, i.e. the risk of deterioration of female fertility cannot be ruled out.

Plasma level monitoring.

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 "Administration and dosage" section);
- pregnancy (see "Pregnancy and lactation" section);
- concomitant use of liver enzyme-inducing medicines (see "Drug interactions and other types of interactions" section).

Pregnancy and lactation.

Pregnancy.

Risk related to epilepsy and antiepileptic medicinal products in general.

In the treated population, an increase in malformations has been noted with polytherapy, particularly in polytherapy including valproate. Moreover, effective anti-epileptic therapy must not be interrupted during pregnancy, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to oxcarbazepine.

There is moderate amount of data on pregnant women (300–1000 pregnancy outcomes). However, the data on oxcarbazepine associated with congenital malformation is limited. There is no increase in the total rate of malformations with oxcarbazepine as compared with the rate observed in the general population (2–3%). Nevertheless, with this amount of data, a moderate teratogenic risk cannot be completely excluded. The results of studies on the risk of nervous system disorders in children exposed to oxcarbazepine during foetal development are conflicting and such a risk cannot be excluded.

Taking these data into consideration:

- if women receiving oxcarbazepine become pregnant or plan to become pregnant, the use of this product should be carefully re-evaluated. Minimum effective oxcarbazepine doses should be given, and monotherapy whenever possible should be preferred at least during the first three months of pregnancy;
- during pregnancy, an effective antiepileptic oxcarbazepine treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention.

Antiepileptic medicinal products may contribute to folic acid deficiency, a possible contributory cause of foetal abnormality. Folic acid supplementation is recommended before and during pregnancy. As the efficacy of this supplementation is not proved, a specific antenatal diagnosis can be offered even for women with a supplementary treatment of folic acid.

The data obtained in a limited number of women indicate that plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy.

The close monitoring of clinical response in women receiving oxcarbazepine is recommended during pregnancy to ensure adequate control of seizures that persist. The necessity to identify changes of MHD plasma concentrations should be considered. If drug doses rose during pregnancy, the possibility of MHD plasma levels in postpartum period should be considered. Postpartum MHD plasma levels may also be considered for monitoring especially in the event that drug doses were increased during pregnancy.
Newborn children.
Coagulation failure in the newborns caused by antiepileptic agents has been reported. Vitamin K_1 should be administered as a preventive measure in the last few weeks of pregnancy and to the newborn.
Cases of hypocalcaemia have been reported rarely in neonates whose mothers were treated with antiepileptic drugs during pregnancy. These cases were due to disturbances in calcium phosphate metabolism and bone mineralization.
Women of childbearing potential and contraceptives.
Oxcarbazepine may impair the therapeutic effect of oral contraceptives containing ethinyl estradiol and levonorgestrel (see "Special warnings and precautions for use" and "Interaction with other medicinal products and other forms of interaction" sections). Highly effective contraceptives should be recommended during treatment with oxcarbazepine in women with preserved reproductive potential (non-hormonal contraceptives, such as intrauterine implants) should be preferred.
Lactation.
Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. According to some data, the concentration of MHD in the blood plasma of breastfed babies is 0.2–0.8 μg/ml – up to 5% of the concentration of MHD in the mother's blood plasma. Although the effect is likely to be small, a risk to the infant cannot be ruled out. Therefore, when deciding on the necessity of breastfeeding during Oxapin® therapy, one should take into account both the benefits of breastfeeding and the potential risk of adverse reactions in the infant. If the baby is breastfed, adverse effects such as drowsiness and poor weight gain should be monitored.

Effects on ability to drive and use machines.
Oxcarbazepine has been associated with adverse reactions such as dizziness, somnolence, ataxia, diplopia, blurred vision, visual disturbances, hyponatraemia, and depression of consciousness, especially at the beginning of treatment or in connection with dose adjustment (usually during the dose titration phase). Therefore, patients should exercise due caution when driving or operating machines.

Administration and dosage.
In mono- and adjunctive therapy, treatment with oxcarbazepine is initiated with a clinically effective dose given in 2 divided doses. The dose may be increased depending on the clinical response of the patient. When other antiepileptic medicinal products are replaced by oxcarbazepine, the dose of the concomitant antiepileptic medicinal product(s) should be reduced gradually on initiation of oxcarbazepine therapy. As the total antiepileptic medicinal product load of the patient is increased, the dose of concomitant antiepileptic medicinal products may need to be reduced and/or the oxcarbazepine dose increased more slowly.
The drug can be used regardless of food intake.
The following dosing recommendations apply to all patients, in the absence of impaired renal function. Drug plasma level monitoring is not required for optimization of oxcarbazepine therapy.
However, monitoring of plasma MHD levels should be performed during treatment with oxcarbazepine to rule out treatment inadequacy or in situations where changes in MHD clearance are expected, such as:

- changes in renal function (see "Patients with renal impairment" below);
- pregnancy (see "Pregnancy and lactation" and "Pharmacological properties" sections);
- concomitant use of liver enzyme-inducing medicines (see "Drug interactions and other types of interactions" section).

