

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Timonil 300 retard,
300 mg/prolonged-release tablets

Timonil 600 retard,
600 mg/prolonged-release tablets

Active substance: Carbamazepine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 prolonged-release tablet contains: 300 or 600 mg carbamazepine.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets

Timonil 300 retard
Round, white, flat tablet cross-scored on both sides
The tablet can be divided into equal doses.

Timonil 600 retard
White, oval, biconvex tablet scored on one side and engraved 'T' on the other side and with a protruding edge.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the treatment of:

- Epilepsy
- Trigeminal neuralgia
- Mania
- Prophylactic in manic depressive illness.

Note:

When switching from previous (non-prolonged release) pharmaceutical forms to Timonil retard, ensure a sufficiently high serum carbamazepine concentration.

4.2. Posology and method of administration

Posology

Treatment with Timonil retard should be started with a low, individualised, initial dose depending on the nature and severity of the disease. This is then gradually increased until the most effective maintenance dose is found.

The daily dose is generally given in 1 – 2 single doses.

The general daily dosage range lies between 400 -1200 mg carbamazepine.

A total daily dose of 1600 mg should generally not be exceeded, since increased side effects occur at higher doses.

The therapeutic dose should be established, especially in combination therapy, by measuring the plasma levels and depending on the efficacy. Experience has shown that the therapeutic carbamazepine concentration is between 4 and 12 µg/mL.

In some instances the required dosage can vary considerably from the specified initial and maintenance doses (e.g. due to acceleration of metabolism by enzyme induction or due to drug interactions in combined medication).

Timonil retard should preferably be used to treat epilepsy as the sole drug (monotherapy). The treatment should be supervised by a specialist with experience in the treatment of epilepsy. If the patient is switched to Timonil retard, the dose of the previously used antiepileptic must be slowly reduced.

The following general dosage scheme is recommended for the treatment of **epileptic seizures**:

	Timonil retard Initial daily dose	Timonil retard Daily maintenance dose
Adults	200 – 300 mg in the evening	200 – 600 mg in the morning 400 – 600 mg in the evening
Children		
6 - 10 years	150 – 200 mg in the evening	200 mg in the morning 200 – 400 mg in the evening
11 - 15 years	150 – 200 mg in the evening	200 – 400 mg in the morning 400 – 600 mg in the evening

Paediatric population

For children under the age of 6 years non-prolonged release pharmaceutical forms are available for initial and maintenance doses (suspension or tablets).

For children under the age of 4 years, clinical experience has shown that, after initial doses (20 - 60 mg) of rapid release pharmaceutical forms, it is preferable to use Timonil retard in the daily dosage to date divided into two doses (as ½ or ¼ prolonged-release tablet if necessary). This can be increased by 20 - 60 mg carbamazepine every second day to the therapeutically required dose. However, the dose ranges given below should not be exceeded.

For children over the age of 4 years, clinical experience has shown that the initial dose may be 100 mg carbamazepine per day. This daily dose can be increased by up to 100 mg carbamazepine every second day or weekly to the required dose. However, the dose ranges given below should not be exceeded.

The following dosage recommendations apply to prolonged-release tablets:

Epilepsy:

In general the adult initial dose of 200 – 400 mg carbamazepine/day can slowly be increased to the maintenance dose of 600 – 1200 mg/day.

In general the maintenance dose in children is 10 – 20 mg/kg body weight per day.

Recommended dosage scheme: see above.

Trigeminal neuralgia:

The daily dose is increased from an initial dose of 150 - 400 mg carbamazepine until freedom from pain is achieved - with an average dose of 300 - 900 mg carbamazepine (in 1 -

2 divided doses). In some cases it is then possible to continue treatment with a lower maintenance dose of 300 - 450 mg carbamazepine/day. An initial dose of 150 - 200 mg carbamazepine/day in the morning or evening is adequate in elderly and sensitive patients.

Mania and Prophylaxis of manic-depressive phases:

The initial dose, which is usually sufficient as a maintenance dose as well, is 200 – 400 mg carbamazepine daily. If necessary, the dose may be increased to 600 – 900 mg carbamazepine daily (in 2 divided doses).

Warnings:

A lower dosage is indicated in patients with serious cardiovascular diseases, in liver or kidney dysfunction and in the elderly.

Before deciding to initiate treatment, patients of Han-Chinese or Thai origin should whenever possible be screened for HLA-B*1502 as this allele strongly predicts the risk of severe carbamazepine-associated SJS (see information on genetic testings and cutaneous reactions in section 4.4).

Method of administration

The prolonged-release tablets are divisible and may either be swallowed whole during or after meals with sufficient liquid (e.g. a glass of water) or first be allowed to dissolve (become suspended) in water. If the tablets are suspended this should be done immediately before being administered.

In some cases, division of the daily dose into 4 - 5 doses has proved particularly effective. In these cases, non-prolonged release pharmaceutical forms of carbamazepine are to be preferred to prolonged release pharmaceutical forms.

The duration of treatment depends on the indication and the individual response of the patient. The medication must never be discontinued by the patient him/herself without permission.

The duration of treatment varies from individual to individual and is set by the attending physician.

Antiepileptic treatment is fundamentally a long-term therapy. The decision concerning dosage adjustment, duration and cessation of treatment with Timonil retard must be made in each case by a specialist with experience in the treatment of epilepsy.

On the basis of fundamental considerations, the medicinal product should not be changed for patients free of seizures, except for medical reasons, as even slight plasma level fluctuations might cause relapses or intoxication due to the narrow therapeutic range of the active ingredient.

In general, a reduction in dose or cessation of treatment should not be considered before the patient has been free of seizures for at least two or three years.

Treatment must be discontinued with a stepwise reduction in dose over one to two years. Children can be allowed to outgrow their dose per kg body weight instead of carrying out an age-appropriate adjustment of the dosage, provided the EEG findings do not deteriorate.

When treating neuralgia, it has proved effective to give a maintenance dose just sufficient to abolish pain for a few weeks. The dose should then be cautiously reduced to determine whether spontaneous remission has occurred in the meantime.

If pain recurs, then the original maintenance dose should be continued.

Prophylaxis of manic-depressive phases is long term treatment.

4.3. Contraindications

Timonil retard must not be used in:

- patients with a history of bone marrow damage or bone marrow depression
- atrioventricular block
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- known hypersensitivity to structurally related medicinal products such as tricyclic antidepressants (e.g. amitriptyline, desipramine, nortriptyline)
- hepatic porphyria or even a history thereof (e.g. acute intermittent porphyria, porphyria variegata, porphyria cutanea tarda)
- concomitant treatment with monoamine oxidase inhibitors (MAOI) or within 14 days after discontinuation of treatment with MAOI
- concomitant treatment with voriconazole, since patients may fail to respond to this medicinal product.

