# Annex III

# SUMMARY OF PRODUCT CHARACTERISTICS,

# LABELLING AND PACKAGE LEAFLET

Note:

This product information is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Saroten and associated names 25 mg prolonged-release capsules, hard
Saroten and associated names 50 mg prolonged-release capsules, hard
Saroten and associated names 75 mg, modified release tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

## 3. PHARMACEUTICAL FORM

[To be completed nationally]

<[Saroten and associated names 75 mg, modified release tablets]
The tablet can be divided into 3 equal doses .>

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Saroten and associated names is indicated for:

- the treatment of major depressive disorder in adults
- the treatment of neuropathic pain in adults
- the prophylactic treatment of chronic tension type headache (CTTH) in adults
- the prophylactic treatment of migraine in adults
- the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products. This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

### 4.2 Posology and method of administration

Posology

Not all dosage schemes can be achieved with all the pharmaceutical forms/strengths. The appropriate formulation/strength should be selected for the starting doses and any subsequent dose increments.

*Major depressive disorder*

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerability.

*Adults*
Initially 50 mg daily in the evening. If necessary the dose can be increased by 25 mg or 50 mg after 1 week up to 150 mg daily.

The maintenance dose is the lowest effective dose.

<[Saroten and associated names 75 mg, modified release tablets]
Due to the two score lines the Saroten and associated names 75 mg can be divided into three parts. The dosage therefore can be increased in 25 mg amitriptyline hydrochloride steps>.

*Elderly patients over 65 years of age and patients with cardiovascular disease*
Initially 25 mg in the evening.
The daily dose may be increased up to 100 mg – 150 mg, depending on individual patient response and tolerability.
Daily doses above 100 mg should be used with caution.

The maintenance dose is the lowest effective dose.

*Paediatric population*
Amitriptyline should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established (see section 4.4).

*Duration of treatment*
The antidepressant effect usually sets in after 2 - 4 weeks. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after recovery in order to prevent relapse.

*Neuropathic pain, prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine in adults*

Patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions. Generally, the lowest effective dose should be used for the shortest duration required to treat the symptoms.

*Adults*
The initial dose should be 10 mg - 25 mg in the evening.

Recommended doses are 25 mg - 75 mg in the evening. Doses above 100 mg should be used with caution.

The analgesic effect is normally seen after 2 - 4 weeks of dosing.

*Elderly patients over 65 years of age and patients with cardiovascular disease*

A starting dose of 10 mg - 25 mg in the evening is recommended.

Doses above 75 mg should be used with caution.

It is generally recommended to initiate treatment in the lower dose range as recommended for adult. The dose may be increased depending on individual patient response and tolerability.

*Paediatric population*
Amitriptyline should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established (see section 4.4).

*Duration of treatment*
*Neuropathic pain*

Treatment is symptomatic and should therefore be continued for an appropriate length of time. In many patients, therapy may be needed for several years. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

*Prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine in adults*
Treatment must be continued for an appropriate length of time. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

*Nocturnal enuresis*

*Paediatric population*
The recommended doses for:

- children aged 6 to 10 years: 10 mg - 20 mg. A more suitable dosage form should be used for this age group.
- children aged 11 years and above: 25 mg – 50 mg daily

The dose should be increased gradually.

Dose to be administered 1-1½ hours before bedtime.

An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.

*Duration of treatment*
The maximum period of treatment course should not exceed 3 months.

If repeated courses of amitriptyline are needed, a medical review should be conducted every 3 months.

When stopping treatment, amitriptyline should be withdrawn gradually.

Special populations

*Reduced renal function*
This medicinal product can be given in usual doses to patients with renal failure.

*Reduced liver function*
Careful dosing and, if possible, a serum level determination is advisable.

*Cytochrome P450 inhibitors of CYP2D6*
Depending on individual patient response, a lower dose of amitriptyline should be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to amitriptyline treatment (see section 4.5).

*Known poor metabolisers of CYP2D6 or CYP2C19*
These patients may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose.

Method of administration

Saroten and associated names is for oral use.

<[Saroten and associated names prolonged-release capsules, hard]
The capsules should be swallowed with water.
However, the capsules can be opened and the pellets swallowed with a cold drink or e.g. yoghurt. The pellets must not be chewed.>

<[Saroten and associated names 75 mg, modified release tablets]
Saroten retard Tabs 75 mg are dividable retard tablets with two score lines. The score line facilitates breaking of the retard tablet into 3 parts. Those parts currently not needed can be stored in the reservoir of the tablet box (under the slide of the closure), until the next administration.
The tablets should be swallowed with water independent of meals.>

Discontinuation of treatment

When stopping therapy the drug should be gradually withdrawn over several weeks.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Recent myocardial infarction. Any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency.

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (see section 4.5). Simultaneous administration of amitriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

Treatment with amitriptyline may be instituted 14 days after discontinuation of irreversible non-selective MAOIs and minimum one day after discontinuation of the reversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of amitriptyline.

Severe liver disease.

In children under 6 years of age.

## 4.4 Special warnings and precautions for use

Cardiac arrhythmias and severe hypotension are likely to occur with high dosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

QT interval prolongation
Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the proarrythmic risk.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue this medicinal product several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated.

Great care is necessary if amitriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Elderly patients are particularly susceptible to orthostatic hypotension.

This medical product should be used with caution in patients with convulsive disorders, urinary retention, prostatic hypertrophy, hyperthyroidism, paranoid symptomatology and advanced hepatic or cardiovascular disease, pylorus stenosis and paralytic ileus.

In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked.

Suicide/suicidal thoughts
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In manic-depressives, a shift towards the manic phase may occur; should the patient enter a manic phase amitriptyline should be discontinued.

As described for other psychotropics, amitriptyline may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition the depressive illness itself may affect patients' glucose balance.

Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic or with neuroleptic medications, especially in hot weather.

After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability.

Amitriptyline should be used with caution in patients receiving SSRIs (see sections 4.2 and 4.5).

*Nocturnal enuresis*
An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.
Amitriptyline for enuresis should not be combined with an anticholinergic drug.
Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis.

Paediatric population
Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see section 4.2).

