*Your doctor has prescribed Neurotop Tablets for the treatment of your complaints. Please read this leaflet carefully – it contains important information on the use of this medicinal product.*
*This medicine has been prescribed for you personally and you should not pass it on to others even if their symptoms may be similar to yours.*

Patient Information

# Neurotop®
# Neurotop® retard
# Neurotop® retard

## 200 mg Tablets
## 300 mg Prolonged-release Tablets
## 600 mg Prolonged-release Tablets

**Active Ingredient:** Carbamazepine

**Reg. No. (Austria):**
200 mg: 1-17282
300 mg: 1-18147
600 mg: 1-18146

**What is in Neurotop 200 mg Tablets?**
1 tablet contains:
carbamazepine 200 mg

Other ingredients: lactose, corn starch, gelatine, sodium starch glycolate, talc, magnesium stearate.

**What is in Neurotop retard 300 mg Tablets?**
1 prolonged-release tablet contains:
carbamazepine 300 mg

Other ingredients: Eudragit (RS PM and L 30D), colloidal anhydrous silica, magnesium stearate, talcum, sodium starch glycolate, microcrystalline cellulose.

**What is in Neurotop retard 600 mg Tablets?**
1 prolonged-release tablet contains:
carbamazepine 600 mg

Other ingredients: Eudragit (RS PM and L 30D), colloidal anhydrous silica, magnesium stearate, talcum, sodium starch glycolate, microcrystalline cellulose.

**Dosage Form:**
200 mg: Tablets
300 and 600 mg: Prolonged-release Tablets

**Package Sizes:** 50 and 100 tablets

**How does Neurotop work?**
Absorption
Carbamazepine is absorbed almost completely from the tablets and relatively slowly depending on the dosage form: following a single dose, tmax is attained after 12 (tablets) or 24 hours (prolonged-release tablets).
Bioavailability: The bioavailability of carbamazepine following administration of the tablets is almost 100%; with the prolonged-release tablets it is approximately 15% lower. Food intake has no effect on bioavailability.
Plasma concentrations: The $C_{max}$ of carbamazepine following a single dose of 400 mg (tablets) is approx. 4.5 $\mu$g/ml.
With the prolonged-release tablets there was a statistically significant reduction in fluctuation index and $C_{max}$ at steady state, and a non·significant reduction in $C_{min}$. The plasma concentration in the „therapeutic range" at steady state is approx. 4–12 $\mu$g/ml, equivalent to 17–50 $\mu$mol/litre carbamazepine; the concentration of carbamazepine-10,11-epoxide (pharmacologically active metabolite) is approx. 30% of the carbamazepine concentration.
Steady-state plasma concentrations of carbamazepine are reached within 1–2 weeks, depending individually on carbamazepine autoinduction and on heteroinduction by other enzyme-inducing drugs, as well as on pretreatment status, dosage and duration of treatment.

**Distribution**
Carbamazepine is 70–80% bound to serum proteins. The concentration of unchanged substance in the CSF and saliva is equivalent to the non-protein-bound portion in the plasma (20–30%). The concentrations found in breast milk are equivalent to 25–60% of those in the plasma. Carbamazepine crosses the placental barrier.
The apparent distribution volume is 0.8–1.9 litres/kg.

**Metabolism**
Carbamazepine is metabolized in the liver, primarily via the epoxide-diol pathway. The first step involves oxidation to carbamazepine-10,11-epoxide, mainly via the cytochrome P450 3A4 isoenzyme. Carbamazepine-10,11-epoxide is pharmacologically active and is almost completely transformed to the 10,11·transdiol derivative and its glucuronides. 9-hydroxy-methyl-10-carbamoyl acridan is a less important metabolite. Other important biotransformation pathways for carbamazepine lead to various mono-hydroxylated compounds, as well as to the N-glucuronide of carbamazepine.
Carbamazepine induces its own metabolism.

**Elimination**
The mean plasma elimination half-life is 36 hours following a single-dose, 16–24 hours following repeated administration (autoinduction of the hepatic mono-oxygenase enzyme system), and 9–10 hours following concomitant administration of other liver-enzyme-inducing drugs (e.g. phenytoin, phenobarbital).
Excretion: After a single dose of 400 mg carbamazepine, 72% is excreted in the urine (2% unchanged, 1% epoxide, approx. 30% carbamazepine-10,11-transdiol and other inactive metabolites) and 28% in the faeces.
Pharmacokinetics in special clinical situations:
Note: The pharmacokinetics of carbamazepine are unaltered in the elderly. No data are available on patients with impaired liver or kidney function.