4.4. Special warnings and precautions for use

Since carbamazepine can cause absences or potentiate existing absences, Timonil retard should not be used in patients suffering from absences or mixed seizures involving absences.

If an exacerbation of convulsions occurs, the treatment with carbamazepine should be discontinued.

Timonil retard may only be used after careful weighing up of the possible benefits against the potential risks, and with appropriate precautionary measures in:

- previous or existing haematological disorders, a history of haematological reactions to other medicinal products
- abnormal sodium metabolism
- severe heart disease, hepatic or renal dysfunction (see section 4.2 and 4.8)
- patients with myotonic dystrophy because cardiac conduction anomalies often occur in this patient group
- concomitant treatment with stiripentol (used in the treatment of severe myoclonic epilepsy in infancy [SMEI]), see section 4.5

Warnings and other precautions

Timonil retard may only be used for children under 6 years of age after a careful risk/benefit analysis. Please note the warnings in the dosage scheme of this Information for Healthcare Professionals.

Haematological disorders

Agranulocytosis and aplastic anaemia are known to be associated with carbamazepine. However, due to the low frequency it is difficult to evaluate the risk. The probability of occurrence of agranulocytosis is 4.7 cases/million/year and of aplastic anaemia 2.0 cases/million/year within the untreated population.

Under carbamazepine use a temporary or permanent reduction of platelet or white blood cell counts occurs very commonly. In most cases this is only temporary and does not necessarily prognose the beginning of an agranulocytosis or aplastic anaemia. It is recommended to have the blood count (including thrombocytes, reticulocytes and serum iron) checked before beginning treatment with carbamazepine, and then at weekly intervals in the first month of treatment, and subsequently in monthly intervals. After completion of 6 months treatment, 2-4 controls per year are adequate.

Patients should be made aware of early signs of potential haematological disorders, and of symptoms of dermatological and hepatic reactions. If fever, sore throat, allergic skin reactions such as rashes with lymph node swelling and/or influenza-like symptoms, mouth

ulceration, tendency for haematoma, petechiae or purpura occur during treatment with Timonil retard, the patient should be instructed to consult his/her doctor immediately and have the blood count checked. In the case of severe allergic reactions, Timonil retard must be discontinued immediately.

In certain blood picture changes (especially leukocytopenia and thrombocytopenia) it may be necessary to discontinue Timonil retard; this is always the case if complaints such as allergic symptoms, fever, sore throat or skin haemorrhage occur at the same time.

1. Urgent checks required (within 1 week) if one of the following occurs:
 - pyrexia, infection
 - skin rash
 - general asthenia
 - oropharyngeal pain, mouth ulceration
 - increased tendency to bruise
 - rise in transaminases
 - fall in leucocytes below 3,000/ μ l or in granulocytes to under 1,500/ μ l
 - fall in platelets below 125,000/ μ l
 - decrease in reticulocytes to under 0.3% = 20,000/ μ l
 - increase in serum iron to more than 150 μ g/dl

2. Withdrawal of carbamazepine is necessary if one of the following occurs:
 - petechial or purpural bleeding
 - fall in red blood cells below 4 million/ μ l
 - reduction of haematocrit below 32%
 - fall in haemoglobin to under 11 g/dl
 - fall in leucocytes to under 2,000/ μ l or of granulocytes to under 1,000/ μ l or of platelets to under 80,000/ μ l
 - or symptomatic blood count abnormalities

Liver function

It is recommended that liver function tests be carried out before beginning treatment with Timonil retard, and then at weekly intervals in the first month of treatment, and subsequently at monthly intervals. This especially applies for patients with known liver disorder and elderly patients. After completion of 6 months treatment, 2-4 controls per year are adequate.

The patient is to be instructed to consult his/her doctor straight away if symptoms of hepatitis such as fatigue, decreased appetite, nausea, yellow skin or hepatomegaly occur.

If a liver disorder deteriorates, or a florid liver disorder occurs, treatment with carbamazepine should be discontinued immediately.

Renal function

It is recommended to test the urinary status and the urea nitrogen before and routinely during the treatment with carbamazepine.

Caution should be taking with patients that have problems in the kidneys relate to low level of sodium in the blood, or patients who being treated with diuretics e.g. Hydrochlorothiazide, Furosemide which decrease the sodium levels in the blood.

Hypersensitivity reactions

Carbamazepine can trigger hypersensitivity reactions, including drug rash with eosinophilia and systemic symptoms (DRESS), delayed, multi-organ hypersensitivity reactions with fever, skin rash, vasculitis, lymph node swelling, arthralgia, leukopenia, eosinophilia, hepatomegaly and splenomegaly, altered liver function tests and vanishing bile duct syndrome (destruction and loss of intrahepatic bile ducts), which may occur in various combinations. Other organs may also be affected (e.g. lung, kidney, pancreas, heart muscle, colon) (see section 4.8).

In patients with hypersensitivity to oxcarbazepine, phenytoin, phenobarbital or lamotrigine, Timonil retard should only be administered after careful evaluation of the possible risks and expected benefits, since these patients have an increased risk of developing hypersensitivity to carbamazepine as well.

Twenty-five to thirty percent of patients who had hypersensitivity reactions to carbamazepine exhibit cross-reactions with oxcarbazepine. The risk of cross-reactions between carbamazepine and phenobarbital or phenytoin is about 75 %. If signs or symptoms of a hypersensitivity reaction occur, carbamazepine should be discontinued immediately.

General anaesthesia

If the patient needs to go through surgical procedure which involves general anaesthesia, the anesthesiologist should be informed about the treatment with Timonil.

Hyponatraemia

Hyponatraemia is known to occur in patients taking carbamazepine. In patients with pre-existing renal disorders associated with low serum sodium concentration, or in patients treated concomitantly with medicines that lower sodium concentrations (e.g. diuretics, medicinal products associated with inadequate ADH secretion), the serum sodium concentration should be determined prior to treatment. Thereafter, serum sodium concentrations should initially be determined after about two weeks and then during the first three months of treatment at monthly intervals or according to clinical need. The above-mentioned risk factors occur particularly in elderly patients. If hyponatraemia is detected, fluid restriction is an important countermeasure, if clinically indicated.