<[Saroten and associated names prolonged-release capsules, hard ]
Excipients
The pellets in the capsule contain sucrose.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not receive this medicine.>

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

**Potential for amitriptyline to affect other medicinal products**

Contraindicated combinations

*MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline))* - risk of "serotonin syndrome" (see section 4.3).

Combinations that are not recommended

*Sympathomimetic agents*: Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

*Adrenergic neurone blockers*: Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

*Anticholinergic agents:* Tricyclic antidepressants may potentiate the effects of these drugs on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, etc.

*Drugs which prolong the QT-interval* including antiarrhythmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants.
Use caution when using amitriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.
Caution is also advised for co-administration of amitriptyline and diuretics inducing hypokalaemia (e.g. furosemide)

*Thioridazine*: Co-administration of amitriptyline and thioridazine (CYP2D6 substrate) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects

*Tramadol*: Concomitant use of tramadol (a CYP2D6 substrate) and tricyclic antidepressants (TCAs), such as amitriptyline increases the risk for seizures and serotonin syndrome. Additionally, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

*Antifungals* such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsade de pointes have occurred.

Combinations requiring precautions for use

*CNS depressants*: Amitriptyline may enhance the sedative effects of alcohol, barbiturates and other CNS depressants.

**Potential of other medicinal products to affect amitriptyline**

Tricyclic antidepressants (TCA) including amitriptyline are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population. Other isozymes involved in the metabolism of amitriptyline are CYP3A4, CYP1A2 and CYP2C9.

*CYP2D6 inhibitors*: The CYP2D6 isozyme can be inhibited by a variety of drugs, e.g. neuroleptics, serotonin reuptake inhibitors, beta blockers, and antiarrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine and quinidine. These drugs may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Consider to monitor TCA plasma levels, whenever a TCA is to be co-administered with another drug known to be an inhibitor of CYP2D6. Dose adjustment of amitriptyline may be necessary (see section 4.2).

*Other Cytochrome P450 inhibitors*: Cimetidine, methylphenidate and calcium-channel blockers (e.g. diltiazem and verapamil) may increase plasma levels of tricyclic antidepressants and accompanying toxicity. Antifungals such as fluconazole (CYP2C9 inhibitor) and terbinafine (CYP2D6 inhibitor) have been observed to increase serum levels of amitriptyline and nortriptyline.

*The CYP3A4 and CYP1A2 isozymes* metabolise amitriptyline to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase amitriptyline plasma concentrations and this combination should be avoided. Clinically relevant interactions may be expected with concomitant use of amitriptyline and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir.

*Tricyclic antidepressants and neuroleptics* mutually inhibit the metabolism of each other; this may lead to a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these drugs.

*Cytochrome P450 inducers*: Oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine and St. John's Wort (Hypericum perforatum) may increase the metabolism of tricyclic antidepressants and result in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

*In the presence of ethanol* amitriptyline free plasma concentrations and nortriptyline concentrations were increased.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

For amitriptyline only limited clinical data are available regarding exposed pregnancies.

Animal studies have shown reproductive toxicity (see section 5.3).
Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

During chronic use and after administration in the final weeks of pregnancy, neonatal withdrawal symptoms can occur. This may include irritability, hypertonia , tremor, irregular breathing, poor drinking and loud crying and possibly anticholinergic symptoms (urinary retention, constipation).

Breast-feeding

Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from the therapy of this medicinal product taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amitriptyline reduced the pregnancy rate in rats (see section 5.3).
No data on the effects of amitriptyline on human fertility are available.

## 4.7 Effects on ability to drive and use machines

Amitriptyline is a sedative drug.
Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery. These adverse effects can be potentiated by the concomitant intake of alcohol.

## 4.8 Undesirable effects

Amitriptyline may induce side effects similar to other tricyclic antidepressants. Some of the below mentioned side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressive state improves.

In the listing below the following convention is used:
MedDRA system organ class / preferred term;
Very common (> 1/10);
Common (> 1/100, < 1/10);
Uncommon (> 1/1,000, < 1/100);
Rare (> 1/10,000, < 1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

| MedDRA SOC | Frequency | Preferred Term |
|---|---|---|
| Blood and lymphatic system disorders | Rare | Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia. |
| Metabolism and nutrition disorders | Rare | Decreased appetite. |
| Metabolism and nutrition disorders | Not known | Anorexia, elevation or lowering of blood sugar levels. |
| Psychiatric disorders | Very common | Aggression. |
| | Common | Confusional state, libido decreased, agitation. |
| | Uncommon | Hypomania, mania, anxiety, insomnia, nightmare. |
| | Rare | Delirium (in elderly patients), hallucination (in schizophrenic patients), suicidal thoughts or behaviour*. |
| | Not Known | Paranoia. |
| Nervous system disorders | Very common | Somnolence, tremor, dizziness, headache, drowsiness, speech disorder (dysarthria). |
| | Common | Disturbance in attention, dysgeusia. paresthesia, ataxia. |
| | Uncommon | Convulsion. |
| | Very rare | Akathisia, polyneuropathy. |
| | Not known | Extrapyramidal disorder. |
| Eye disorders | Very common | Accommodation disorder. |
| | Common | Mydriasis. |
| | Very rare | Acute glaucoma. |
| Ear and labyrinth disorders | Uncommon | Tinnitus. |
| Cardiac disorders | Very common | Palpitations, tachycardia |
| | Common | Atrioventricular block, bundle branch block. |
| | Uncommon | Collapse conditions, worsening of cardiac failure. |
| | Rare | Arrhythmia. |
| | Very rare | Cardiomyopathies, torsades de pointes. |
| | Not known | Hypersensitivity myocarditis. |
| Vascular disorders | Very common | Orthostatic hypotension. |
| | Uncommon | Hypertension. |
| | Not known | Hyperthermia. |

| | | |
|---|---|---|
| Respiratory, thoracic, and mediastinal disorders | Very common | Congested nose. |
| | Very rare | Allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome). |
| Gastrointestinal disorders | Very common | Dry mouth, constipation, nausea. |
| | Uncommon | Diarrhoea, vomiting, tongue oedema. |
| | Rare | Salivary gland enlargement, ileus paralytic. |
| Hepatobiliary disorders | Rare | Jaundice. |
| | Uncommon | Hepatic impairment (e.g. cholestatic liver disease). |
| | Not known | Hepatitis. |
| Skin and subcutaneous tissue disorders | Very common | Hyperhidrosis. |
| | Uncommon | Rash, urticaria, face oedema. |
| | Rare | Alopecia, photosensitivity reaction. |
| Renal and urinary disorders | Common | Micturition disorders. |
| | Uncommon | Urinary retention. |
| Reproductive system and breast disorders | Common | Erectile dysfunction. |
| | Uncommon | Galactorrhoea. |
| | Rare | Gynaecomastia. |
| General disorders and administration site conditions | Common | Fatigue, feeling thirst. |
| | Rare | Pyrexia. |
| Investigations | Very common | Weight increased. |
| | Common | Electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia. |
| | Uncommon | Intraocular pressure increased. |
| | Rare | Weight decreased.<br>Liver function test abnormal, blood alkaline phosphatase increased, transaminases increased. |