**Marketing Authorisation Holder:**
Gerot Pharmazeutika, Vienna

**What are Neurotop Tablets used for?**
Epilepsy
- Partial seizures (simple or complex, with or without loss of consciousness), with or without secondary generalization.
- Generalized tonic·clonic seizures.
- Mixed forms of these seizures.

Neurotop is suitable for both monotherapy and combination therapy.
Neurotop is not normally effective in absence (petit mal) seizures or in myoclonic seizures (see Precautions).
Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.
Alcohol withdrawal syndrome
Idiopathic trigeminal neuralgia and trigeminal neuralgia secondary to multiple sclerosis (typical or atypical).
Idiopathic glossopharyngeal neuralgia.

**When should you not use Neurotop Tablets?**
The product must not be used in case of:
Known hypersensitivity to carbamazepine and oxcarbazepine or structurally related drugs (e.g. tricyclic antidepressants), or to any of the other components of the formulation.
Atrioventricular (AV) block, history of bone-marrow depression or history of acute intermittent porphyria. Due to its structural similarity to tricyclic antidepressants, use of Neurotop in combination with monoamino-oxidase inhibitors (MAOIs) is not recommended.
MAOIs should therefore be discontinued a minimum of two weeks before Neurotop is started, or even earlier if the clinical situation permits.

**When do you have to take special care with Neurotop?**
***General***
Neurotop should only be given under medical supervision.
Neurotop should be used with caution in patients with mixed seizures that include absences, (typical or atypical). In all these conditions, Neurotop may exacerbate seizures. If this happens, Neurotop should be discontinued.
Although correlations between dosage and plasma concentrations of carbamazepine, and between plasma concentrations and clinical efficacy or to tolerability, are rather tenuous, monitoring of plasma concentrations may be useful in the following circumstances: dramatic increase in seizure frequency/ verification of patient compliance; during pregnancy; where the patient is a child or adolescent; where an absorption disorder or toxicity is suspected; where the patient is taking more than one drug (see Interactions).

***Discontinuation of treatment***
Abrupt withdrawal of Neurotop may precipitate seizures.
If Neurotop therapy has to be withdrawn abruptly in epileptic patients, the switch to an alternative anti epileptic should be made under cover of a suitable drug (e.g. diazepam i.v. or rectal, or phenytoin i.v.).

***Hypersensitivity reactions, intoxication***
Neurotop may trigger hypersensitivity reactions, which can affect the skin, liver, haematopoietic organs and lymphatic system, either individually or together in the context of a systemic reaction (see Adverse effects). Patients should be informed about the signs of incipient intoxication and the symptoms of possible haematological complications, as well as about the symptoms of cutaneous or hepatic hypersensitivity reactions. They should be instructed to consult the doctor immediately in the event of reactions such as fever, sore throat, perineal infection, exanthema, mouth ulcers, easy bruising, petechiae or idiopathic thrombocytopenic purpura.
Mild cutaneous reactions, such as isolated macular or maculopapular eruptions, are frequently transient and not dangerous; they usually disappear within a few days or weeks, with or without a change in dosage. Close monitoring is, however, necessary, and the drug should be discontinued immediately in the event of progression or signs of a systemic hypersensitivity reaction.
In the event of signs or symptoms suggestive of severe cutaneous reactions (e.g. Stevens-Johnson syndrome, Lyell's syndrome), Neurotop should be discontinued at once.
Cross-hypersensitivity can occur between carbamazepine and oxcarbazepine (Trileptal*) in approximately 25–30% of patients.
Cross-hypersensitivity can occur between carbamazepine and phenytoin.

