PACKAGE LEAFLET

Package leaflet: Information for the patient

Curatil 200 mg Prolonged-Release Tablets

Curatil 400 mg Prolonged-Release Tablets

carbamazepine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Curatil is and what it is used for

Curatil contains the active substance carbamazepine.
Curatil is specially formulated to release the active ingredient gradually.
Carbamazepine, the active ingredient, can affect the body in several different ways. It is an anti-convulsant medicine (prevents fits), it can also modify some types of pain and can control mood disorders.

Curatil is used

• To treat some forms of epilepsy
• To treat a painful condition of the face called trigeminal neuralgia
• To help control serious mood disorders when some other medicines don't work.

2. What you need to know before you take Curatil

Do not take Curatil:

- if you are allergic to carbamazepine, structurally related drugs (e.g. tricyclic antidepressants i.e. certain antidepressant medicines) or any of the other ingredients listed in section 6;
- if you have a history of bone marrow damage or a disorder of blood formation in the bone marrow;
- if you have conduction disorders of the heart (atrioventricular block);
- if you have certain inherited metabolic defects (acute intermittent porphyria, porphyria variegata, porphyria cutanea tarda);
- if you are being treated concomittantly with a monoamine oxidase inhibitors (MAOIs), used to treat depression, within the last 14 days:

Warnings and precautions

- If you suffer from absences (clouded consciousness), then you should not use carbamazepine, as this medicine can cause such types of seizures or intensify existing ones.
- Severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis), which can be life-threatening, have been reported with the use of carbamazepine. These appear initially as reddish, target-like or circular patches (often with a bubble in the center) on the trunk. The rash can result in widespread blistering or peeling of the skin. Additional symptoms to look out for include open, sore spots (ulcers) in the mouth, throat, nose, and genitals, and red and swollen eyes (conjunctivitis). These potentially life-threatening skin reactions are often accompanied by flu-like symptoms (headache, fever and body aches).

  The highest risk of these severe skin reactions occurring is in the first few weeks of treatment. If you have developed Stevens-Johnson syndrome or toxic epidermal necrolysis in connection with the use of carbamazepine, you must never be treated with carbamazepine again.

  If you develop a skin rash or any of the other skin symptoms listed, seek medical attention immediately. Let them know that you are taking carbamazepine.

  The severe skin reactions described may be more common in people from certain Asian countries. If you are belong to the Han Chinese or Thai population, your doctor can do a blood test to determine if you are at increased risk of these serious skin reactions. Your doctor can tell you if a blood test is needed before taking carbamazepine.

Talk to your doctor or pharmacist before taking Curatil

If you suffer from any of the following diseases:

- Diseases of the blood-forming organs (haematological diseases);
- Signs of unusual sensitivity (skin rash or other signs of allergy) to oxcarbazepine or any other medicine. If you are allergic to carbamazepine there is about a 25% chance that you are also allergic to oxcarbazepine;
- Impaired sodium metabolism;
- Heart, liver and kidney disorders, even if you have previously suffered from them (see "What are the possible side effects?" and "How to take Curatil?");
- increased pressure in the eye (glaucoma) or difficulty or pain when urinating; in this case you should be carefully monitored;
- Myotonic dystrophy (degenerative muscle disease, cardiac conduction abnormalities are common in these patients).

if you have previously stopped treatment with carbamazepine.

if your doctor has diagnosed you with a mental illness called psychosis, which may be accompanied by states of confusion and over-excitement.

There is a risk of harm to the unborn baby, if carbamzepine is used during pregnancy. Women of childbearing potential should use effective contraception during treatment with carbamazepine and for two weeks after the last dose (see pregnancy and breast-feeding).

If you are taking a hormonal contraceptive (the "pill"), you need to know that carbamazpine can make it ineffective. You should use different or an additional non-

hormonal method of contraception. In this way you can reduce the risk of an unwanted pregnancy.

Please inform your doctor immediately if you experience irregular vaginal bleeding or spotting.

Please inform your doctor if you are pregnant or planning to become pregnant. Your doctor will discuss with you the possible risks of taking carbamazepine during pregnancy, as it may cause harm or birth defects to an unborn baby (see the section "Pregnancy").

A small number of people being treated with anti-epileptics such as Curatil have had thoughts of harming or killing themselves. If at any time you have such thoughts, contact your doctor immediately.

If any of the above applies to you, be sure to discuss it with your doctor. You may then only take carbamazepine if you take the appropriate precautions.

Due to the possibility of increased sensitivity of the skin to light (photosensitization), you should protect yourself from strong sunlight during treatment with carbamazepine.

Please inform your doctor immediately if any of the following apply to you:

- If you experience symptoms such as fever, sore throat, allergic skin reactions such as rash with swelling of the lymph nodes and/or flu-like illness symptoms, ulcers in the mouth, tendency to develop "bruises", pinpoint or extensive bleeding of the skin, consult your doctor immediately.

- If you notice signs of an allergic reaction, which may be accompanied by symptoms such as fever, skin rash, vascular inflammation, swelling of the lymph nodes or joint pain, talk to your doctor immediately or go to the emergency room of the nearest hospital (see "Possible side effects are possible?").