*Case reports of suicidal thoughts or behaviour were reported during the treatment with or just after conclusion of the treatment with amitriptyline (see section 4.4).

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

Symptoms

*Anticholinergic symptoms*: Mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility. Convulsions. Fever. Sudden occurrence of CNS depression. Lowered consciousness progressing into coma. Respiratory depression.

*Cardiac symptoms*: Arrhythmias (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation). The ECG characteristically show prolonged PR interval, widening of the QRS-complex, QT prolongation, T-wave flattening or inversion, ST segment depression, and varying degrees of heart block progressing to cardiac standstill. Widening of the QRS-complex usually correlates well with the severity of the toxicity following acute overdoses. Heart failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia.

**Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic**. There is considerably individual variability in response to overdose. Children are especially susceptible to cardiotoxicity and seizures.

During awakening possibly again confusion, agitation and hallucinations and ataxia.

Treatment

1. Admission to hospital (intensive care unit) if required. Treatment is symptomatic and supportive.
2. Assess and treat ABC's (airway, breathing and circulation) as appropriate. Secure an IV access. Close monitoring even in apparently uncomplicated cases.
3. Examine for clinical features. Check urea and electrolytes—look for low potassium and monitor urine output. Check arterial blood gases—look for acidosis. Perform electrocardiograph—look for QRS>0.16 seconds
4. Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.
5. Consider gastric lavage only if within one hour of a potentially fatal overdose.
6. Give 50 g of charcoal if within one hour of ingestion.
7. Patency of the airway is maintained by intubation, where required. Treatment in respirator is advised to prevent a possible respiratory arrest. Continuous ECG-monitoring of cardiac function for 3-5 days. Treatment of the following will be decided on a case by case basis:
   - Wide QRS-intervals, cardiac failure and ventricular arrhythmias
   - Circulatory failure
   - Hypotension
   - Hyperthermia
   - Convulsions
   - Metabolic acidosis.
8. Unrest and convulsions may be treated with diazepam.
9. Patients who display signs of toxicity should be monitored for a minimum of 12 hours.
10. Monitor for rhabdomyolysis if the patient has been unconscious for a considerable time.
11. Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of medicament.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant)
ATC code: N 06 AA 09

Mechanism of action

Amitriptyline is a tricyclic antidepressant and an analgesic. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiate their action in the brain. This appears to be associated with the antidepressant activity.

The mechanism of action also includes ion-channel blocking effects on sodium, potassium and NMDA channel at both central and spinal cord level. The noradrenaline, sodium and the NMDA effects are mechanisms known to be involved in the maintenance of neuropathic pain, chronic tension type headache prophylaxis and migraine prophylaxis. The pain-reducing effect of amitriptyline is not linked to its anti-depressive properties.

Tricyclic antidepressants possess affinity for muscarinic and histamine H1 receptors to varying degrees.

Clinical efficacy and safety

The efficacy and safety of amitriptyline has been demonstrated in treatments of the following indications in adults:

- Major Depressive Disorder
- Neuropathic pain
- Chronic tension type headache prophylaxis
- Migraine prophylaxis

The efficacy and safety of amitriptyline has been demonstrated for treatments of nocturnal enuresis in children aged 6 years and above (see section 4.1).

The recommended doses are provided in section 4.2. For treatment of depression, doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients in hospital only.

The antidepressant and analgesic effects usually set in after 2-4 weeks; the sedative action is not delayed.

## 5.2 Pharmacokinetic properties

Absorption

<[Saroten and associated names prolonged-release capsules, hard ]
*Film-coated tablets*
Oral administration of tablets results in maximum serum levels in about 4 hours. ($t_{max}$ = 3.89±1.87 hours; range 1.93-7.98 hours). After peroral administration of 50 mg the mean $C_{max}$ = 30.95±9.61 ng/ml; range 10.85-45.70 ng/ml (111.57±34.64 nmol/l; range 39.06-164.52 nmol/l). The mean absolute oral bioavailability is 53% ($F_{abs}$ = 0.527±0.123; range 0.219-0.756).

*Prolonged-release Capsules, hard*
In contrast to the tablet serum curves which show a distinct initial peak, the capsule curves rise slowly to a plateau level with lower concentrations than the peak of the tablet curves. $t_{max}$ = 7.1±1.9 hours; range 2.0-10.0 hours. After oral administration of 50 mg the mean $C_{max}$ =21.5±9.0 ng/ml; range 13.2-35.8 ng/ml (77.5±32.4 nmol/L).>

<[Saroten and associated names 75 mg, modified release tablets]
In contrast to the tablet serum curves which show a distinct initial peak, the modified release tablets curves rise slowly to a plateau level with lower concentrations than the peak of the tablet curves. The maximum plasma concentration is reached only after 1 to 5 (-8) hours.
The systemic bioavailability is about 50% of the intravenous injection.>

Distribution

The apparent volume of distribution $(V_d)_\beta$ estimated after intravenous administration is 1221 L±280 L; range 769-1702 L (16±3 L/kg).
The plasma protein binding is about 95%.
Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

In nursing mothers amitriptyline and nortriptyline are excreted in small amounts with the breast milk. The ratio milk concentration/plasma concentration in women is around 1:1. The estimated daily infant exposure (amitriptyline + nortriptyline) averages 2% of the corresponding maternal weight related doses of amitriptyline (in mg/kg) (see section 4.6).