***Heart, liver or kidney disease***
Neurotop should be prescribed only after critical benefit-risk appraisal and under close monitoring in patients with heart, liver or kidney disease, with a history of haematological adverse reactions to other drugs, or with previous interrupted courses of therapy with Neurotop.
Baseline and periodic evaluations of liver function must be performed before and during Neurotop therapy, particularly in patients with a history of liver disease and in the elderly. Neurotop should be discontinued immediately in the event of liver function deterioration or active hepatitis.
Baseline and periodic complete urinalysis and BUN determinations are recommended.
SIADH (syndrome of inappropriate secretion of antidiuretic hormone) may occur during carbamazepine therapy.
Close monitoring is necessary in patients with existing renal disease who require high fluid intake, in patients receiving diuretic therapy and in the event of signs of hyponatraemia (see Adverse effects).

***Haematology***
Agranulocytosis and aplastic anaemia have been associated with Neurotop but the very low incidence makes it difficult to derive a meaningful risk estimate. There are estimates that the incidence is not considerably higher than that calculated for spontaneous occurrences in the general population (4.7 cases per million per year for agranulocytosis and 2.0 cases per million per year for aplastic anaemia).
Slightly decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Neurotop.
In the majority of cases they are transient and are unlikely to signal the onset of aplastic anaemia or agranulocytosis.
Nonetheless, complete blood counts, including platelels and possibly reticulocytes and serum iron, should be performed at baseline and at regular intervals thereafter.
If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count must be closely monitored. Neurotop should be discontinued if any evidence of significant bone-marrow depression appears.

***Central nervous system***
Neurotop shows slight anticholinergic activity and patients with increased intraocular pressure should therefore be closely monitored during therapy.
The possibility of activation of latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

***Reproductive ability***
There have been isolated reports of impaired male fertility and/or abnormal spermatogenesis; a causal relationship has not been established.
Breakthrough bleeding has been reported in women taking oral contraceptives. The reliability of oral contraceptives may be adversely affected by Neurotop. Women of child·bearing potential should therefore be advised to use an alternative method of contraception during Neurotop therapy.
Due to enzyme induction, Neurotop may cause failure of the therapeutic effect of drugs containing oestrogen and/or progesterone (e.g. failure of contraception).

**Pregnancy, breast-feeding:**
***Pregnancy***
There is definite evidence of risks to the human fetus, but these may be outweighed by the therapeutic benefit for the mother.
As with other antiepileptic drugs, ingestion of carbamazepine during pregnancy has been associated with reports of various types of embryonic malformation, including spina bifida and other congenital anomalies such as craniofacial defects, cardiovascular malformations and anomalies involving various body systems. It should, however, be borne in mind that developmental disturbances, including malformations, are observed 2–3 times more frequently in the offspring of epileptic mothers than in healthy control groups. The extent to which these effects can be attributed to carbamazepine or to the underlying disease has not been fully elucidated.
The nature of, and need for, treatment should always be carefully planned in epileptic women wishing to conceive and should be reassessed when necessary. Necessary antiepileptic therapy should not be withdrawn during pregnancy, as deterioration of the condition could have a negative impact on the development of the fetus.
Between days 20 and 40 of pregnancy in particular, the dose administered should be as low as possible. Malformations are probably triggered by peak plasma concentrations, and during this period in particular the total daily amount should therefore be given in several small divided doses spread over the day.
Monitoring of plasma levels is recommended.
Throughout pregnancy and postpartum, the patient must be kept under close surveillance (monitoring of serum levels and EEG). The plasma level should remain at the lower end of the therapeutic range (3–7 $\mu$g carbamazepine/ml).In order to reduce the risk further, combination with other antiepileptics or other drugs should be avoided. The risk of malformations is higher with combination therapy, and monotherapy is therefore recommended.
On account of the enzyme-inducing properties of carbamazepine, administration of folic acid is generally recommended before and during pregnancy (prevention of neural tube defects).
In order to avoid haemorrhagic complications, vitamin K should be administered to the mother during the final weeks of pregnancy, and postpartum to the neonate.
There have been some reports of seizures and/or respiratory depression in neonates whose mothers took Neurotop or another anticonvulsant shortly before or during the birth. Regular intake of carbamazepine by the mother can also produce withdrawal symptoms (vomiting, diarrhoea and/or nutritional disturbances) in the neonate.
***Lactation***
Carbamazepine is excreted in breast milk in concentrations approx. 25–60% of those found in the plasma. The benefits of breastfeeding generally outweigh the risks of possible adverse effects. Breastfeeding should be discontinued if the infant is found to have poor weight gain, excessive drowsiness or an allergic skin reaction.