- If you find that you are having seizures more often.

- If you notice signs of liver inflammation such as fatigue, loss of appetite, nausea, yellowing of the skin and/or eyes, enlargement of the liver.

- If you have kidney problems associated with low levels of sodium in your blood or if you have kidney problems and you are taking medicines that lower sodium levels in your blood (diuretics such as hydrochlorothiazide, furosemide) at the same time.

- If you have symptoms such as dizziness, light-headedness, drop in blood pressure, confusion due to taking carbamazepine, which can lead to falls.

Other medicines and Curatil

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those obtained without a prescription. This includes herbal medicines.

Treatment with MAO inhibitors (medicines used to treat depression) must have been stopped at least 2 weeks before starting treatment with carbamazepine.

Please note that the following information may also apply to recently used medicines.

Influence of carbamazepine on the plasma concentrations of other medicinal products

Carbamazepine can increase the activity of certain liver enzymes and thereby reduce the plasma levels of other medicines.

The effect of some other medicines taken at the same time, which are broken down in the same way as carbamazepine, may therefore be weakened or even reversed.

If carbamazepine is administered at the same time, the dosage of the following active ingredients from different areas of application may need to be adjusted to clinical requirements:

- Painkillers, anti-inflammatory substances: buprenorphine, fentanyl, methadone, paracetamol (long-term use of carbamazepine and paracetamol (acetaminophen) may result in hepatotoxicity), phenazone, tramadol
- Antiparasitic medicines: praziquantel, albendazole
- Anticoagulants: warfarin, phenprocoumon, dicoumarol, acenocoumarol, rivaroxaban, dabigatran, apixaban, edoxaban
- Medicines for treating depression: bupropion, citalopram, mianserin, nefazodone, sertraline, trazodone (but appears to increase the antidepressant effect)
- Other medications used to treat depression (so-called tricyclic antidepressants): imipramine, amitriptyline, nortriptyline, clomipramine
- Medicines for nausea and vomiting: aprepitant
- Antiepileptics, other medicines used to treat seizure disorders: clonazepam, ethosuximide, felbamate, eslicarbazepine, oxcarbazepine, primidone, lamotrigine, tiagabine, topiramate, valproic acid, zonisamide, phenytoin (the plasma level of phenytoin may be increased or decreased)
- Medicines used to treat (systemic) fungal infections: caspofungin, azole-type antifungals: e.g. itraconazole, voriconazole. Alternative anticonvulsants are recommended for patients treated with voriconazole or itraconazole.
- Medicines for viral diseases/HIV: e.g. indinavir, ritonavir, saquinavir
- Anxiolytic medicines: alprazolam, midazolam, clobazam
- Medicines used to treat respiratory diseases: theophylline
- Medicines used to treat heart disease: digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine
- Medicines for inhibiting defence mechanisms after organ transplants, immunosuppressant: ciclosporin, tacrolimus, sirolimus, everolimus
- Calcium antagonists (medicines to treat dizziness, migraine, high blood pressure): felodipine, flunarizine
- Medicines to prevent pregnancy: hormonal contraceptives
- Corticosteroids: e.g. prednisolone, dexamethasone
- Medicines for the treatment of mental illnesses: haloperidol, bromperidol, clozapine, olanzapine, risperidone, quetiapine, ziprasonide, zotepine (accelerate metabolism), aripiprazole, paliperidone
- Thyroid hormones: levothyroxine
- Antibiotics: rifabutin, tetracyclines e.g. doxycycline
- Medicines used to treat cancer: imatinib, cyclophosphamide, lapatinib, temsirolimus
- Other: quinidine (used to treat cardiac arrhythmias), oestrogens (hormones), methylphenidate (psychostimulant, medicine used to treat attention deficit disorders), progesterone derivatives (hormones), propranolol (beta-blocker, antihypertensive medicine)
- Medicines used to treat erectile dysfunction: tadalafil

Hormone contraceptives, e.g. pills, patches, injections or implants.
Carbamazepine may affect how hormonal contraceptives work and make them less effective at preventing pregnancy. Talk to your doctor, who will discuss with you the most suitable type of contraception to use while you are taking carbamazepine.

Carbamazepine can reduce plasma levels of bupropion (a medicine to help you stop smoking) and increase levels of the breakdown product hydroxybupropion, thus reducing the clinical efficacy and safety of bupropion.

Decreased plasma concentrations of carbamazepine due to other medicinal products

Carbamazepine plasma levels may be reduced by:

- Antiepileptics, other medicines used to treat seizure disorders: felbamate, methosuximide, oxcarbazepine, phenobarbital, phensuximide, phenytoin, fosphenytoin, primidone, progabid and possibly (here the data are partially contradictory) clonazepam, valproic acid, valpromide
- Anti-tuberculosis medicine: rifampicin
- Medicines to treat respiratory diseases, anti-asthmatics: theophylline, aminophylline
- Medicines for skin diseases: isotretinoin
- Medicines used to treat cancer: cisplatin, doxorubicin
- Other: St. John's Wort (Hypericum perforatum, herbal remedy for depressive moods)

On the other hand, the plasma levels of the pharmacologically active breakdown product of carbamazepine (carbamazepin-10,11-epoxide) can be increased by valproic acid and primidone.