Biotransformation

*In vitro* the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are CYP1A2 and CYP2C9. The metabolism is subject to genetic polymorphism. The main active metabolite is the secondary amine, nortriptyline.
Nortriptyline is a more potent inhibitor of noradrenaline than of serotonin uptake, while amitriptyline inhibits the uptake of noradrenaline and serotonin equally well. Other metabolites such as cis- and trans-10-hydroxyamitriptyline and cis- and trans-10-hydroxynortriptyline have the same profile as nortriptyline but is considerably weaker. Demethylnortriptyline and amitriptyline N oxide are only present in plasma in minute amounts; the latter is almost inactive. All the metabolites are less anticholinergic than amitriptyline and nortriptyline. In plasma the amount of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

Elimination

The elimination half-life ($t_{½}$ β) amitriptyline after peroral administration is about 25 hours (24.65±6.31 hours; range 16.49-40.36 hours). The mean systemic clearance ($Cl_s$) is 39.24±10.18 L/h, range 24.53-53.73 L/h.

The excretion proceeds mainly with urine. The renal elimination of unchanged amitriptyline is insignificant (about 2%).

Steady state plasma levels of amitriptyline + nortriptyline are reached within a week for most patients, and in steady state the plasma level comprises approximately equal parts of amitriptyline and nortriptyline around the clock following treatment with conventional tablets 3 times a day.

<[Saroten and associated names prolonged-release capsules, hard ]
When the prolonged-release capsules are administered in the evening the concentration of amitriptyline is highest late in the night and decreases during the day whilst the concentration of nortriptyline is constant around the clock and thus predominates during daytime.

<[Saroten and associated names 75 mg, modified release tablets]
When the modified-release tablets are administered in the evening the concentration of amitriptyline is highest late in the night and decreases during the day whilst the concentration of nortriptyline is constant around the clock and thus predominates during daytime.>

*Elderly patients*
Longer half-lives and decreased oral ($Cl_o$) clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

*Reduced hepatic function*
Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients (see section 4.2).

*Reduced renal function*
Renal failure has no influence on the kinetics.

Polymorphism

The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19) (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship

Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.
The therapeutic plasma concentration in major depression is around 80 – 200 ng/ml (≈ 280 – 700 nmol/l) (for amitriptyline + nortriptyline). Levels above 300-400 ng/ml are associated with increased risk of disturbance in cardiac conduction in terms of prolonged QRS-complex or AV block.

### 5.3 Preclinical safety data

Amitriptyline inhibited ion channels, which are responsible for cardiac repolarization (hERG channels), in the upper micromolar range of therapeutic plasma concentrations. Therefore, amitriptyline may increase the risk for cardiac arrhythmia (see section 4.4).

The genotoxic potential of amitriptyline has been investigated in various *in vitro* and *in vivo* studies. Although these investigations revealed partially contradictory results, particularly a potential to induce chromosome aberrations cannot be excluded. Long-term carcinogenicity studies have not been performed.

In reproductive studies teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2-40 mg/kg/day (up to 13 times the maximum recommended human amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50-kg patient). However, literature data suggested a risk for malformations and delays in ossification of mice, hamsters, rats and rabbits at 9 33 times the maximum recommended dose. There was a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for the effect on fertility is unknown.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

[To be completed nationally]

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

[To be completed nationally]

### 6.4 Special precautions for storage

[To be completed nationally]

### 6.5 Nature and contents of container <and special equipment for use, administration or implantation>

[To be completed nationally]

### 6.6 Special precautions for disposal <and other handling>

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

## 1. NAME OF THE MEDICINAL PRODUCT

Saroten and associated names 10 mg film-coated tablets
Saroten and associated names 25 mg film-coated tablets
Saroten and associated names 50 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

## 3. PHARMACEUTICAL FORM

[To be completed nationally]

<[Saroten and associated names 50 mg film-coated tablets]
The tablet can be divided into 4 equal doses.>

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Saroten and associated names is indicated for:

- the treatment of major depressive disorder in adults
- the treatment of neuropathic pain in adults
- the prophylactic treatment of chronic tension type headache (CTTH) in adults
- the prophylactic treatment of migraine in adults
- the treatment of nocturnal enuresis in children aged 6 years and above when organic pathology, including spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including antispasmodics and vasopressin-related products. This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

### 4.2 Posology and method of administration

Posology

Not all dosage schemes can be achieved with all the pharmaceutical forms/strengths. The appropriate formulation/strength should be selected for the starting doses and any subsequent dose increments.

*Major depressive disorder*

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerability.

*Adults*
Initially 25 mg 2 times daily (50 mg daily). If necessary, the dose can be increased by 25 mg every other day up to 150 mg daily divided into two doses.

The maintenance dose is the lowest effective dose.

*Elderly patients over 65 years of age and patients with cardiovascular disease*
Initially 10 mg – 25 mg daily.

The daily dose may be increased up to 100 mg – 150 mg divided into two doses, depending on individual patient response and tolerability.
Doses above 100 mg should be used with caution.

The maintenance dose is the lowest effective dose.

*Paediatric population*
Amitriptyline should not be used in children and adolescents aged less than 18 years, as long term safety and efficacy have not been established (see section 4.4).

*Duration of treatment*
The antidepressant effect usually sets in after 2 - 4 weeks. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after recovery in order to prevent relapse.

*Neuropathic pain, prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine prophylaxis*

Patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions. Generally, the lowest effective dose should be used for the shortest duration required to treat the symptoms.

*Adults*
Recommended doses are 25 mg - 75 mg daily in the evening. Doses above 100 mg should be used with caution.

The initial dose should be 10 mg - 25 mg in the evening. Doses can be increased with 10 mg - 25 mg every 3 – 7 days as tolerated.

The dose can be taken once daily, or be divided into two doses. A single dose above 75 mg is not recommended.

The analgesic effect is normally seen after 2 - 4 weeks of dosing.

*Elderly patients over 65 years of age and patients with cardiovascular disease*

A starting dose of 10 mg - 25 mg in the evening is recommended.
Doses above 75 mg should be used with caution.

It is generally recommended to initiate treatment in the lower dose range as recommended for adult. The dose may be increased depending on individual patient response and tolerability.