**What other precautions are required?**
⚠ Caution: use of this drug may affect reactivity and your ability to drive.
Neurotop decreases reactivity. Caution is therefore required when driving or operating machinery.

**Which interactions with other substances may occur?**
Cytochrome P450 3A4(CYP 3A4) is the main enzyme catalyzing the formation of carbamazepine-10,11-epoxide. Coadministration of CYP 3A4 inhibitors may result in increased plasma levels of carbamazepine, which could induce adverse reactions. Coadministration of CYP 3A4 inducers might increase the rate of Neurotop metabolism, leading to a decrease in serum carbamazepine and, possibly, a reduction in the therapeutic effect.
Similarly, discontinuation of a CYP 3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine serum levels.
Substances that may increase plasma concentrations of Neurotop: Isoniazid, verapamil, diltiazem, dextropropoxyphene, viloxazine, fluoxetine, fluvoxamine, possibly cimetidine, acetazolamide, danazol, desipramine (possibly), nicotinamide (in adults, only at high doses), nefazodone, macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin), azole derivatives (e.g. itraconazale, keto-conazole, fluconazole), terfenadine, loratadine, grapefruit juice, protease inhibitors for HIV therapy (e.g. ritonavir). Since raised plasma carbamazepine concentrations may result in adverse effects (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of Neurotop should be adjusted accordingly and/or plasma concentrations monitored.
Substances that may reduce plasma concentrations of Neurotop:
Phenobarbital, primidone, progabide, theophylline, methsuximide, rifampicin, cisplatin or doxorubicin and, although the data are partly contradictory, possibly also clonazepam, valproic acid or valpromide. Oxcarbazepine; herbal preparations containing St John's wort (Hypericum perfotalum). Plasma phenytoin levels have been reported to be both raised and lowered by carbamazepine.
On the other hand, valproic acid, valpromide and primidone have been reported to raise the plasma levels of the pharmacologically active metabolite, carbamazepine·10,11-epoxide.
Neurotop dosage should be adjusted where necessary.
Coadministration of felbamate may decrease the serum carbamazepine concentration associated with an increase in the carbamazepine-epoxide concentration and might decrease the serum felbamate concentration.

Isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and carbamazepine·10,11-epoxide; plasma carbamazepine concentrations should be monitored.

Effect of Neurotop on plasma levels of concomitantly administered substances: Carbamazepine may lower the plasma concentration, or diminish or even abolish the activity of certain drugs.
The dosage of the following drugs may have to be adjusted to clinical requirements: clobazam, clonazepam, ethosuximide, primidone, valproic acid, alprazolam; corticosteroids (e.g. prednisolone, dexamethasone); ciclosporin, digoxin, doxycycline, felodipine, haloperidol, imipramine, methadone, oral contraceptives (alternative contraceptive methods should be used), theophylline, oral anticoagulants (warfarin, phenprocumon, dicoumarol), felbamate, lamotrigine, zonisamide, tiagabine, topiramate, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine), clozapine, oxcarbazepine; protease inhibitors for HIV therapy, e.g. indinavir, ritonavir, saquinavir; calcium channel blockers (dihydropyridine group), e.g. felodipine; itraconazole; levothyroxine; midazolam; olanzapine; products containing oestrogens and/or progesterones; praziquantel; risperidone; tramadol; ziprasidone.

**Combinations to be taken into consideration**
Concomitant administration of carbamazepine and paracetamol may reduce the bioavailability of paracetamol.
Concomitant administration of carbamazepine and isoniazid has been reported to result in increased hepatotoxicity of isoniazid.
Combined use of carbamazepine and lithium or metoclopramide on the one hand, and of carbamazepine and neuroleptics (haloperidol, thioridazine) on the other, may lead to an increase in neurological adverse effects (with the latter combination even in the presence of „therapeutic plasma concentrations").
Concomitant administration of Neurotop and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.
Carbamazepine may antagonize the effects of non-depolarizing muscle relaxants (e.g. pancuronium), the dosage of which may therefore need to be raised. Patients should be monitored closely for unexpectedly rapid recovery from neuromuscular blockade.
Like other psychoactive drugs, Neurotop may reduce alcohol tolerance. Abstention from alcohol is therefore advised.