In such situations, the dose of oxcarbazepine may be adjusted (based on plasma levels measured 2–4 hours post dose) to maintain peak MHD plasma levels <35 mg/L. Weight-adjusted MHD clearance

(L/h/kg) in children is significantly higher than in adults.
The tablets are scored and can be broken into two halves in order to make it easier for the patient to swallow the tablet. However, the tablet cannot be divided into equal doses.
Adults.
Monotherapy.
Oxcarbazepine should be initiated with a dose of 600 mg/day (8–10 mg/kg/day) given in 2 divided doses.
If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic effects are seen at doses between 600–2400 mg/day.
Findings in patients, not currently being treated with antiepileptic medicinal products, showed 1200 mg/day to be an effective dose of oxcarbazepine as monotherapy. However, a dose of 2400 mg/day has been shown to be effective in more refractory patients converted from other antiepileptic medicinal products to oxcarbazepine monotherapy.
In a controlled hospital setting, dose increases up to 2400 mg/day have been achieved over 48 hours.
Adjunctive therapy.
Oxcarbazepine should be initiated with a dose of 600 mg/day (8–10 mg/kg/day) given in 2 divided doses.
If clinically indicated, the dose may be increased by a maximum of 600 mg/day increments at approximately weekly intervals from the starting dose to achieve the desired clinical response. Therapeutic responses are seen at doses between 600–2400 mg/day.
There is evidence that daily doses from 600 to 2400 mg/day have been shown to be effective in patients, receiving oxcarbazepine as an adjunctive therapy, although most patients were not able to tolerate the 2400 mg/day dose without reduction of concomitant antiepileptic medicinal products, mainly because of CNS-related adverse events.
Daily doses above 2400 mg/day of oxcarbazepine have not been studied.
Elderly patients (over 65 years of age).
No special dose recommendations are necessary in elderly patients because therapeutic doses are individually adjusted. Dosage adjustments are recommended in elderly patients with renal impairment (creatinine clearance less than 30 ml/min).
Patients with hyponatremia or risk of hyponatremia.
Close monitoring of sodium levels is required (see “Special warnings and precautions for use” section).
Patients with hepatic impairment.
No dosage adjustment is required for patients with mild to moderate hepatic impairment. Oxcarbazepine has not been studied in patients with severe hepatic impairment. Therefore, caution should be exercised when dosing severely impaired patients.
Patients with renal impairment.
In patients with impaired renal function (creatinine clearance less than 30 ml/min) oxcarbazepine therapy should be initiated at half the usual starting dose (300 mg/day) and increased, in at least weekly intervals, to achieve the desired clinical response.
Dose escalation in renally impaired patients may require more careful observation.
Children.
Oxapin® is not recommended in children aged less than 6 years since safety and efficacy have not been adequately demonstrated.
In mono- and adjunctive therapy, oxcarbazepine should be initiated with a dose of 8–10 mg/kg/day given in 2 divided doses.
With adjunctive therapy, therapeutic effects are observed at a maintenance dose of 30–46 mg/kg/day, achieved over two weeks. This dose range of oxcarbazepine has been shown to be effective and well tolerated in children. Therapeutic effects were observed at an average maintenance dose of oxcarbazepine of about 30 mg/kg/day.
If clinically indicated, the dose may be increased by a maximum of 10 mg/kg/day at approximately weekly intervals from the starting dose, to a maximum dose of 46 mg/kg/day, to achieve the desired clinical response, and it should be achieved within two weeks.

In all categories of patients (adults, elderly patients, and children), lower doses can be used if necessary.

Children.
Oxcarbazepine is not recommended for children under 6 years of age, since safety and efficacy have not been adequately proven.