Simultaneous administration of felbamate can reduce the plasma level of carbamazepine and increase that of carbamazepine-10,11-epoxide, while the felbamate level can be reduced at the same time.

Due to the mutual influence, especially when several antiepileptic medicines are administered at the same time, it is advisable to check the plasma levels and adjust the dosage of carbamazepine if necessary.

Increased plasma concentrations of carbamazepine due to other medicinal products

The following active substances can increase the plasma concentrations of carbamazepine:

- Analgesics, anti-inflammatory substances: dextropropoxyphene / propoxyphene, ibuprofen
- Medicines that inhibit the sex hormone gonadotropin: danazol
- Antibiotics, agents used to treat bacterial infections: macrolide antibiotics (e.g., erythromycin, troleandomycin, josamycin, clarithromycin, ciprofloxacin)
- Medicines for treating depression: fluoxetine, fluvoxamine, nefazodone, paroxetine, trazodone, viloxazine, possibly also desipramine
- Antiepileptics, other medicines used to treat seizure disorders: stiripentol, vigabatrin
- Agents for the treatment of (systemic) fungal infections, azole-type antimycotics such as e.g. itraconazole, ketoconazole, fluconazole, voriconazole. Alternative anticonvulsants are recommended for patients treated with voriconazole or itraconazole
- Medicines used to treat allergic reactions: loratadine, terfenadine
- Medicines used to treat tuberculosis: isoniazid
- Medicines against viral diseases/HIV, e.g. ritonavir
- Medicines used to treat glaucoma: acetazolamide
- Calcium antagonists (active ingredients for the treatment of cardiovascular diseases): diltiazem, verapamil
- Medicines used to relax muscles (muscle relaxants): oxybutynin, dantrolene
- Medicines used to treat mental disorders: loxapine, olanzapine, quetiapine
- Anticoagulants: ticlopidine
- Medicines used to treat gastrointestinal ulcers: omeprazole, possibly cimetidine
- Other: grapefruit juice, nicotinamide (B group vitamin, in high doses)

Increased plasma levels of carbamazepine can lead to the symptoms mentioned under section 4 “Possible side effects" mentioned symptoms (e.g. dizziness, tiredness, unsteady gait, double vision). If you experience such symptoms, talk to your doctor; he will then check the plasma levels and change the dose if necessary.

Other Interactions
The simultaneous use of carbamazepine and loxapine, quetiapine (medicines used to treat mental disorders), primidone, progabid, valproic acid, valnoctamide, valpromide and brivaracetam (antiepileptics, other medicines used to treat seizure disorders) can lead to an increase in the plasma levels of the active metabolite carbamazepine-10,11-epoxide and thus to the same side effects as too high a dose of carbamazepine.

Concomitant use of carbamazepine and levetiracetam may increase carbamazepine toxicity.

Carbamazepine can increase the liver damage caused by isoniazid (a medicine used to treat tuberculosis).
Simultaneous use of carbamazepine and lithium (medicines used to treat psychiatric disorders), metoclopramide (medicines used to treat gastrointestinal disorders) or neuroleptics (haloperidol, thioridazine: medicines for the treatment of mental disorders) can promote the occurrence of neurological side effects.

On the other hand, in patients treated with antipsychotics, carbamazepine may decrease the plasma levels of these medicines, thereby causing a worsening of the clinical picture. The doctor may therefore also consider an increase in the dose of the respective neuroleptic to be necessary.

It is pointed out that in particular the simultaneous use of lithium (medicine for the treatment and prevention of certain mental and emotional disorders) and carbamazepine can enhance the nervous system-damaging effects of both active ingredients. Therefore, careful monitoring of blood levels of both is necessary. A previous treatment with neuroleptics should be more than 8 weeks ago and not at the same time. Look out for the following signs: Unsteady gait (ataxia), twitching or trembling of the eyes (horizontal nystagmus), increased muscle reflexes, muscle twitching (muscle fasciculations).

The combined administration of carbamazepine and some diuretics (hydrochlorothiazide, furosemide) can lead to a reduced sodium content in the blood serum.

Carbamazepine may reduce the effectiveness of certain medicines used during anaesthesia to relax muscles (non-depolarizing muscle relaxants such as pancuronium). This allows the neuromuscular blockade to be removed more quickly. Patients treated with muscle relaxants should be monitored for this and their dosage increased if necessary.

Co-administration of carbamazepine and direct-acting oral anticoagulants (rivaroxaban, dabigatran, apixaban and edoxaban) can lead to reduced plasma levels of direct-acting oral anticoagulants. For more details, please refer to the table below:

Direct-acting oral anticoagulants (DOAC)	**Recommendations for the simultaneous use of DOAC and carbamazepine**
Apixaban	In the prophylaxis of venous thromboembolism (VTE) after elective hip or knee replacement surgery, in the prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) as well as in the prophylaxis of recurrent deep vein

	thrombosis (DVT) and pulmonary embolism (PE), concomitant use should be undertaken with caution. Concomitant use should be avoided when treating DVT and PE.
Rivaroxaban	Concomitant use should be avoided unless the patient is closely monitored for signs and symptoms of thrombosis.
Dabigatran	Concomitant use should be avoided.
Edoxaban	Co-administration should be done with caution.