Hypothyroidism

Carbamazepine can reduce serum concentrations of thyroid hormones through enzyme induction, thus necessitating an increase in the dose of thyroid hormone replacement therapy in patients with hypothyroidism. Therefore, monitoring of thyroid function is recommended, in order to adjust the dosage of thyroid hormone replacement therapy.

Anticholinergic effects

Carbamazepine has weak anticholinergic activity. Patients with glaucoma and urinary retention should therefore be carefully monitored during treatment (see section 4.8 Undesirable effects).

Caution should be taking with patients that have no ability to retain the urine.

Transfer of patients to another therapy

An abrupt withdrawal of carbamazepine treatment may lead to convulsions. Carbamazepine should therefore be withdrawn gradually over a period of 6 months. If it is necessary to transfer patients with epilepsy from Timonil retard to another form of therapy, the switch to treatment with another antiepileptic must not be abrupt, but gradual.

If an abrupt switch from carbamazepine to another antiepileptic agent is required in patients with epilepsy, this should take place under the safeguard of a suitable antiepileptic.

Alcohol withdrawal syndrome

Warning: Timonil retard may only be used under inpatient conditions for the indication "Prevention of seizures in alcohol withdrawal syndrome".

It should be noted that the adverse reactions to carbamazepine in the treatment of alcohol withdrawal syndrome are themselves similar to, and can be confused with, the withdrawal symptoms.

Coadministration of lithium

In order to prevent undesirable interactions (see "Interaction with other medicinal products and other forms of interaction") when, in exceptional cases, Timonil retard is to be given together with lithium because lithium alone is inadequate for the prophylaxis of manic-depressive phases, it must be ensured that a specific carbamazepine plasma concentration

(8 µg/mL) is not exceeded, that the lithium level is kept in the lower therapeutic range (0.3 to 0.8 mval/L) and that any treatment with neuroleptics has been discontinued at least 8 weeks previously and not given simultaneously.

Photosensitivity reaction

Due to the possibility of photosensitisation, patients should protect themselves from strong sunlight during treatment with carbamazepine.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised, placebo-controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for carbamazepine.

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

Hormonal contraceptives

Breakthrough bleeding has been reported in patients treated with carbamazepine who concomitantly use hormonal contraceptives ("the Pill"). The reliability of hormonal contraception with oestrogen and/or progesterone derivatives may be adversely affected or even abolished due to the enzyme-inducing properties of carbamazepine. Therefore, other non-hormonal methods of contraception are recommended for women of childbearing potential (see section 4.6).

Monitoring of plasma level

Although the correlation between carbamazepine dosage and plasma level and the correlation between plasma level and clinical efficacy or drug tolerability is extremely doubtful, monitoring of plasma level may be beneficial in the following cases: noticeable increase in frequency of convulsions, monitoring of patient compliance, during pregnancy, during treatment of children and adolescent, if malabsorption or if toxic effects are suspected in the presence of concomitant medication (see 4.5 Interaction with other medicinal products and other forms of interaction).

Cutaneous reactions

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of carbamazepine. Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, carbamazepine treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of carbamazepine, carbamazepine must not be re-started in this patient at any time.

Serious and sometimes fatal cutaneous reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are estimated to occur in 1-6 per 10 000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher.

There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions (see section 4.2).

*HLA-A*3101 allele - European descent and Japanese populations*

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash (see section 4.8) in people of European descent and the Japanese.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population.

The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%. There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine treatment.

If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed risks.

*HLA-B*1502 allele – in Han Chinese, Thai and other Asian populations*

HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing severe cutaneous reactions known as Stevens-Johnson syndrome (SJS), when treated with carbamazepine. 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 (see section 4.2). If these individuals test positive, carbamazepine should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still rarely occur.

There are some data that suggest an increased risk of serious carbamazepine-associated TEN/SJS in other Asian populations. 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 in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (< 1%).

Other dermatologic reactions

Mild skin reactions, e.g. isolated macular and maculopapular exanthema may occur. Usually, these are temporary and not serious, and they disappear within a few days or weeks, either without changes in therapy or after reducing the dosage. Since it may be difficult to distinguish the first symptoms of a serious dermatological reaction from those of mild and temporary reactions, the patient should be monitored in short time intervals. Treatment with carbamazepine should be discontinued immediately, if reactions exacerbate with continuing therapy.

Investigations

On the basis of the above-mentioned possible adverse reactions and hypersensitivity reactions, it is essential, especially for long term therapy, to carry out regular blood counts and tests of liver and kidney function. Carbamazepine levels and, in the case of combination therapy, also plasma concentrations of the other antiepileptics should be routinely monitored and daily doses reduced if necessary.

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant treatment with monoamine oxidase inhibitors (MAO) is contraindicated (see section 4.3). Before commencing treatment with Timonil retard, any therapy with MAO inhibitors must have been discontinued at least two weeks earlier.

Concomitant treatment with Timonil may require dose adjustment or ceasing treatment with one of the medicines.

Effects of carbamazepine on the plasma concentrations of other drugs

Carbamazepine induces the cytochrome-P450 system (predominantly isoenzyme CYP3A4) so that the plasma concentrations of substances that are metabolised by the cytochrome-P450 system may be diminished, and their dosage may need to be adjusted according to the clinical requirements. The inducing effect of carbamazepine may remain for about two weeks after cessation of treatment.

This applies, for example, to:

- analgetics, anti-inflammatory agents: buprenorphine, fentanyl, methadone, paracetamol, phenazone, tramadol
- anthelmintics: praziquantel, albendazole
- anticoagulants: warfarin, phenprocoumon, dicumarole, acenocoumarole
- antidepressants: bupropion, citalopram, mianserin, mirtazapine, nefazodone, sertraline, trazodon, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine)
- antiemetics: aprepitant, ondansetron
- other anticonvulsants (clonazepam, ethosuximide, felbamate, primidone, lamotrigine, oxcarbazepine, phenytoin, tiagabine, topiramate, valproic acid, zonisamide). To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine, it is recommended that the plasma concentration of phenytoin be adjusted to 13 micrograms/mL before incorporating adjunctive treatment with carbamazepine.
- Antifungal agents: caspofungin, azole-derivative antifungals (e.g. voriconazole, itraconazole, with the result that patients may fail to respond to the antimycotics). For patients treated with voriconazole or itraconazole, alternative anticonvulsants are to be recommended.
- antiviral substances: protease-inhibitors for treatment of HIV, e.g. indinavir, ritonavir, saquinavir
- benzodiazepines (alprazolam, clobazam, midazolam – with the result that patients may fail to respond to midazolam)
- bronchodilators, antiasthmatics: theophylline
- cardiovascular medications: calcium antagonists (of the dihydropyridine type, e.g. felodipine, nimodipine), digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradin
- hormonal contraceptives
- immunosuppressives: ciclosporin, tacrolimus, sirolimus, everolimus
- corticosteroids (e.g. prednisolon, dexamethason)
- typical neuroleptics (haloperidol, bromperidol) and atypical neuroleptics (clozapine, olanzapine, paliperidone, risperidone, quetiapine, aripiprazole, ziprasidone)
- thyroid hormones: levothyroxine
- tetracyclines (e.g. doxycycline)
- cytostatics: cyclophosphamide, imatinib, lapatinib, temsirolimus
- others: methylphenidate, quinidine, propranolol, flunarizine, rifabutin, tadalafil, toremifene, gestrinone, oestrogens, progesterone derivatives