**Dosage and administration:**
*Tablets:* The tablets may be taken, with liquid, during, after or between meals.

*Prolonged-release tablets:*
The prolonged-release tablets (either a whole tablet or, if so prescribed, half a tablet) should be swallowed unchewed with liquid.
Owing to the slow, controlled release of the active substance from the prolonged-release tablets, these can normally be prescribed for twice-daily dosage.
If required, the prolonged-release tablets can also be dissolved in a glass of water, milk, tea or orange juice (but not grapefruit juice! as it may increase the concentration of carbamazepine in the blood). This solution is to be drunk up immediately after preparing it.

During treatment the consumption of alcohol and of grapefruit juice should be avoided.

**Switching dosage forms**
Switching from standard tablets to prolonged-release tablets: Clinical experience shows that the dosage may need to be increased in some patients.
Due to possible drug interactions and different antiepileptic drug pharmacokinetics, the dosage of Neurotop should be selected with caution in elderly patients.

**Epilepsy**
Neurotop should be prescribed as monotherapy whenever possible.
Treatment should be initiated with a low daily dosage, slowly increasing until an optimum effect is achieved. Determination of plasma concentrations may be helpful in determining the optimum dose (see Precautions).
When Neurotop is added to existing antiepileptic therapy, this should be done gradually while maintaining, or if necessary adapting, the dosage of the other drug(s) (see Interactions).

*Adults*
Initially 100–200 mg once or twice daily, slowly increasing until an optimum response is achieved (generally with 400 mg two or three times daily). In some patients 1600 mg or even 2000 mg daily may be appropriate.

*Children*
10–20 mg/kg/daily in divided doses, e.g.

| | |
|---|---|
| up to one year of age: | 100–200 mg daily |
| 1–5 years of age: | 200–400 mg daily |
| 6–10 years of age: | 400–600 mg daily |
| 11–15 years of age: | 600–1000 mg daily |

A starting dose of 20–60 mg/day, increasing by 20–60 mg every second day, is recommended in children aged 4 years or less. In children aged over 4 years, treatment may be started at 100 mg/day, increasing by 100 mg al weekly intervals.

**Trigeminal neuralgia**
A starting dose of 200–400 mg/day should be gradually increased until freedom from pain is achieved (normally with 200 mg t.i.d. or q.i.d.). The dose should then be gradually reduced to the lowest possible maintenance level. A starting dose of 100 mg b.i.d. is recommended in elderly patients.

**Alcohol-withdrawal syndrome**
On the first two days of treatment patients should be given 200 mg t.i.d. or q.i.d. In severe cases, the dosage can be increased in the first few days of treatment to a maximum of 1200 mg/day. Dosage should subsequently be reduced slowly and treatment gradually withdrawn (see Discontinuation of treatment under Precautions).

**Acute mania and maintenance treatment of bipolar affective disorders**
Dosage range: approx. 400–600 mg daily. The normal daily dose is 400–600 mg, given in 1–3 divided doses. The dosage should be increased fairly rapidly in acute mania, whereas small increments are recommended for maintenance therapy of bipolar disorders to ensure optimum tolerability.

Overdose:
**Signs and symptoms**
The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular and respiratory systems.

***Central nervous system***
CNS depression, disorientation, drowsiness, agitation, hallucinations, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia; hyperreflexia followed by hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

***Respiratory tract***
Respiratory depression, pulmonary oedema.

***Cardiovascular system***
Tachycardia, hypotension, occasionally hypertension, conduction disturbances with widening of QRS complex; syncope ill association with cardiac arrest.

***Gastrointestinal tract***
Vomiting, delayed gastric emptying, reduced bowel motility.

***Kidney function***
Urinary retention, oliguria or anuria; fluid retention, water intoxication due to an ADH-like effect of carbamazepine.

***Laboratory findings***
Hyponatraemia, metabolic acidosis (possibly), hyperglycaemia (possibly), increased muscle creatinine phosphokinase.

**Management**
There is no specific antidote.
Management should initially be determined by the patient's clinical condition. The patient should be hospitalized. Determination of plasma concentrations to confirm carbamazepine intoxication and ascertain the size of the overdose.
Gastric evacuation, gastric lavage and administration of activated charcoal. Delayed gastric emptying may result in delayed absorption, leading to relapse during recovery from intoxication.
Supportive medical care in an intensive care unit, with cardiac monitoring and careful correction of electrolyte balance.