There are indications in the literature that the additional intake of carbamazepine in the case of pre-existing neuroleptic therapy increases the risk of the occurrence of a so-called neuroleptic malignant syndrome (possibly life-threatening condition with increase in body temperature and muscle stiffness) or Stevens-Johnson syndrome (severe skin reaction).

If isotretinoin (active ingredient for acne treatment) and carbamazepine are given at the same time, the carbamazepine plasma level should be checked.

The simultaneous administration of carbamazepine with paracetamol (analgesic and antipyretic medicine) can reduce the bioavailability and thus the effectiveness of paracetamol.

Carbamazepine seems to increase the excretion (elimination) of thyroid hormones and increase the need for them in patients with hypothyroidism. For this reason, the thyroid parameters must be determined in these patients who are receiving substitution therapy at the beginning and end of therapy with carbamazepine. If necessary, the dose of the thyroid hormone preparations should be adjusted.

Concomitant administration of antidepressants of the serotonin reuptake inhibitor type (depression-relieving medicines such as fluoxetine) can lead to toxic serotonin syndrome.

It is recommended not to use carbamazepine in combination with nefazodone (antidepressant) since carbamazepine can lead to a significant reduction in the nefazodone plasma level up to a loss of effect. In addition, when nefazodone and carbamazepine are taken at the same time, the carbamazepine plasma level increases and that of its active degradation product, carbamazepine-10,11-epoxide, decreases.

Concomitant administration of carbamazepine and other medicines that can cause cardiac conduction disorders (arrhythmia in the heart), like antiarrhythmics (medicines against cardiac arrhythmia), cyclic antidepressants (medication to relieve depression) or erythromycin (antibiotic), increases the risk of cardiac conduction disorders.

Curatil with food, drink and alcohol

• Drinking alcohol may affect you more than usual. Discuss whether you should stop drinking with your doctor.

• Eating grapefruit, or drinking grapefruit juice, may increase your chance of experiencing side effects.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

Curatil can cause major birth defects. If you take carbamazepine during pregnancy your baby has up to 3 times the risk of having a birth defect than women not taking an antiepileptic medication. Major birth defects include neural tube defect (opening in the spine), birth defect of the face such as cleft of the upper lip and palate, birth defect of the head, heart defects, birth defect of the penis involving the urinary opening (hypospadias) and finger defects have been reported. Your unborn baby should be closely monitored if you have taken Curatil while pregnant.

Problems with neurodevelopment (development of the brain) have been reported in babies born to mothers who used Curatil during pregnancy. Some studies have shown that carbamazepine negatively affects neurodevelopment of children exposed to carbamazepine in the womb, while other studies have not found such an effect. The possibility of an effect on neurodevelopment cannot be ruled out.

If you are a woman of childbearing age and are not planning a pregnancy, you should use effective contraception during treatment with carbamazepine. Curatil may affect how hormonal contraceptives, such as the contraceptive (birth control) pill, work and make them less effective at preventing pregnancy. You may get breakthrough bleeding or spotting. Talk to your doctor, who will discuss with you the most suitable type of contraception to use while you are taking Curatil. If treatment with Curatil is discontinued you should continue using effective contraception for 2 weeks following discontinuation.

If you are a woman of childbearing age and are planning a pregnancy, talk to your doctor before you stop contraception and before you become pregnant about switching to other suitable treatments in order to avoid exposing the unborn baby to carbamazepine.

If you are or think you might be pregnant, tell your doctor straight away. You should not stop taking your medicine until you have discussed this with your doctor. Stopping your medication without consulting your doctor could cause seizures which could be dangerous to you and your unborn child. Your doctor may decide to change your treatment.

If you take Curatil during pregnancy, your baby is also at risk for bleeding problems right after birth. Your doctor may give you and your baby a medicine to prevent this.

Breast-feeding

Carbamazepine passes into breast milk. The benefits of breast-feeding should be weighed against the risk of adverse effects in the infant. Breast-fed infants of mothers treated with carbamazepine should be carefully observed for side effects such as poor weight gain, excessive sleepiness or allergic skin reaction.

Fertility

There have been isolated cases of sexual dysfunction, such as impotence or decreased libido. Reduced male fertility and/or abnormal sperm production have been reported very rarely.

Driving and using machines:

Curatil can make you feel dizzy or drowsy, or may cause blurred vision, double vision, or you may have a lack of muscular coordination, especially at the start of treatment or when the dose is changed. If you are affected in this way, or if your eyesight is affected, you should not drive or operate machinery.

Curatil contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Curatil

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The dosage is to be determined and checked individually by the (specialist) doctor, whereby freedom from seizures should be aimed for at the lowest possible dosage, especially during pregnancy.

You must not make any changes to the treatment or dose without first consulting your doctor, in order not to jeopardize the success of the treatment.

A gradually (creeping) increase in dosage up to the optimally effective dose is recommended.

The daily dose is usually administered in 1 to 2 single doses.

The general daily dose range is between 400 and 1,200 mg of carbamazepine.

A total daily dose of 1,600 mg carbamazepine should generally not be exceeded, since higher doses increase the number of side effects.