When taking the “pill”, in addition to the reduction in activity of the hormones contained in the oral contraceptive pill, sudden breakthrough bleeding or spotting may occur. Therefore other, non-hormonal means of contraception should be recommended. Due to its enzyme-inducing character, carbamazepine may neutralize the effects of oestrogens and/or progesterone derivatives which may lead e.g. to contraceptive failure..

The plasma concentration of phenytoin can be either reduced or increased by carbamazepine, which can lead in exceptional cases to states of confusion or even coma. Carbamazepine can lower the plasma level of bupropion and increase that of its metabolite hydroxybupropion thus diminishing the clinical efficacy and safety of bupropion.

Although carbamazepine can lower the plasma level of trazodone, it appears to potentiate the antidepressive effect of trazodone.

Carbamazepine may possibly accelerate the metabolism of zotepine.

Reduced plasma concentration of carbamazepine:

Carbamazepine is metabolised by the cytochrome-P450 system (predominantly by the isoenzyme CYP3A4). Inducers of CYP3A4 may increase the carbamazepine metabolism and with this may possibly lead to a decrease in the carbamazepine plasma concentration and in therapeutic efficacy. Vice versa, it may come to a decreased metabolism of carbamazepine after discontinuation of a CYP-3A4-inducer and consequently to an increased carbamazepine plasma concentration.

A decrease in the carbamazepine plasma concentration may be caused e.g. by:

- other anticonvulsants: methosuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, progabide, valproic acid, valpromide and possibly clonazepam (data is in parts contradictory). To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine, it is recommended that the plasma concentration of phenytoin be adjusted to 13 micrograms/mL before incorporating adjunctive treatment with carbamazepine.
- bronchodilators, antiasthmatics: theophylline, aminophylline
- dermatics: isotretinoin
- antituberculous drug: rifampicin
- cytostatics: doxorubicin, cisplatin
- others: St. John's wort (*Hypericum perforatum*)

Alternatively, the plasma levels of the pharmacologically effective metabolite carbamazepine-10,11-epoxide may be increased by valproic acid and primidone.

The concomitant administration of felbamate can diminish the plasma level of carbamazepine and increase that of carbamazepine-10,11-epoxide; at the same time, that of felbamate can be diminished.

Due to these mutual interactions, it is recommended that the plasma levels are monitored especially during concomitant therapy with several antiepileptics, and the dosage of Timonil retard should be adjusted if necessary.

Too low carbamazepine plasma levels may cause an aggravation of the disease, e.g. recurrence of epileptic seizures, seizures in multiple sclerosis or recurrence of facial pain or pain in the oropharyngeal space.

Increased plasma concentration of carbamazepine:

Carbamazepine is metabolised by the cytochrome-P450 system (predominantly by the isoenzyme CYP3A4) to the active metabolite carbamazepine-10,11-epoxid. Thus, the carbamazepine plasma concentration may also be increased by inhibitors of the cytochrome-P450 system, e.g. by:

- analgetics, anti-inflammatory agents: ibuprofen, dextropropoxyphene/propoxyphene – combination with dextropropoxyphene may lead to carbamazepine toxicity
- androgens: danazol
- antibiotics: ciprofloxacin, macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin)
- antidepressants: desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazodon, viloxazine
- antifungal agents: azole-derivative antifungal agents (e.g. itraconazole, ketoconazole, fluconazole, voriconazole). For patients treated with voriconazole or itraconazole, alternative anticonvulsants are to be recommended.
- antihistaminics: terfenadine, loratadine

- antiviral substances: protease inhibitors for the treatment of HIV, e.g. ritonavir
- calcium antagonists (e.g. verapamil, diltiazem)
- carboanhydrase inhibitors (diuretics): acetazolamide
- muscle relaxants: oxybutynine, dantrolene
- neuroleptics: loxapine, olanazapine
- antiplatelet drug: ticlopidine
- antituberculous: isoniazid
- ulcer therapeutic agents: cimetidine, omeprazole
- others: grapefruit juice, nicotinamide (in high doses)

Increased plasma levels of carbamazepine can lead to the symptoms described under undesirable effects (e.g. dizziness, tiredness, unsteadiness of gait, double vision). Therefore, if such symptoms occur, the carbamazepine plasma concentrations must be checked and the dose reduced if necessary.

Increased plasma concentration of the active metabolite carbamazepine-10,11-epoxide:
Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations. Increased plasma levels of carbamazepine-10,11-epoxide can lead to the symptoms described in section 4.8 (e.g. dizziness, fatigue, gait disturbance, diplopia). Therefore, if such symptoms occur, the plasma concentration must be checked and the dose reduced as necessary if any of the following substances are administered concomitantly: loxapine, quetiapine, oxcarbazepine, primidone, progabide, valproic acid, valnoctamide and valpromide.

Other interactions:

Concomitant use of carbamazepine and levetiracetam may increase carbamazepine toxicity.

Simultaneous use of carbamazepine and lithium, neuroleptics or metoclopramide can promote the occurrence of neurological side effects. In the case of patients who are being treated with neuroleptics it must be remembered that carbamazepine reduces the plasma levels of these medicinal products and thus may cause deterioration in the clinical picture. A dose adjustment of the respective neuroleptic drug may be necessary.

It is important to note that concomitant use of lithium and carbamazepine can, in particular, potentiate the neurotoxicity of each drug. It is therefore necessary to monitor plasma levels of the two drugs carefully. Treatment with neuroleptics should have been discontinued at least 8 weeks previously and not be given simultaneously. The following signs of neurotoxicity should be looked for: unsteady gait, ataxia, horizontal nystagmus, hyperreflexia, muscle twitches (muscle fasciculation).