*Paediatric population*
Amitriptyline should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established (see section 4.4).

*Duration of treatment*
*Neuropathic pain*

Treatment is symptomatic and should therefore be continued for an appropriate length of time. In many patients, therapy may be needed for several years. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

*Prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine in adults*
Treatment must be continued for an appropriate length of time. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

*Nocturnal enuresis*

*Paediatric population*
The recommended doses for:
- children aged 6 to 10 years: 10 mg – 20 mg. A suitable dosage form should be used for this age group.
- children aged 11 years and above: 25 mg – 50 mg daily

The dose should be increased gradually.

Dose to be administered 1-1½ hours before bedtime.

An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.

The maximum period of treatment course should not exceed 3 months.

If repeated courses of amitriptyline are needed, a medical review should be conducted every 3 months.

When stopping treatment, amitriptyline should be withdrawn gradually.

*Special populations*

*Reduced renal function*
This medicinal product can be given in usual doses to patients with renal failure.

*Reduced liver function*
Careful dosing and, if possible, a serum level determination is advisable.

*Cytochrome P450 inhibitors of CYP2D6*
Depending on individual patient response, a lower dose of amitriptyline should be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to amitriptyline treatment (see section 4.5).

*Known poor metabolisers of CYP2D6 or CYP2C19*
These patients may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose.

Method of administration

Saroten and associated names is for oral use.

<[Saroten and associated names 50 mg film-coated tablets]
Saroten and associated names 50 mg film-coated tablets are dividable tablets with three score lines. The score line facilitates breaking of the tablet into 4 parts (12.5 mg/part). Those parts currently not needed can be stored in the reservoir of the tablet box (under the slide of the closure), until the next administration.>

The tablets should be swallowed with water.

Discontinuation of treatment

When stopping therapy the drug should be gradually withdrawn during several weeks.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Recent myocardial infarction. Any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency.

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (see section 4.5). Simultaneous administration of amitriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

Treatment with amitriptyline may be instituted 14 days after discontinuation of irreversible non-selective MAOIs and minimum one day after discontinuation of the reversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of amitriptyline.

Severe liver disease.

In children under 6 years of age.

## 4.4 Special warnings and precautions for use

Cardiac arrhythmias and severe hypotension are likely to occur with high dosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

QT interval prolongation
Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the proarrythmic risk.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue this medicinal product several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated.

Great care is necessary if amitriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Elderly patients are particularly susceptible to orthostatic hypotension.

This medical product should be used with caution in patients with convulsive disorders, urinary retention, prostatic hypertrophy, hyperthyroidism, paranoid symptomatology and advanced hepatic or cardiovascular disease, pylorus stenosis and paralytic ileus.

In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked.

Suicide/suicidal thoughts
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the

first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In manic-depressives, a shift towards the manic phase may occur; should the patient enter a manic phase amitriptyline should be discontinued.

As described for other psychotropics, amitriptyline may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition the depressive illness itself may affect patients' glucose balance.

Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic or with neuroleptic medications, especially in hot weather.

After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability.

Amitriptyline should be used with caution in patients receiving SSRIs (see sections 4.2 and 4.5).

*Nocturnal enuresis*
An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.
Amitriptyline for enuresis should not be combined with an anticholinergic drug.
Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis.

Paediatric population
Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see section 4.2).

Excipients
The tablets contain lactose.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive this medicine.

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

**Potential for amitriptyline to affect other medicinal products**

Contraindicated combinations

*MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline))* - risk of "serotonin syndrome" (see section 4.3).

Combinations that are not recommended

*Sympathomimetic agents*: Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

*Adrenergic neurone blockers*: Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

*Anticholinergic agents:* Tricyclic antidepressants may potentiate the effects of these drugs on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, etc.

*Drugs which prolong the QT-interval* including antiarrhythmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants.
Use caution when using amitriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.
Caution is also advised for co-administration of amitriptyline and diuretics inducing hypokalaemia (e.g. furosemide)

*Thioridazine*: Co-administration of amitriptyline and thioridazine (CYP2D6 substrate) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects

*Tramadol*: Concomitant use of tramadol (a CYP2D6 substrate) and tricyclic antidepressants (TCAs), such as amitriptyline increases the risk for seizures and serotonin syndrome. Additionally, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

*Antifungals* such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsade de pointes have occurred.

Combinations requiring precautions for use

*CNS depressants*: Amitriptyline may enhance the sedative effects of alcohol, barbiturates and other CNS depressants.

**Potential of other medicinal products to affect amitriptyline**

Tricyclic antidepressants (TCA) including amitriptyline are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population. Other isozymes involved in the metabolism of amitriptyline are CYP3A4, CYP1A2 and CYP2C9.

*CYP2D6 inhibitors*: The CYP2D6 isozyme can be inhibited by a variety of drugs, e.g. neuroleptics, serotonin reuptake inhibitors, beta blockers, and antiarrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine and quinidine. These drugs may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Consider to monitor TCA plasma levels, whenever a TCA is to be co-administered with another drug known to be an inhibitor of CYP2D6. Dose adjustment of amitriptyline may be necessary (see section 4.2).

*Other Cytochrome P450 inhibitors*: Cimetidine, methylphenidate and calcium-channel blockers (e.g. diltiazem and verapamil) may increase plasma levels of tricyclic antidepressants and accompanying toxicity. Antifungals such as fluconazole (CYP2C9 inhibitor) and terbinafine (CYP2D6 inhibitor) have been observed to increase serum levels of amitriptyline and nortriptyline.

*The CYP3A4 and CYP1A2 isozymes* metabolise amitriptyline to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase amitriptyline plasma concentrations and this combination should be avoided. Clinically relevant interactions may be expected with concomitant use of amitriptyline and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir.

*Tricyclic antidepressants and neuroleptics* mutually inhibit the metabolism of each other; this may lead to a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these drugs.

*Cytochrome P450 inducers*: Oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine and St. John's Wort (Hypericum perforatum) may increase the metabolism of tricyclic antidepressants and result in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

*In the presence of ethanol* amitriptyline free plasma concentrations and nortriptyline concentrations were increased.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

For amitriptyline only limited clinical data are available regarding exposed pregnancies.