The therapeutic dose should be determined, particularly in combination therapy, by determining the plasma levels and depending on the effectiveness. Experience has shown that the therapeutic carbamazepine level is between 4 and 12 micrograms/ml.

In individual cases, the required dose can deviate significantly from the specified starting and maintenance dose (e.g. due to accelerated degradation by enzyme induction or due to drug interactions when other medicines are taken at the same time).

Carbamazepine should preferably be used only (monotherapy) for the treatment of epilepsy. Treatment should be supervised by a specialist doctor experienced in the treatment of epilepsy.

When changing to treatment with carbamazepine, the dose of the anti-seizure medicine to be discontinued should be reduced gradually.

The following general dosing schedule is recommended for the treatment of epileptic seizure disorders:

	Daily starting dose in mg (or number of prolonged-release tablets)	**Daily maintenance dose in mg (or number of prolonged-release tablets)**
Adults	200 mg in the evening (1 prolonged-release tablet)	200 to 600 mg in the morning (1 to 3 prolonged-release tablets) 400 to 600 mg in the evening (2 to 3 prolonged-release tablets)
Children* **6 to 10 years**	200 mg in the evening (1 prolonged-release tablet)	200 mg in the morning (1 prolonged-release tablet)

		200 to 400 mg in the evening (1 to 2 prolonged-release tablets)
15 years	200 mg in the evening (1 prolonged-release tablet)	200 to 400 mg in the morning (1 to 2 prolonged-release tablets) 400 to 600 mg in the evening (2 to 3 prolonged-release tablets)
> 15 years	According to the adult dose	

* Note:

For children under 6 years of age, non-delayed-release dosage forms are available for starting and maintenance dosing (Suspension or tablets). The administration of prolonged-release tablets cannot be recommended due to insufficient knowledge..

Recommended maximum dose:

6 to 15 years: 1,000 mg/day

Over 15 years: 1,200 mg/day

Seizure disorders (Epilepsy):

In general, in adults the starting dose of 1 to 2 prolonged-release tablets of carbamazepine (equivalent to 200 to 400 mg carbamazepine/day) should be gradually increased to the maintenance dose of 4 to 6 prolonged-release tablets of carbamazepine (equivalent to 800 to 1200 mg carbamazepine/day).

In general, the maintenance dose for children is an average of 10 to 20 mg carbamazepine/kg body weight/day.

For recommended dosing schedule, see above.

Paroxysmal facial pain (trigeminal neuralgia):

The usual dose is 600-800 mg a day.

The maximum dose is 1200mg a day.

If you are elderly you might require a lower dose.

Prophylaxis of manic-depressive phases:
The starting dose, which is usually sufficient as a maintenance dose, is 1 to 2 prolonged-release tablets of carbamazepine (equivalent to 200 to 400 mg carbamazepine) daily.

If necessary, the dose can be increased to 2 prolonged-release tablets of carbamazepine (equivalent to 800 mg carbamazepine) 2 times daily.

Note:

A lower dosage is indicated in patients with severe cardiovascular disease, liver and kidney disease and in the elderly.

Method of application

The prolonged-release tablets should be swallowed whole and not chewed or crushed.

Please take the prolonged-release tablets during or after meals with sufficient liquid (e.g. 1 glass of drinking water (200 ml)).

In some cases, dividing the daily dose into 4 to 5 individual doses has proven to be particularly effective. In these cases, non-extended-release formulations of carbamazepine are preferable to sustained-release formulations.

Duration of application

The duration of use depends on the respective indication and the individual reaction of the patient and is determined by the attending physician.

The antiepileptic therapy is basically a long-term therapy.

A specialist doctor experienced in the treatment of epilepsy should decide on the setting, duration of treatment and discontinuation of carbamazepine in individual cases.

In general, a dose reduction and discontinuation of the medication should be considered after two to three years of seizure free period at the earliest.

Discontinuation must take place in gradual dose reductions over one to two years; children can outgrow the dose per kg body weight instead of age-appropriate dose adjustment, whereby the EEG findings should not deteriorate.

In the treatment of neuralgia, it has proven useful to carry out the therapy over a period of a few weeks with a maintenance dose that is just about sufficient for relief from pain. Careful dose reduction should be used to determine whether spontaneous remission has occurred in the meantime. If pain attacks recur, the original maintenance dose should be continued.

The prophylaxis of manic-depressive phases is a long-term treatment.

Please talk to your doctor or pharmacist if you have the impression that the effect of carbamazepine is too strong or too weak.

If you forget to take Curatil

Do not take a double dose to make up for a forgotten dose. Please continue to take your medication as directed in its application.

If you take more Curatil than you should

If you accidentally take too many tablets, contact your doctor or your nearest hospital emergency department immediately.

In the event of an overdose of carbamazepine, the undesirable symptoms mentioned under section 4 “Possible side effects" may become more pronounced.