The literature indicates that the additional administration of carbamazepine in patients already taking neuroleptic drugs increases the risk of onset of a malignant neuroleptic syndrome or a Stevens-Johnson syndrome.

The hepatotoxicity of isoniazid can be increased by carbamazepine.

Combined administration of carbamazepine and some diuretics (hydrochlorothiazide, furosemide) can lead to symptomatic hyponatraemia.

The effectiveness of drugs used as muscle relaxants, e.g. pancuronium, can be impaired by carbamazepine. Because of this, a more rapid clearing of the neuromuscular blockade is possible.

Patients treated with muscle relaxants should therefore be carefully monitored and the dose of these drugs increased if necessary.

Carbamazepine plasma levels should be monitored during concomitant administration of carbamazepine and isotretinoin (active substance for the treatment of acne).

The concomitant administration of carbamazepine and paracetamol may reduce the bioavailability of paracetamol. Long-term use of carbamazepine and paracetamol (acetaminophen) can lead to hepatotoxicity.

Carbamazepine appears to enhance the elimination of thyroid hormones and to increase the requirement for these substances in patients with hypothyroidism. Therefore thyroid function parameters should be measured at the start and end of carbamazepine treatment in patients receiving substitution therapy. The dosage of the thyroid hormones should be modified if required. In particular, concomitant treatment with carbamazepine and other anticonvulsant drugs (e.g. phenobarbital) can alter thyroid function.

Simultaneous administration of antidepressants of the serotonin reuptake inhibitor type (e.g. fluoxetine) can lead to a toxic serotonin syndrome.

It is recommended not to use carbamazepine in combination with nefazodone (agent that relieves depression) because carbamazepine leads to a pronounced reduction of the nefazodone plasma level or even a complete loss of action. Further, during concomitant administration of nefazodone and Timonil retard, the carbamazepine plasma level is increased and that of its active metabolite, carbamazepine-10,11-epoxide, reduced.

The concomitant administration of carbamazepine and antiarrhythmic agents, cyclic antidepressants or erythromycin increases the risk of cardiac conduction anomalies.

The concomitant administration of carbamazepine and eslicarbazepine acetate may increase eslicarbazepine acetate toxicity. Diplopia, coordination disturbances and dizziness occurred more commonly with the concomitant administration of eslicarbazepine acetate and carbamazepine than with the combination of eslicarbazepine acetate with other anticonvulsants.

With the concomitant administration of carbamazepine and oxcarbazepine. drops in carbamazepine plasma levels of 0-22% with a simultaneous increase in carbamazepine epoxide by 30% have occurred.

There have been reports of increased bioavailability and raised plasma levels of carbamazepine in connection with drinking grapefruit juice.

Like other psychoactive substances, carbamazepine can reduce the patients' alcohol tolerance. Therefore, patients should not drink alcohol during treatment.

Interference with serological tests

Due to interference in HPLC analysis, carbamazepine can lead to false-positive perphenazine concentrations. Carbamazepine and its 10,11-epoxide metabolite can lead to false-positive concentrations of tricyclic antidepressants in fluorescence polarisation immunoassays.

4.6. Fertility, pregnancy and lactation

Contraception in women of childbearing potential

Carbamazepine impairs the effect of oral contraceptives containing oestrogen and/or progesterone derivatives. An alternative, effective and safe method of contraception should therefore be used during treatment with carbamazepine.

Pregnancy

Carbamazepine may only be prescribed during pregnancy after careful weighing of the possible benefits against the potential risks. Women of childbearing age must be informed of the necessity of planning and monitoring a pregnancy. If possible, carbamazepine should be used as monotherapy by women of childbearing potential, especially during pregnancy, since the risk of malformation is increased by combination therapy with other antiepileptic agents. The risk of malformations after carbamazepine exposure as polytherapy varies depending on the individual medications used and may be higher especially in polytherapy with valproate.

If pregnancy occurs during treatment with carbamazepine, or if treatment with carbamazepine becomes necessary during pregnancy, the necessity of controlling seizures must be carefully weighed against the risk of this therapy for the unborn child. During the first three months of pregnancy, during which the fetus is particularly susceptible to malformation, and particularly between the 20th and 40th days after conception, the lowest effective dose should be used because malformations are probably caused by high plasma concentrations. Monitoring of the plasma level is recommended. The level should lie within the lower therapeutic range (3 - 7 µg/mL). At a dose of <400 mg carbamazepine per day, malformation rates are lower than at higher doses. Under no circumstances may the treatment be stopped without consulting a doctor since epileptic seizures may damage the child and also represent a risk for the mother.

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. The possibility that carbamazepine, like all major antiepileptic drugs, increases the risk has been reported, although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. However, there are reports on developmental disorders and malformations, including spina bifida, and also other congenital abnormalities, e.g. craniofacial defects, cardiovascular malformations, finger nail hypoplasia and anomalies involving various body systems (also known/described as fetal anticonvulsant syndrome), have been reported in association with carbamazepine. Epidemiological studies indicate that the risk of spina bifida is increased to 1%, i.e. approximately 10 times higher than the normal rate. The patients must be informed of the increased risk of malformations and the possibility of antenatal screening.

Folic acid deficiency, caused by the enzyme-inducing action of the carbamazepine, may be an additional factor for the development of malformations. Therefore the administration of folic acid before and during pregnancy may be expedient. In order to prevent coagulation disorders, the prophylactic administration of vitamin K1 to the mother during the last weeks of pregnancy or to the child post partum is recommended.

A few cases of seizures and/or respiratory depression in neonates have been reported in connection with taking carbamazepine and other antiepileptic agents, as have a few cases of vomiting, diarrhoea and/or reduced feeding. These may be signs of withdrawal symptoms in neonates.

Breast-feeding

Carbamazepine and its active metabolite pass in low quantities into breast milk (milk/plasma concentration ratio of 0.24-0.69). However, the benefits of breastfeeding should be weighed against the risk of side effects in the infant. Timonil may be taken during lactation provided that the breast-fed infant is observed for possible effects of the substance (reduced weight gain, sedation, allergic skin reactions). The infant should be weaned if these effects develop. There are a few reports of cholestatic hepatitis in newborns exposed to carbamazepine prenatally or during breast-feeding. Therefore, breast-fed infants whose mothers are being treated with carbamazepine should be carefully monitored for adverse hepatobiliary effects.

Fertility

Very rarely, sexual dysfunction, e.g. erectile dysfunction or decreased libido as well as decreased male fertility and/or abnormal spermatogenesis were reported.