Animal studies have shown reproductive toxicity (see section 5.3).
Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

During chronic use and after administration in the final weeks of pregnancy, neonatal withdrawal symptoms can occur. This may include irritability, hypertonia , tremor, irregular breathing, poor drinking and loud crying and possibly anticholinergic symptoms (urinary retention, constipation).

Breast-feeding

Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from the therapy of this medicinal product taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Amitriptyline reduced the pregnancy rate in rats (see section 5.3).
No data on the effects of amitriptyline on human fertility are available.

## 4.7 Effects on ability to drive and use machines

Amitriptyline is a sedative drug.
Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery. These adverse effects can be potentiated by the concomitant intake of alcohol.

## 4.8 Undesirable effects

Amitriptyline may induce side effects similar to other tricyclic antidepressants. Some of the below mentioned side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressive state improves.

In the listing below the following convention is used:

MedDRA system organ class / preferred term;
Very common (> 1/10);
Common (> 1/100, < 1/10);
Uncommon (> 1/1,000, < 1/100);
Rare (> 1/10,000, < 1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

| MedDRA SOC | Frequency | Preferred Term |
|---|---|---|
| Blood and lymphatic system disorders | Rare | Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia. |
| Metabolism and nutrition disorders | Rare | Decreased appetite. |
| Metabolism and nutrition disorders | Not known | Anorexia, elevation or lowering of blood sugar levels. |
| Psychiatric disorders | Very common | Aggression. |
| | Common | Confusional state, libido decreased, agitation. |
| | Uncommon | Hypomania, mania, anxiety, insomnia, nightmare. |
| | Rare | Delirium (in elderly patients), hallucination (in schizophrenic patients), suicidal thoughts or behaviour*. |
| | Not Known | Paranoia. |
| Nervous system disorders | Very common | Somnolence, tremor, dizziness, headache, drowsiness, speech disorder (dysarthria). |
| | Common | Disturbance in attention, dysgeusia. paresthesia, ataxia. |
| | Uncommon | Convulsion. |
| | Very rare | Akathisia, polyneuropathy. |
| | Not known | Extrapyramidal disorder. |
| Eye disorders | Very common | Accommodation disorder. |
| | Common | Mydriasis. |
| | Very rare | Acute glaucoma. |
| Ear and labyrinth disorders | Uncommon | Tinnitus. |
| Cardiac disorders | Very common | Palpitations, tachycardia. |
| | Common | Atrioventricular block, bundle branch block. |
| | Uncommon | Collapse conditions, worsening of cardiac failure. |
| | Rare | Arrhythmia. |
| | Very rare | Cardiomyopathies, torsades de pointes. |
| | Not known | Hypersensitivity myocarditis. |
| Vascular disorders | Very common | Orthostatic hypotension. |
| | Uncommon | Hypertension. |
| | Not known | Hyperthermia. |
| Respiratory, thoracic, and mediastinal disorders | Very common | Congested nose. |
| | Very rare | Allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome). |

| | | |
|---|---|---|
| Gastrointestinal disorders | Very common | Dry mouth, constipation, nausea. |
| | Uncommon | Diarrhoea, vomiting, tongue oedema. |
| | Rare | Salivary gland enlargement, ileus paralytic. |
| Hepatobiliary disorders | Rare | Jaundice. |
| | Uncommon | Hepatic impairment (e.g. cholestatic liver disease). |
| | Not known | Hepatitis. |
| Skin and subcutaneous tissue disorders | Very common | Hyperhidrosis. |
| | Uncommon | Rash, urticaria, face oedema. |
| | Rare | Alopecia, photosensitivity reaction. |
| Renal and urinary disorders | Common | Micturition disorders. |
| | Uncommon | Urinary retention. |
| Reproductive system and breast disorders | Common | Erectile dysfunction. |
| | Uncommon | Galactorrhoea. |
| | Rare | Gynaecomastia. |
| General disorders and administration site conditions | Common | Fatigue, feeling thirst. |
| | Rare | Pyrexia. |
| Investigations | Very common | Weight increased. |
| | Common | Electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia. |
| | Uncommon | Intraocular pressure increased. |
| | Rare | Weight decreased.<br>Liver function test abnormal, blood alkaline phosphatase increased, transaminases increased. |

*Case reports of suicidal thoughts or behaviour were reported during the treatment with or just after conclusion of the treatment with amitriptyline (see section 4.4).

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

Symptoms

*Anticholinergic symptoms*: Mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility. Convulsions. Fever. Sudden occurrence of CNS depression. Lowered consciousness progressing into coma. Respiratory depression.

*Cardiac symptoms*: Arrhythmias (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation). The ECG characteristically show prolonged PR interval, widening of the QRS-complex, QT prolongation, T-wave flattening or inversion, ST segment depression, and varying degrees of heart block progressing to cardiac standstill. Widening of the QRS-complex usually correlates well with the severity

of the toxicity following acute overdoses. Heart failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia.

**Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic**. There is considerably individual variability in response to overdose. Children are especially susceptible to cardiotoxicity and seizures.

During awakening possibly again confusion, agitation and hallucinations and ataxia.

Treatment

1. Admission to hospital (intensive care unit) if required. Treatment is symptomatic and supportive.
2. Assess and treat ABC's (airway, breathing and circulation) as appropriate. Secure an IV access. Close monitoring even in apparently uncomplicated cases.
3. Examine for clinical features. Check urea and electrolytes—look for low potassium and monitor urine output. Check arterial blood gases—look for acidosis. Perform electrocardiograph—look for QRS>0.16 seconds
4. Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.
5. Consider gastric lavage only if within one hour of a potentially fatal overdose.
6. Give 50 g of charcoal if within one hour of ingestion.
7. Patency of the airway is maintained by intubation, where required. Treatment in respirator is advised to prevent a possible respiratory arrest. Continuous ECG-monitoring of cardiac function for 3-5 days. Treatment of the following will be decided on a case by case basis:
   - Wide QRS-intervals, cardiac failure and ventricular arrhythmias
   - Circulatory failure
   - Hypotension
   - Hyperthermia
   - Convulsions
   - Metabolic acidosis.
8. Unrest and convulsions may be treated with diazepam.
9. Patients who display signs of toxicity should be monitored for a minimum of 12 hours.
10. Monitor for rhabdomyolysis if the patient has been unconscious for a considerable time.
11. Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of medicament.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant)
ATC code: N 06 AA 09

Mechanism of action

Amitriptyline is a tricyclic antidepressant and an analgesic. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiate their action in the brain. This appears to be associated with the antidepressant activity.