Central nervous system
Depression of the nervous system, disturbances of consciousness (drowsiness, sleepiness (somnolence), rigidity (stupor), coma, dizziness, disorientation, restlessness, agitation, confusion, feeling hot (flushing), hallucinations, blurred vision, inarticulate or slurred speech, Trembling eyes (nystagmus), unsteady gait (ataxia), Disturbances or malfunctions of movement sequences (dyskinesias), Reflex abnormalities (first increased, then weakened reflexes), seizures of the brain (tonic-clonic convulsions), psychomotor disorders, muscle twitching (myoclonia), opisthotonus, involuntary movements, shaking (tremor), low body temperature (hypothermia), dilated pupils (mydriasis), EEG disorders.

Respiratory system
Disturbances in breathing (respiratory depression), water in the lungs (pulmonary oedema), blue discolouration of the face (cyanosis), respiratory arrest.

Cardiovascular system

Increased heart rate (tachycardia) usually reduced (hypotonic) blood pressure, possibly also high blood pressure (hypertension), disorders of the spread of excitation in the heart (ECG changes, arrhythmias, AV block), syncope, cardiac arrest, intense reddening with a feeling of heat (flushing).

Gastrointestinal tract
Nausea, vomiting, delayed gastric emptying, decreased intestinal motility.

Urinary tract, genitals
Urinary retention, reduced or no urine production, retention of water in the body.

Laboratory findings
low levels of sodium in the blood serum (hyponatraemia), possibly acidification of the blood, possibly increased blood sugar (hyperglycaemia), increased muscle creatine phosphokinase, increased or decreased white blood cell count (leukocytosis, leukopenia, neutropenia), excretion of sugar in the urine (glycosuria), increase in a specific metabolic product in the urine (acetonuria).

In the event of any application error, a doctor must be informed immediately. If high doses have been ingested, emergency measures should be taken (admission to hospital).

A specific antidote for acute poisoning with carbamazepine does not yet exist. The treatment of an overdose with carbamazepine depends on the symptoms that occur and usually has to be done in hospital.

If you stop taking Curatil

Under no circumstances should you interrupt treatment with carbamazepine or prematurely end it on your own initiative. You can endanger the success of the treatment and trigger epileptic seizures again. Please talk to your doctor beforehand if you experience any intolerance or a change in your clinical picture.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The frequency of side effects is based on the following categories:

Very common: may affect more than 1 in 10 people

Common: may affect up to 1 in 10 people

Uncommon: may affect up to 1 in 100 people

Rare: may affect up to 1 in 1,000 people

Very rare: may affect up to 1 in 10,000 people

Not known: frequency cannot be estimated from the available data

The following side effects can have serious consequences:
Contact your doctor **immediately** if you experience any of the following adverse reactions. These can be early signs of serious damage to blood, liver, kidney or other organs and may require urgent medical attention.

- If you develop flu-like symptoms, fever, sore throat, skin rash, mouth ulcers, swelling of the lymph glands or increased susceptibility to infection (signs of certain changes in the blood count, in particular a reduction in white blood cells)

- If you experience fatigue, headache, shortness of breath during physical exertion, dizziness, pale appearance, frequent infections leading to fever, chills, sore throat, mouth ulcers, bruising more easily than normal, nosebleeds (signs of certain changes in the blood count, in particular pancytopenia)
- If you develop a red, blotchy rash mainly on the face and simultaneous exhaustion, fever, nausea, loss of appetite (signs of systemic lupus erythematosus)
- In the event of yellow discoloration of the skin or whiteness in the eye (signs of hepatitis)
- In the event of dark urine (signs of porphyria or hepatitis)
- In the event of reduced urinary excretion due to renal failure and blood in the urine
- In the event of severe pain in the upper abdomen, vomiting, loss of appetite (signs of pancreatitis)
- In the event of skin rash, skin redness, blisters on lips, eyes or in the mouth, peeling of the skin and simultaneous fever, chills, headache, cough, pain all over the body (signs of severe skin reactions)
- In the event of swelling of the face, eyes or tongue, difficulty swallowing, wheezing, hives or itching all over your body, skin rash, fever, abdominal cramps, chest discomfort or tightness around the chest, difficulty breathing, loss of consciousness (signs of angioedema or severe allergic reactions)
- If you feel drowsy, confusion, muscle twitching or your seizures get worse (symptoms that may be related to low blood sodium levels)
- In the event of fever, nausea, vomiting, headache, stiff neck and extreme sensitivity to light (signs of meningitis)
- In the event of muscle stiffness, high fever, changes in consciousness, high blood pressure, excessive salivation (signs of neuroleptic malignant syndrome)
- In the event of irregular heartbeat and chest pain
- In the event of impaired consciousness and fainting
- In the event of diarrhoea, abdominal pain and fever (signs of bowel inflammation). The frequency of this side effect is not known*
- In the event of falls due to dizziness, drowsiness, drop in blood pressure, confusion.

Other possible side effects:

The observed side effects occur less frequently when carbamazepine is administered alone (monotherapy) than when other antiepileptic medicines are administered at the same time (combination therapy).

Some of the side effects are dose-dependent, especially at the beginning of treatment, if the initial dose is too high or in elderly patients, such as central nervous disorders (dizziness, headache, gait disturbances, drowsiness, sedation, fatigue, double vision, accommodation disorders such as blurred vision), gastrointestinal disorders (nausea, vomiting) and allergic skin reactions.