***Special recommendations***
*Hypotension*
Give dopamine or dobutamine i.v.

*Disturbances of cardiac rhythm*
Management on a case-by-case basis.

*Convulsions*
Give a benzodiazepine (e.g. diazepam), another antiepileptic such as phenobarbital (with caution because of risk of increased respiratory depression) or paraldehyde.

*Hyponatraemia (water intoxication)*
Fluid restriction and slow and careful i.v. infusion of 0.9% NaCl to reduce the risk of brain damage.
Charcoal haemoperfusion has been recommended. Forced diuresis, haemodialysis and peritoneal dialysis have been reported to be ineffective.
Relapse and aggravation of symptoms should be anticipated on the second and third days following overdosage due to delayed absorption.

**Which side effects may occur?**
Particularly at the start of Neurotop therapy, if the initial dosage is too high, and in elderly patients, certain types of adverse effect occur occasionally or commonly, e.g. CNS adverse effects (dizziness, headache, ataxia, drowsiness, exhaustion, diplopia), gastrointestinal disturbances (nausea, vomiting) and allergic skin reactions.
Dose-dependent adverse effects usually abate within a few days, either spontaneously or after transient dose reduction.
The occurrence of CNS adverse effects may be a manifestation of relative overdosage or of significant fluctuation of plasma concentrations. In such cases it is advisable to monitor plasma concentrations.

Frequency estimates: very common: ≥10%;
common ≥5% to <10%;
uncommon ≥0.1 % to <5%;
rare ≥0,01 % to <0.1 %; very rare <0.01 %.

**Central and peripheral nervous systems**
Very common: Dizziness (10–50%), ataxia (children: 10.4%; adults: 50%), drowsiness (children: 8.2%; adults: 20–40%), exhaustion.
Common: Headache, diplopia, disturbances of visual accommodation (e.g. blurred Vision).
Uncommon: Abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics); nystagmus.
Rare: Orofacial dyskinesias, oculomotor disturbances, speech disturbances (e.g. dysarthria, slurred speech), choreoathetoid disturbances, peripheral neuritis, paraesthesias, muscle weakness, paretic symptoms.
The causative role of carbamazepine in inducing or contributing to the development of a neuromalignant syndrome (NMS), especially in conjunction with neuroleptics, is unclear. The main symptoms of NMS are hyperthermia, rhabdomyolysis, CNS symptoms (agitation, confusion, sedation and even coma) and autonomic nervous system symptoms (sweating, tachycardia, unstable blood pressure).

**Mental function**
Rare: Hallucinations (visual or acoustic), depression, loss of appetite, restlessness, aggressive behaviour, agitation, confusion.
Very rare: Activation of psychosis.

**Skin**
Common: Allergic skin reactions (which may be severe), urticaria.
Uncommon: Exfoliative dermatitis and erythroderma.
Rare: Systemic lupus erythematosus-like syndrome, Stevens·Johnson syndrome, pruritus.
Very rare: Toxic epidermal necrolysis, photosensitivity, erythema multiforme and nodosum, changes in skin pigmentation, purpura, acne, sweating, hair loss.
Isolated cases of hirsutism have been observed. It is not known whether there is a causal relationship.

**Blood**
Very uncommon: Leucopenia (11%).
Uncommon: Eosinophilia, thrombocytopenia.
Rare: Leucocytosis, lymphadenopathy, folic acid deficiency.
Very rare: Agranulocytosis, aplastic anaemia, pure red cell aplasia, megaloblastic anaemia, acute intermittent porphyria, reticulocytosis, and possibly haemolytic anaemia.

**Liver**
Common: Elevated gamma-GT (9.1%; due 10 hepatic enzyme induction), normally not clinically relevant increased alkaline phosphatase and transaminases.
Rare: Jaundice, cholestatic, parenchymal (hepatocellular) or mixed-type hepatitis,
Very rare: Granulomatous hepatitis, liver failure.

**Gastrointestinal tract**
Common: Nausea, vomiting (both 8%). Dry mouth.
Uncommon: Diarrhoea or constipation.
Very rare: Abdominal pain, glossitis, stomatitis, pancreatitis.