The mechanism of action also includes ion-channel blocking effects on sodium, potassium and NMDA channel at both central and spinal cord level. The noradrenaline, sodium and the NMDA effects are mechanisms known to be involved in the maintenance of neuropathic pain, chronic tension type headache

prophylaxis and migraine prophylaxis. The pain-reducing effect of amitriptyline is not linked to its anti-depressive properties.

Tricyclic antidepressants possess affinity for muscarinic and histamine H1 receptors to varying degrees.

Clinical efficacy and safety

The efficacy and safety of amitriptyline has been demonstrated in treatments of the following indications in adults:

- Major Depressive Disorder
- Neuropathic Pain
- Chronic tension type headache prophylaxis
- Migraine prophylaxis

The efficacy and safety of amitriptyline has been demonstrated for treatments of nocturnal enuresis in children aged 6 years and above (see section 4.1).

The recommended doses are provided in section 4.2. For treatment of depression, doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients in hospital.

The antidepressant and analgesic effects usually set in after 2-4 weeks; the sedative action is not delayed.

## 5.2 Pharmacokinetic properties

Absorption

*Film-coated tablets*
<[Saroten and associated names 10 mg film-coated tablets, Saroten and associated names 25 mg film-coated tablets]
Oral administration of tablets results in maximum serum levels in about 4 hours. ($t_{max}$ = 3.89±1.87 hours; range 1.93-7.98 hours). After peroral administration of 50 mg the mean $C_{max}$ = 30.95±9.61 ng/ml; range 10.85-45.70 ng/ml (111.57±34.64 nmol/l; range 39.06-164.52 nmol/l). The mean absolute oral bioavailability is 53% ($F_{abs}$ = 0.527±0.123; range 0.219-0.756).>

<[Saroten and associated names 50 mg film-coated tablets]
After oral administration amitriptyline is absorbed slowly but completely. Due to the often delayed gastrointestinal tract passage maximum plasma concentrations are reached after 1 to 5 (-8) hours.
The systemic bioavailability is about 50% of the intravenous injection.>

Distribution

The apparent volume of distribution $(V_d)_\beta$ estimated after intravenous administration is 1221 L±280 L; range 769-1702 L (16±3 L/kg).
The plasma protein binding is about 95%.
Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

In nursing mothers amitriptyline and nortriptyline are excreted in small amounts with the breast milk. The ratio milk concentration/plasma concentration in women is around 1:1. The estimated daily infant exposure (amitriptyline + nortriptyline) averages 2% of the corresponding maternal weight related doses of amitriptyline (in mg/kg) (see section 4.6).

Biotransformation

*In vitro* the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are

CYP1A2 and CYP2C9. The metabolism is subject to genetic polymorphism. The main active metabolite is the secondary amine, nortriptyline.
Nortriptyline is a more potent inhibitor of noradrenaline than of serotonin uptake, while amitriptyline inhibits the uptake of noradrenaline and serotonin equally well. Other metabolites such as cis- and trans-10-hydroxyamitriptyline and cis- and trans-10-hydroxynortriptyline have the same profile as nortriptyline but is considerably weaker. Demethylnortriptyline and amitriptyline N oxide are only present in plasma in minute amounts; the latter is almost inactive. All the metabolites are less anticholinergic than amitriptyline and nortriptyline. In plasma the amount of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

Elimination

The elimination half-life ($t_{½}$ β) amitriptyline after peroral administration is about 25 hours (24.65±6.31 hours; range 16.49-40.36 hours). The mean systemic clearance ($Cl_s$) is 39.24±10.18 L/h, range 24.53-53.73 L/h.

The excretion proceeds mainly with urine. The renal elimination of unchanged amitriptyline is insignificant (about 2%).

Steady state plasma levels of amitriptyline + nortriptyline are reached within a week for most patients, and in steady state the plasma level comprises approximately equal parts of amitriptyline and nortriptyline around the clock following treatment with conventional tablets 3 times a day.

*Elderly patients*
Longer half-lives and decreased oral ($Cl_o$) clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

*Reduced hepatic function*
Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients (see section 4.2).

*Reduced renal function*
Renal failure has no influence on the kinetics.

Polymorphism

The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19) (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship

Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.
The therapeutic plasma concentration in major depression is around 80 – 200 ng/ml (≈ 280 – 700 nmol/l) (for amitriptyline + nortriptyline). Levels above 300-400 ng/ml are associated with increased risk of disturbance in cardiac conduction in terms of prolonged QRS-complex or AV block.

## 5.3 Preclinical safety data

Amitriptyline inhibited ion channels, which are responsible for cardiac repolarization (hERG channels), in the upper micromolar range of therapeutic plasma concentrations. Therefore, amitriptyline may increase the risk for cardiac arrhythmia (see section 4.4).

The genotoxic potential of amitriptyline has been investigated in various *in vitro* and *in vivo* studies. Although these investigations revealed partially contradictory results, particularly a potential to induce chromosome aberrations cannot be excluded. Long-term carcinogenicity studies have not been performed.

In reproductive studies teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2-40 mg/kg/day (up to 13 times the maximum recommended human amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50-kg patient). However, literature data suggested a risk for malformations and delays in ossification of mice, hamsters, rats and rabbits at 9 33 times the maximum recommended dose. There was a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for the effect on fertility is unknown.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

[To be completed nationally]

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

[To be completed nationally]

### 6.4 Special precautions for storage

[To be completed nationally]

### 6.5 Nature and contents of container <and special equipment for use, administration or implantation>

[To be completed nationally]

### 6.6 Special precautions for disposal <and other handling>

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

## 1. NAME OF THE MEDICINAL PRODUCT

Saroten and associated names 2 ml, 50 mg solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

## 3. PHARMACEUTICAL FORM

[To be completed nationally]

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Saroten and associated names is indicated for in-hospital treatment of major depressive disorders in adults.