4.7. Effects on ability to drive and use machines

Due to the occurrence of central nervous side effects such as dizziness, somnolence, fatigue, lack of coordination in the muscles, ataxia, diplopia, accommodation disorders and blurred vision, either at the beginning of treatment or at higher doses and/or concomitant treatment with other drugs that also affect the central nervous system, Timonil retard may, even when used as directed and independent of the underlying disease, impair the reaction capacity to such an extent that the ability to drive a motor vehicle, to operate machines or to carry out work without a safe hold is impaired. This applies particularly when alcohol is also consumed.

4.8. Undesirable effects

The undesirable effects were categorised based on the following frequency conventions:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (frequency cannot be estimated from the available data)

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous ADRs such as SJS, TEN, DRESS, AGEP and maculopapular rash. In Japanese and European patients, these reactions have been reported to be associated with the use of carbamazepine and the presence of the HLA-A*3101 allele. Another marker, HLA-B*1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry (see sections 4.2 and 4.4 for further information).

The observed undesirable effects occurred less often when carbamazepine was administered alone (monotherapy) than in combination with other antiepileptic agents (combination therapy).

Some of the adverse reactions were dose-dependent, in particular at the start of treatment, if the initial dose is too high or very commonly or commonly in elderly patients. These include central nervous system disorders (dizziness, headache, ataxia, drowsiness, sedation, double vision), gastrointestinal disorders (nausea, vomiting) and allergic skin reactions.

Dose-dependent adverse reactions usually abate within a few days on their own or after a temporary dosage reduction. Therefore, the Timonil retard dosage should be titrated if at all possible. Central nervous system disturbances may be a sign of a relative overdose or large fluctuations in the plasma levels, therefore in these cases it is recommended that the plasma levels be checked.

Infections and infestations

Not known: Reactivation of Human herpesvirus 6 infection.

Blood and lymphatic system disorders

Very common: Leucopenia. According to the literature, benign leucopenia is the most frequent, transient in about 10% of cases, persistent in 2%. Benign leucopenia develops mostly during the first four months of therapy. Leucocytosis, thrombocytopenia, eosinophilia.

Rare: Lymphadenopathy, drop in serum folic acid levels

Very rare: Agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, possibly haemolytic anaemia, enlarged spleen.

Not known: Bone marrow depression.

Immune system disorders

Uncommon: A delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (progressive cholestatic hepatopathy with destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).

Very rare: Aseptic meningitis, with myoclonus and eosinophilia; acute allergic general reactions, anaphylactic reactions, angio-oedema.

Not known: Allergic cross-reactions with other antiepileptics, reactivation of Herpes virus (might be series when immune system is suppressed).

Endocrine disorders

Common: Oedema, fluid retention, weight gain, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confused states, and other neurological disorders.

Very rare: Elevated prolactin levels with or without clinical manifestations such as galactorrhoea and gynaecomastia, abnormal thyroid function tests: low l-thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and elevated thyroid stimulating hormone in the blood, usually without clinical symptoms, bone metabolism disorders (decrease in serum calcium and 25-hydroxy-cholecalciferol), leading very rarely to osteomalacia or osteoporosis; high cholesterol, including HDL cholesterol and triglycerides, elevated serum free cortisol levels.

There are indications of reduced vitamin B 12 levels and raised serum homocysteine levels.

Psychiatric disorders

Uncommon: In elderly patients, states of confusion and restlessness (agitation)

Rare: Hallucinations (auditory or visual), depression, depressive or manic moods, anorexia, restlessness, aggressive behaviour, other mental changes.

Very rare: Activation of latent psychosis, mood changes such as phobic disorders, impaired thought processes, lack of drive.

Nervous system disorders

Very common: Dizziness, ataxia (atactic and cerebellar dysfunctions), somnolence, sedation, drowsiness, fatigue.

Common: Headache, diplopia, accommodation disorders (e.g. blurred vision).

Uncommon: Involuntary movements (e.g. tremor, asterixis, dystonia, tics); eye movement disturbances, including nystagmus.

Rare: Dyskinetic disturbances such as orofacial dyskinesia, choreoathetosis (involuntary movements in the orofacial region such as grimaces, contorted movements), speech disorders (e.g. dysarthria or slurred speech), polyneuropathy, peripheral neuritis,

peripheral neuropathy, paraesthesia, paresis.
Very rare: Taste disturbances, neuroleptic malignant syndrome.
Not known: Memory impairment, memory loss, drowsiness.
There are indications that carbamazepine can lead to exacerbation of the symptoms of multiple sclerosis. Like other antiepileptics seizures may occur more frequently under carbamazepine; absences in particular may be aggravated or may be developed.
Cases of aseptic meningitis have been reported under carbamazepine therapy.

Eye disorders

Very rare: Cataracts, conjunctivitis, elevated intraocular pressure. Reports have been received of retinotoxicity in two patients on long-term carbamazepine therapy; this resolved after discontinuing carbamazepine.

Ear and labyrinth disorders

Very rare: Hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.

Cardiac disorders

Uncommon: Cardiac conduction disorders, atrioventricular block in isolated cases with syncope, hypertension or hypotension.
Uncommon to rare: Bradycardia, arrhythmia, circulatory collapse, heart failure, aggravation of coronary artery disease, thrombophlebitis, thrombo-embolism (e.g. pulmonary embolism).

Respiratory, thoracic and mediastinal disorders

Very rare: Pulmonary hypersensitivity with fever, dyspnoea, and pneumonitis or pneumonia (alveolitis), single cases of pulmonary fibrosis have been described in the literature.

Gastrointestinal disorders

Very common : Nausea, vomiting.
Common: Loss of appetite, dry mouth
Uncommon: Diarrhoea, constipation.
Rare: Abdominal pain.
Very rare: Inflammation of the oral and pharyngeal mucosa (stomatitis, gingivitis, glossitis), pancreatitis.
Not known: Colitis, diarrhea, abdominal pain, fever (signs to inflammatory bowel disease).

Hepatobiliary disorders

Very common: Increased-gamma-GT values (due to hepatic enzyme induction), usually not clinically relevant.
Common: Increased blood alkaline phosphatase.
Uncommon: Increased transaminases.
Rare: Various forms of hepatitis (cholestatic, hepatocellular, or mixed type), vanishing bile duct syndrome, jaundice, acute life-threatening hepatitis, particularly during the first months of therapy, hepatic failure.
Very rare: Granulomatous liver disease.