**Hypersensitivity reactions**
Rare: Delayed multi-organ-hypersensitivity syndrome with various combinations of fever, exanthema, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepatosplenomegaly and abnormal liver function tests. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).
Very rare: Anaphylactic reactions, aseptic meningitis with myoclonus and peripheral eosinophilia, angioedema. Treatment should be discontinued if such hypersensitivity reactions occur.

**Cardiovascular system**
Rare: Cardiac conduction disturbances, hypertension or hypotension.
Very rare: Bradycardia, arrhythmias, AV block with syncope, collapse, cardiac insufficiency, aggravation of corollary heart disease, thrombophlebitis, thromboembolism.

**Endocrine system and metabolism**
Common: Oedema, fluid retention, weight gain; hyponatraemia and reduced plasma osmolality due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication with lethargy, nausea, vomiting, headache, confusion, neurological disturbances, seizures, disorientation, reduced perception, visual disturbances or encephalopathy (SIADH).
Very rare: Increase in prolactin, with or without clinical manifestations (gynaecomastia, galactorrhoea). Abnormal thyroid function tests: decreased L-thyroxine ($FT_4$,$T_4$,$T_3$) and increased TSH values. Disturbances of bone metabolism (decrease in plasma calcium and 25-0H-cholecalciferol), leading to osteomalacia; increased levels of cholesterol, including HDL cholesterol, and triglycerides.

**Urogenital system**
Very rare: Interstitial nephritis, kidney failure, kidney function impairment (e.g. albuminuria, haematuria, oliguria and elevated BUN/azotaemia), urinary frequency, urinary retention, disturbances of libido/impotence.

**Sensory organs**
Very rare: Dysgeusia, lens opacities, conjunctivitis, disturbances of hearing (e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception).

**Musculoskeletal system**
Very rare: Arthralgia, muscle pain or cramps.

**Respiratory tract**
Very rare: Pulmonary hypersensitivity characterized, for example, by fever, dyspnoea, pneumonitis or pneumonia.

**In case of an overdose**
**Signs and symptoms**
The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular and respiratory systems.

***Central nervous system***
CNS depression, disorientation, drowsiness, agitation, hallucinations, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia; hyperreflexia followed by hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

***Respiratory tract***
Respiratory depression, pulmonary oedema.

***Cardiovascular system***
Tachycardia, hypotension, occasionally hypertension, conduction disturbances with widening of QRS complex; syncope ill association with cardiac arrest.

***Gastrointestinal tract***
Vomiting, delayed gastric emptying, reduced bowel motility.

***Kidney function***
Urinary retention, oliguria or anuria; fluid retention, water intoxication due to an ADH-like effect of carbamazepine.

***Laboratory findings***
Hyponatraemia, metabolic acidosis (possibly), hyperglycaemia (possibly), increased muscle creatinine phosphokinase.

**Management**
There is no specific antidote.
Management should initially be determined by the patient's clinical condition. The patient should be hospitalized. Determination of plasma concentrations to confirm carbamazepine intoxication and ascertain the size of the overdose.
Gastric evacuation, gastric lavage and administration of activated charcoal. Delayed gastric emptying may result in delayed absorption, leading to relapse during recovery from intoxication.
Supportive medical care in an intensive care unit, with cardiac monitoring and careful correction of electrolyte balance.

***Special recommendations***
*Hypotension*
Give dopamine or dobutamine i.v.

*Disturbances of cardiac rhythm*
Management on a case-by-case basis.

*Convulsions*
Give a benzodiazepine (e.g. diazepam), another antiepileptic such as phenobarbital (with caution because of risk of increased respiratory depression) or paraldehyde.

*Hyponatraemia (water intoxication)*
Fluid restriction and slow and careful i.v. infusion of 0.9% NaCl to reduce the risk of brain damage.
Charcoal haemoperfusion has been recommended. Forced diuresis, haemodialysis and peritoneal dialysis have been reported to be ineffective.
Relapse and aggravation of symptoms should be anticipated on the second and third days following overdosage due to delayed absorption.

**Expiry date and storage advice:**
Do not use after the expiry date printed on the carton.

Do not store above 25° C. Protect from light.

**Latest update:** March 2011

Contact your physician or pharmacist, if you have further questions regarding Neurotop.

**Gerot Pharmazeutika Vienna, Austria**