Dose-dependent side effects usually subside on their own within a few days or after a temporary dose reduction. Carbamazepine should therefore be dosed gradually if possible. Central nervous system disorders can be a sign of relative overdose or large fluctuations in plasma levels; it is therefore advisable in these cases to determine the plasma levels.

Infections and parasitic diseases
The frequency of reactivation of a herpes virus infection is not known (This can be serious if the immune system is weakened.).*

Blood and lymphatic system
Blood count changes such as a reduced count of white blood cells (leukopenia) occur very commonly. According to the literature, the most common of these is benign leukopenia, which is temporary in about 10% and persistent in 2%. Benign leukopenia mainly occurs within the first four months of therapy.

An increased count of a certain type of white blood cell (eosinophilia) or a reduced count of blood platelets (thrombocytopenia) is common.

Rarely, an increased count of other white blood cells (leukocytosis) or swelling of the lymph nodes as well as folic acid deficiency occur.

Very rarely, sometimes life-threatening blood cell damage, such as agranulocytosis, aplastic anemia, pancytopenia, aplasia of red blood cells, as well as other forms of anemia (megaloblastic, possibly hemolytic), reticulocytosis and various forms of porphyria (acute intermittent porphyria, porphyria variegata, porphyria cutanea tarda) occur. Spleen enlargement has been reported very rarely.

Hypersensitivity reactions
Occasionally delayed hypersensitivity reactions affecting multiple organ systems with fever, skin rash, vascular inflammation, lymph node swelling, pseudolymphoma, joint pain, altered white blood cell count (leukopenia, eosinophilia), Enlargement of the liver and spleen, abnormal liver function tests and liver disease with destruction and atrophy of the intrahepatic bile ducts. These phenomena can occur in various combinations and other organs such as lungs, kidneys, affect the pancreas or heart muscle and large intestine.

Very rarely, an acute general allergic reaction and an aseptic (not caused by bacteria and viruses) meningitis (meningitis) with muscle twitching (myoclonus) and an increase in certain white blood cells (eosinophilia), anaphylactic (shock) reactions and swelling of the skin and mucous membranes (angioedema) have been observed.

The frequency of a skin rash with blood count changes and systemic symptoms (drug rash with eosinophilia and systemic symptoms) is not known.*

Metabolism (water and mineral balance), hormone status
Tissue water retention (oedema), decreased fluid excretion, weight gain, hyponatraemia (decreased blood serum sodium levels) and decreased plasma osmolality are common, which rarely can lead to water intoxication with lethargy, vomiting, headache, confusional states and other neurological disorders.

Very rarely, an increase in prolactin levels has been reported with or without clinical symptoms such as swelling of the male breasts (gynaecomastia) or milk flow (galactorrhea). Thyroid function parameters T3, T4, TSH and FT4 may be affected, particularly when used concomitantly with other anti-seizure medicines. Usually there are no clinical symptoms.

Carbamazepine can lower the serum calcium level by accelerating the breakdown of 25-OH-cholecalciferol. This can very rarely lead to osteomalacia (softening of the bones). Elevated levels of cholesterol, including HDL-cholesterol and triglycerides, may occur very rarely, as may elevation of serum free cortisol.

Carbamazepine can lower serum folic acid levels, and there is also evidence of reduced vitamin B12 levels and increased serum homocysteine levels under carbamazepine. The frequency of high blood ammonia levels is not known (hyperammonemia). Symptoms of hyperammonemia can include irritability, confusion, vomiting, loss of appetite, and drowsiness.

Psyche
Drowsiness, dizziness, tiredness, sleepiness, gait and movement disorders, occasionally headache, confusion and restlessness (agitation) in elderly patients can occur very frequently.

Sensory illusions (optical and acoustic hallucinations), mood changes such as depression, depressive or manic moods (associated with elevated mood, aggression), loss of appetite, restlessness, aggressive behaviour, confusion and restlessness (agitation) have rarely been observed.

Very rarely, phobic disorders (anxiety disorders), difficulty thinking and lack of drive occurred. Latent psychoses (subliminal mental illnesses) can be activated during treatment with carbamazepine.

Nervous system
Drowsiness, dizziness, tiredness, sleepiness, gait and movement disorders and exhaustion can occur very frequently.

Headaches, double vision and accommodation disorders (e.g. blurred vision), occasionally eye movement disorders, accompanied by eye tremors (nystagmus), involuntary movements (e.g. tremors, flutter tremors, tics, dystonia) occur frequently.

In addition, movement disorders e.g. involuntary movements in the mouth-face area such as grimacing (orofacial dyskinesia), twisted movements (choreoathetosis) and speech disorders (dysarthria, slurred speech), discomfort, muscle weakness, nerve diseases (polyneuropathy), nerve inflammation (peripheral neuritis, peripheral neuropathy) and signs of paralysis (paresis).

Taste disturbances or neuroleptic malignant syndrome have been reported very rarely.

The frequency of memory loss is not known.*

There is evidence that carbamazepine can worsen symptoms of multiple sclerosis.

As with other anti-seizure medications, carbamazepine can increase seizures; In particular, absences (special types of seizures originating in both hemispheres of the brain) can occur more frequently or recur.