Skin and subcutaneous tissue disorders:

Very common: Allergic skin reactions with and without fever, such as urticaria, which may be severe.
Uncommon: Exfoliative dermatitis, erythroderma.
Rare: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4), Systemic lupus

Very rare:	erythematosis, pruritus. Photosensitivity, erythema multiforme exudativum and erythema nodosum, alterations in skin pigmentation, purpura, acne, hyperhidrosis, alopecia, hirsutism, and vasculitis have been reported very rarely, but the causal relationship is unclear.
Not known:	Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), acute generalised exanthematic pustulosis (AGEP), lichenoid keratosis, onychomadesis, vitiligo, purple or re-purple swelling that may be itchy.

Musculoskeletal and connective tissue disorders

Rare:	Muscle weakness.
Very rare:	Arthralgia, muscle pain, muscle spasms.
Not known:	Fractures, fall out of the nails, bone fractures, decrease in bone density.

Renal and urinary disorders

Uncommon:	Renal impairment (e.g. albuminuria, haematuria, oliguria, elevated blood urea/azotaemia).
Very rare:	Tubulointerstitial nephritis, renal failure, other urinary complaints (e.g. urinary frequency, dysuria, pollakisuria, urinary retention).

Reproductive system and breast disorders

Very rare:	Sexual dysfunction, reduced libido, erectile dysfunction, reduced male fertility and/or abnormal spermatogenesis (low sperm count and/or motility).
------------	---

Investigations

Very rare:	Hypogammaglobulinaemia.
------------	-------------------------

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with carbamazepine. The mechanism by which carbamazepine affects bone metabolism has not been identified.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<http://forms.gov.it/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.it>

4.9. Overdose

In case of intoxication, the possibility of multiple poisoning, for example through the ingestion of several drugs with suicidal intent, must always be considered.

Carbamazepine intoxication usually occurs with very high doses (4 - 20 g), where the plasma level is always over 20 µg/mL. Accidental or suicidal ingestion with plasma concentrations of 38 µg/mL has been survived.

The literature contains reports of intoxication (after taking carbamazepine with suicidal intent or accidentally), some of which had fatal consequences.

Symptoms of overdose

The symptoms described under undesirable effects can be intensified on overdosing with carbamazepine:

CNS depression, dizziness, ataxia, drowsiness, stupor, coma, nausea, vomiting, delayed gastric emptying, restlessness, confusion, involuntary movements, dysarthria, mydriasis, nystagmus, flushing, urinary retention, cyanosis, respiratory depression, opisthotonus, abnormal reflexes (weakened or enhanced).

The following additional symptoms may occur:
tremor, excitement, tonic-clonic convulsions, respiratory and cardiovascular disturbances with, for the most part, hypotonic blood pressure (but sometimes hypertension), tachycardia and AV block, impaired consciousness up to respiratory and cardiac arrest.

EEG dysrhythmias and ECG changes (arrhythmias, conduction disorders) can arise. Modified laboratory parameters have been measured in isolated cases: leucocytosis, leucopenia, neutropenia, glycosuria, acetonuria.

There have been a few cases in which rhabdomyolysis was reported in association with carbamazepine toxicity.

Management of intoxication

There is to date no specific antidote to acute intoxication with carbamazepine.

Therefore cases of overdose should be treated with symptomatic measures: hospitalisation, check of carbamazepine plasma level to confirm the carbamazepine-intoxication and to determine the degree of overdose, removal of the drug as soon as possible (through induced vomiting and/or gastric lavage) and reduction of absorption by administration of activated charcoal or a laxative. Delayed gastric emptying may result in delayed absorption, leading to relapse during recovery from intoxication.

Vital functions must be safeguarded under clinical conditions: plasma concentration and cardiac function should be monitored, correction of electrolyte balance may be necessary.

Suitable anticonvulsants should be given if seizures occur. The use of barbiturates is not recommended in the literature due to the risk of inducing respiratory depression, especially in children.

A haemoperfusion with activated charcoal was recommended. Haemodialysis is an effective option for treating a carbamazepine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics
ATC Code: N03A F01

Carbamazepine is a dibenzoazepine derivative. Pharmacologically it shares properties with phenytoin.

The mechanism of action is not fully understood to date. Like phenytoin, carbamazepine inhibits synaptic transmission and thereby reduces the propagation of convulsive discharges. In higher concentrations, carbamazepine decreases post-tetanic potentiation.

Pain relief in trigeminal neuralgia is probably attributable to an inhibition of synaptic stimulus transmission in the spinal nucleus of the trigeminal nerve.

5.2. Pharmacokinetic properties

Absorption

Carbamazepine is relatively slowly and almost completely reabsorbed after oral administration (depending on the dosage form).

The absorption half-life averages 8.5 h and shows large intra- and inter-individual variations (ranging from approx. 1.72 to 12 h).

Peak plasma levels after a single dose are reached (depending on the dosage form) after 4 to 16 hours in adults (very rarely up to 35 h) and after about 4 - 6 h in children. Plasma levels are not linearly related to dose and show a flat course in the higher dosage region.

Peak plasma levels are achieved faster after administration of the suspension than after normal tablets or prolonged-release tablets.

Plasma levels after administration of prolonged-release tablets are lower than after non-prolonged release ones.

The steady state is reached after 2 to 8 days. There is no strict correlation between the dose of carbamazepine and the steady state plasma concentration.

With a dosage interval of 8 or 12 h, fluctuations in the plasma levels of carbamazepine and its metabolite carbamazepine-10,11-epoxide in the steady state are small.

In terms of therapeutic and toxic plasma concentrations, it is stated in the literature that a seizure-free state can be achieved with plasma levels of 4 to 12 µg/mL. If a level of 20 µg/mL is exceeded, the clinical picture worsens. Relief of pain in trigeminal neuralgia is achieved with plasma concentrations of 5 to 18 µg/mL.

The threshold concentration for the occurrence of adverse reactions is approx. 8 to 9 µg/mL.

Distribution

The volume of distribution in humans is given as 0.8 - 1.9 L/kg.

Between 70% and 80% of carbamazepine is bound to plasma proteins. The proportion of free carbamazepine is constant up to a concentration of 50 µg/mL. Between 48% and 53% (approx. 0.74 L/kg) of carbamazepine-10,11-epoxide, the pharmacologically active metabolite, is bound to plasma proteins.

Pharmacokinetic interactions should be expected, see section 4.5.

The carbamazepine concentration in cerebrospinal fluid is about 33% of the corresponding plasma concentration.

Salivary carbamazepine levels correspond to the level of the free parent substance and show good correlation with plasma levels (about 20 - 30%). If multiplied by 4, salivary concentrations can be used to estimate plasma levels during the therapy.