Overdose.
Isolated cases of overdose have been reported. The maximum dose taken was approximately 48000 mg. All patients recovered after symptomatic treatment.
Symptoms
Symptoms of overdose may include drowsiness, dizziness, nausea, vomiting, hyperkinesia, fatigue, hyponatremia, respiratory depression, QT prolongation, diplopia, miosis, blurred vision, ataxia, nystagmus, tremor, loss of coordination, convulsions, headache, exanimation, loss of consciousness, dyskinesia, aggression, agitation, confusion, hypotension, and dyspnoea.
Treatment
There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the medicinal product by gastric lavage and/or inactivation by administering activated charcoal should be considered.
Monitoring of vital functions is recommended, with special attention paid to electrolyte imbalance, cardiac conduction and respiration.

Adverse reactions.
The most commonly reported adverse reactions are somnolence, headache, dizziness, diplopia, nausea, vomiting and fatigue occurring in more than 10% of patients.
Frequency category was determined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); and not known – frequency cannot be estimated from available data.
Blood and lymphatic system disorders: uncommon – leukopenia; rare – bone marrow depression, aplastic anaemia, agranulocytosis, pancytopenia, neutropenia; very rare – thrombocytopenia.
Immune system disorders: rare – anaphylactic reactions; very rare – hypersensitivity reactions*.
Endocrine system disorders: common – weight gain; uncommon – hypothyroidism.
Metabolism and nutrition disorders: common – hyponatremia**; rare – inappropriate antidiuretic hormone secretion syndrome (lethargy, nausea, dizziness, decreased serum osmolarity), vomiting, headache, confusion or other neurological signs and symptoms); not known – folic acid deficiency.
Psychiatric disorders: common – agitation (e.g. nervousness), affect lability, emotional lability, confusional state, depression, apathy.
Nervous system disorders: very common – somnolence, headache, dizziness; common – ataxia, tremor, nystagmus, disturbance in attention, amnesia, speech disorders (including dysarthria), more often during dose titration of oxcarbazepine.
Eye disorders: very common – diplopia; common – blurriness, visual disturbance; not known – vision blurred.
Ear and labyrinth disorders: common – vertigo.
Cardiac disorders: uncommon – hypertension; very rare – arrhythmia, atrioventricular block.
Gastrointestinal disorders: very common – nausea, vomiting; common – diarrhoea, constipation, abdominal pain; very rare – pancreatitis and lipase and/or amylase increase.
Hepatobiliary disorders: very rare – hepatitis.
Skin and subcutaneous tissue disorders: common – rash, alopecia, acne; uncommon – urticaria; rare – drug rash with eosinophilia and systemic symptoms (DRESS syndrome), acute generalized exanthematous pustulosis (AGEP syndrome); very rare – angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), erythema multiform, angioedema.
Musculoskeletal, connective tissue and bone disorders: rare – impaired bone metabolism (decreased bone

mineral density, osteopenia, osteoporosis, fractures)***; very rare – systemic lupus erythematosus.
General disorders and administration site conditions: very common – fatigue; common – asthenia.
Laboratory investigations: uncommon – increase liver enzymes, increased alkaline phosphatase blood levels; rare – decreased T4 (clinical significance is unclear).
Injuries, intoxications and complications of manipulations: uncommon – falls.

* Hypersensitivity reactions (including multi-organ hypersensitivity) characterised by features such as rash, fever. With their development, other organs or systems may be affected such as blood and lymphatic system (e.g. eosinophilia, thrombocytopenia, leukopenia, lymphadenopathy, splenomegaly), liver (e.g. abnormal liver function tests, hepatitis), muscles and joints (e.g. joint swelling, myalgia, arthralgia), nervous system (e.g. hepatic encephalopathy), kidneys (e.g. proteinuria, nephritis interstitial, renal failure), lungs (e.g. dyspnoea, pulmonary oedema, asthma, bronchospasms, interstitial lung disease), angioedema.
** Serum sodium levels below 125 mmol/L have been observed in up to 2.7% of oxcarbazepine treated patients. In most cases, the hyponatraemia is asymptomatic and does not require adjustment of therapy. Very rarely, the hyponatraemia is associated with signs and symptoms such as seizures, encephalopathy, depressed level of consciousness, confusion (see also "Nervous system disorders" for further adverse 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, although there were patients who first developed this complication more than 1 year after initiation of therapy.
*** There have been reports of bone metabolism disorders in patients on long-term therapy with oxcarbazepine. The mechanism by which oxcarbazepine affects bone metabolism has not been identified.

Children
In general, the safety profile in children was similar to that observed in the adult population.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life. 3 years.

Storage conditions.
Store at temperature below 25°C.
Keep out of reach of children.

Package.
10 tablets in a blister; 3 blisters in a carton package.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Last revision date.