Ocular
Conjunctivitis, lens opacities and increased intraocular pressure occur very rarely.

Retinotoxicity (damage to the retina) was reported in two patients associated with long-term carbamazepine therapy, which resolved after carbamazepine discontinuation.

Ear and vestibular system
Hearing disorders such as ringing in the ears (tinnitus), excessive or reduced hearing sensitivity (hyper- or hypoacusis) and changes in pitch perception occur very rarely.

Cardiac and circulatory system
Occasionally, conduction disturbances in the heart (AV block) occur, in individual cases with loss of consciousness, as well as increased or low blood pressure.

Occasionally to rarely, a slowing of the heartbeat (bradycardia) and cardiac arrhythmia, circulatory collapse, cardiac insufficiency and worsening of a pre-existing coronary artery disease can occur.

Inflammation of the veins (thrombophlebitis) and blood clots (thromboembolism) have also been observed.

Respiratory system
Very rarely, hypersensitivity reactions of the lungs with fever, shortness of breath, inflammation of the lungs (pneumonitis, pneumonia, alveolitis) and individual cases of pulmonary fibrosis have been described in the scientific literature.

Gastrointestinal tract
Nausea and vomiting are very common, often loss of appetite, dry mouth, occasionally diarrhea or constipation. Rarely, abdominal pain, very rarely inflammation of the mucous membranes in the mouth and throat area (stomatitis, gingivitis, glossitis) or pancreatitis have been reported.

Liver and bile
Changes (increases) in liver function tests are very common with gamma-GT, common with alkaline phosphatase, occasionally with transaminases, rarely jaundice or liver inflammation (hepatitis in various forms: cholestatic, hepatocellular, granulomatous, mixed) and liver disease with destruction and wasting of the intrahepatic bile ducts. Rarely, life-threatening acute hepatitis or liver failure can occur, especially within the first months of therapy.

Skin, mucous membranes, vascular system
Allergic skin reactions, including severe ones, with and without fever and hives (urticaria) are very often reported, occasionally about skin inflammation, where the skin or mucous membranes peel off in a scaly manner (exfoliative dermatitis), inflammatory reddening and scaling of the skin affecting the whole body (erythroderma), rarely about severe and possibly

life-threatening skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) (see section 2), itching (pruritus) or disseminated lupus erythematosus (autoimmune disease with vascular inflammation). Very rarely sensitivity to light (photosensitivity), skin reddening with disc or nodular changes and bleeding (erythema exsudativum multiforme et nodosum), small patchy skin bleeding (purpura) occur, hair loss, increased sweating, changes in skin pigmentation, acne, hirsutism (male-type hair growth in women), inflammation of blood vessels (vasculitis). The frequency of an acute generalized skin rash (acute generalized exanthematous pustulosis), the appearance of purple to red-purple patchy skin lesions that may be itchy and the frequency of nail fallout is not known.*

Musculoskeletal system
Rarely reported muscle weakness, very rarely joint pain (arthralgia), muscle pain (myalgia) as well as muscle cramps have been reported. These symptoms disappeared when carbamazepine was discontinued.

Cases of reduced bone density (osteoporosis up to and including fractures) have been reported. Please consult your doctor or pharmacist if you are taking antiepileptic medicines for a long time, if you have been diagnosed with osteoporosis or if you are taking cortisone or other steroid hormones at the same time.

Urinary tract, genitals
Occasionally, disorders of renal function occur, e.g. excretion of protein in the urine (albuminuria), blood in the urine (hematuria), decreased urine production (oliguria) or increased blood urea nitrogen (azotaemia), very rarely interstitial nephritis (inflammation of the kidney tissue) or kidney failure or other urinary problems (frequent urination, pain when urinating, urge to urinate frequently without increased urination (pollakisuria), urinary retention).

Furthermore, very rarely sexual disorders e.g. impotence, decreased libido, decreased male fertility and/or altered sperm cell formation (decreased sperm count and/or motility).

Laboratory tests
A reduction in the level of gamma globulins in the blood (hypogammaglobulinaemia) has been found very rarely.

* Spontaneous reports and literature cases of side effects (frequency cannot be estimated from the available data).

In post-marketing experience with carbamazepine, side effects have been identified through spontaneous reporting and literature. Since the reports were voluntary and from an unknown population size, the frequency cannot be estimated from the available data.

If you notice one or more of the side effects listed above, tell your doctor immediately so that he can decide on the severity and any necessary measures.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Curatil

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the pack carton after 'Exp'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Curatil contains

Each prolonged-release tablet contains 200 mg carbamazepine.
Each prolonged-release tablet contains 400 mg carbamazepine.

The other ingredients are: microcrystalline cellulose, ammonio methacrylate copolymer**,** lactose monohydrate, maize starch, sodium starch glycolate type A, magnesium stearate, talc, triethyl citrate.

What Curatil looks like and contents of the pack

Curatil 200 mg Prolonged-Release Tablets: White to off-white, round, biconvex tablets, debossed with "297" on one side and "HP" on the other side.

Curatil 400 mg Prolonged-Release Tablets: White to off-white, round, biconvex tablets, debossed with "298" on one side and "HP" on the other side.

They are available in blister packs of 30, 50, 56, 100 and 200 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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