Carbamazepine crosses the placental barrier and passes into breast-milk (about 58% of plasma concentration). The concentrations found in the plasma of breast-fed infants correspond to those in their mothers' milk.

Biotransformation

Carbamazepine undergoes oxidation, deamination, hydroxylation and finally esterification with glucuronic acid in the liver.

To date, seven metabolites of carbamazepine have been found in human urine. The pharmacologically inactive metabolite trans-10,11-dihydroxy-10,11-dihydrocarbamazepine accounts for the largest proportion. Only 0.1% to 2% represents the metabolite carbamazepine 10,11-epoxide, which itself has anticonvulsant activity.

Elimination

The half-life of elimination of carbamazepine from plasma after a single dose is approx. 36 hours (Range: 18 – 65 h).

On long-term administration, the half-life falls by about 50% (10 - 20 hours) due to enzyme induction. In combination with other antiepileptics, the half-life is shorter (average 6 - 10 h) than with monotherapy (11 - 13 h); half-lives are shorter in children than in adults, whilst longer in neonates than in infants

Plasma clearance in healthy subjects is approximately 19.8 ± 2.7 mL/h/kg, in patients receiving monotherapy about 54.6 ± 6.7 mL/h/kg and in those on combination therapy around 113.3 ± 33.4 mL/h/kg

About 72% of a single oral dose is excreted by the kidneys in the form of metabolites. The remaining 28% is excreted via the faeces, some as unchanged carbamazepine. Only 2 - 3% of the amount excreted in the urine is unchanged carbamazepine.

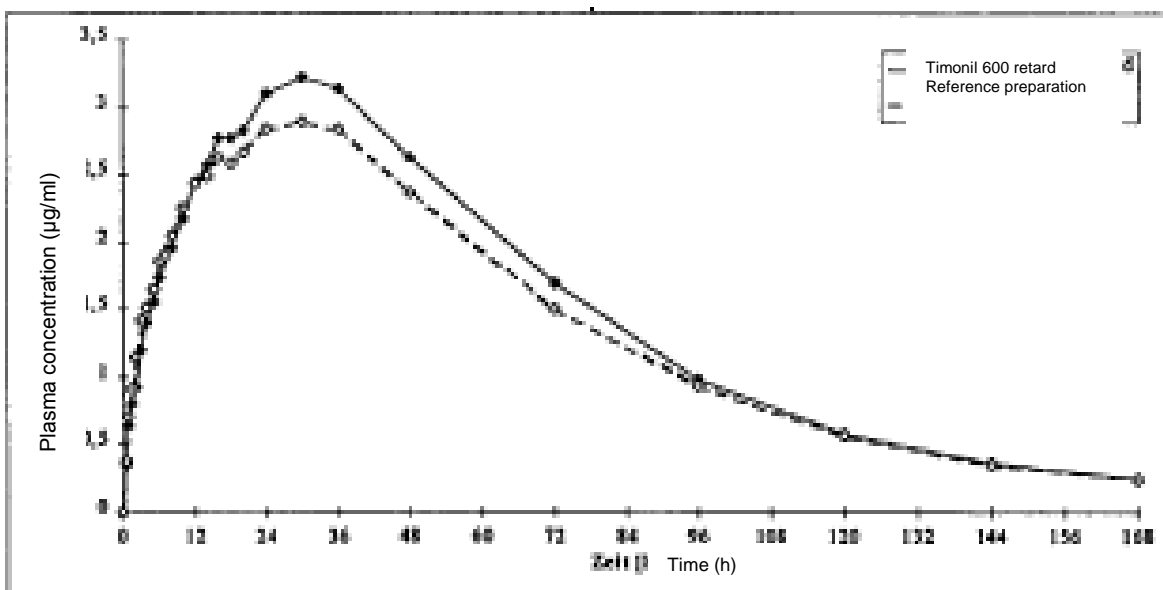
Bioavailability/bioequivalence

A bioavailability study conducted on 12 subjects (23 – 31 years [mean 27], male) in 1995 showed the following data after a single dose of 600 mg carbamazepine as 1 prolonged release Timonil 600 retard or 1½ prolonged-release tablets of the reference preparation on an empty stomach:

	Test preparation Timonil 600 retard	Reference preparation
Peak plasma concentration (C _{max}): µg/mL	3.4 ± 0.6	3.1 ± 0.5
Time to peak plasma concentration (t _{max}): h	27.7 ± 7.9	27.3 ± 8.6
Area under the concentration-time curve (AUC _{0-∞}): µg/mL · h	259 ± 73.5	240 ± 60.3

Figures given as mean and range

Medium serum concentration of Timonil 600 retard in comparison to a reference product in a concentration-time-diagram:



5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeat dose toxicity, genotoxicity and carcinogenic potential. However, the animal studies were insufficient to rule out a teratogenic effect of carbamazepine.

Carcinogenicity

A carcinogenicity study conducted with carbamazepine on rats over a period of 2 years showed increased incidences of hepatocellular tumours in female animals and benign testicular tumours in male animals. However, there are no indications that these observations are important for therapeutic use in humans.

Genotoxicity

Various standard mutagenicity studies in bacteria and mammals showed no indications of genotoxicity for carbamazepine.

Toxicity to reproduction

Cumulative evidence from various animal studies in mice, rats and rabbits demonstrated that carbamazepine at 10- to 20-fold higher doses compared with the recommended human dose during organogenesis led to increased embryonic lethality and growth retardation. In mice, embryonic damage (mainly to the cerebral ventricles) has been observed.

In reproductive studies in rats, suckling offspring demonstrated a reduced weight gain at a maternal dose of 192 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Methacrylic acid-ethyl acrylate copolymer (1:1); Ammonio methacrylate copolymer (Type B); Cellulose, microcrystalline, sodium starch glycolate (Type A); Talc; Silica colloidal anhydrous; Magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 years.

This medicinal product should not be used after the expiry date.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Timonil 300 retard and Timonil 600 retard

Blister consists of PVC and aluminium film with 50, 100, and 200 prolonged-release tablets. Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Megapharm Ltd. P.O.Box 519, Hod-Hasharon 4510501

8. MANUFACTURER

Desitin Arzneimittel GmbH, Hamburg, Germany

9. MARKETING AUTHORISATION NUMBER(S)

Timonil 300 retard license number: 068-94-27055

Timonil 600 retard license number: 067-24-27139

The format of this leaflet was determined by the ministry of health and its content was checked and approved in January 2016.