### 4.2 Posology and method of administration

Posology

Initial treatment:
Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerability.
Saroten injectable solution is used in hospitalized patients especially for the initial treatment of depressive disorders.

Intravenous infusion
Usually the X is added to a solution for infusion. The daily dosage is in general between 1 and 3 ampoules of 2 ml (equivalent to 50-150 mg amitriptyline hydrochloride/day, equivalent to 44.2 – 132.6 mg amitriptyline/day).
Unless prescribed otherwise adults will receive their daily dosages in 250 to 500 ml sodium chloride solution 0.9% for 2-3 hours as a drip infusion under control of blood pressure and ECG.

Intramuscular application
X can also be injected into a big muscle (i.m. injection). Unless prescribed otherwise adults will receive half an ampoule up to 2 ampoules (1 to 4 ml solution for injection, equivalent to 25 to 100 mg amitriptyline hydrochloride per day) in several single injections of no more than 25 mg amitriptyline hydrochloride.

Dose increase
If a dose increase is required this should be done stepwise within 3 to 7 days.
A maximum daily dosage of 150 mg amitriptyline given by injection/infusion should not be exceeded.

Further treatment with oral formulation:
After about 1 to 2 weeks a stepwise reduction together with a change to the oral formulations for further treatment can be initiated. The dosing scheme and treatment duration given for the oral formulation should be followed from henceforward.

*Special populations*

Weakened patients, patients with cerebral or cardiac impairment, as well as patients with poor circulation, breathing problems, impaired liver function or advanced renal impairment a dose reduction is recommended.

*Reduced liver function*
Careful dosing and, if possible, a serum level determination is advisable.

*Elderly patients over 65 years of age:*
Elderly often require a considerably lower dose and often show at half the daily dose a satisfying success of treatment. Doses above 100 mg should be used with caution.

Paediatric population
Amitriptyline should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established (see section 4.4).

*Cytochrome P450 inhibitors of CYP2D6*
Depending on individual patient response, a lower dose of amitriptyline should be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to amitriptyline treatment (see section 4.5).

*Known poor metabolisers of CYP2D6 or CYP2C19*
These patients may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose.

Method of administration

X can be used as drip infusion or as intramuscular injection. The solution for infusion prepared with sodium chloride solution 0.9% must be used immediately.

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerability.

Wrongly administered injections (subcutaneous, paravenous or intra-arterial injection) must be avoided due to the risk of considerable tissue injury.

*Duration of treatment*
The solution for injection should mainly be used for acute treatment. After 1-2 weeks the oral formulations should be used for further treatment. The antidepressant effect usually sets in after 2-4 weeks; the sedative action is not delayed.

Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after recovery in order to prevent relapse.

Discontinuation of treatment
When stopping therapy the drug should be gradually withdrawn during several weeks.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Recent myocardial infarction. Any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency.
Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (see section 4.5).

Simultaneous administration of amitriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

As with other tricyclic antidepressants, amitriptyline should not be given to patients receiving monoamine oxidase inhibitors (MAOIs). Treatment with amitriptyline may be instituted 14 days after discontinuation of irreversible non-selective MAOIs and minimum one day after discontinuation of the reversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of amitriptyline.

Severe liver disease.

**4.4 Special warnings and precautions for use**

Cardiac arrhythmias and severe hypotension are likely to occur with high dosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

QT interval prolongation
Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the proarrythmic risk.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue this medicinal product several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated.

Great care is necessary if amitriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Elderly patients are particularly susceptible to orthostatic hypotension.

This medical product should be used with caution in patients with convulsive disorders, urinary retention, prostatic hypertrophy, hyperthyroidism, paranoid symptomatology and advanced hepatic or cardiovascular disease, pylorus stenosis and paralytic ileus.

In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked.

Suicide/suicidal thoughts
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In manic-depressives, a shift towards the manic phase may occur; should the patient enter a manic phase amitriptyline should be discontinued.

As described for other psychotropics, amitriptyline may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition the depressive illness itself may affect patients' glucose balance.

Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic or with neuroleptic medications, especially in hot weather.

After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability.

Amitriptyline should be used with caution in patients receiving SSRIs (see sections 4.2 and 4.5).

X contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

**Paediatric population**
Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see section 4.2).

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

**Potential for amitriptyline to affect other medicinal products**
Contraindicated combinations

*MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline))* - risk of "serotonin syndrome" (see section 4.3).

Combinations that are not recommended
*Sympathomimetic agents*: Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

*Adrenergic neurone blockers*: Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

*Anticholinergic agents* Tricyclic antidepressants may potentiate the effects of these drugs on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, etc.

*Drugs which prolong the QT-interval* including antiarrhythmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants.
Take Use caution when using amitriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.
Caution is also advised for co-administration of amitriptyline and diuretics inducing hypokalaemia (e.g. furosemide)

*Thioridazine*: Co-administration of amitriptyline and thioridazine (CYP2D6 substrate) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects

*Tramadol*: Concomitant use of tramadol (a CYP2D6 substrate) and tricyclic antidepressants (TCAs), such as amitriptyline increases the risk for seizures and serotonin syndrome. Additionally, this combination can

inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

*Antifungals* such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsade de pointes have occurred.

Combinations requiring precautions for use

*CNS depressants*: Amitriptyline may enhance the sedative effects of alcohol, barbiturates and other CNS depressants.

**Potential of other medicinal products to affect amitriptyline**
*Tricyclic antidepressants (TCA)* including amitriptyline are primarily metabolised by the hepatic cytochrome P450 isozymes CYP2D6 and CYP2C19, which are polymorphic in the population. Other isozymes involved in the metabolism of amitriptyline are CYP3A4, CYP1A2 and CYP2C9.

*CYP2D6 inhibitors*: The CYP2D6 isozyme can be inhibited by a variety of drugs, e.g. neuroleptics, serotonin reuptake inhibitors, beta blockers, and antiarrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine and quinidine. These drugs may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Consider to monitor TCA plasma levels, whenever a TCA is to be co-administered with another drug known to be an inhibitor of CYP2D6. Dose adjustment of amitriptyline may be necessary (see section 4.2).

*Other Cytochrome P450 inhibitors*: Cimetidine, methylphenidate and calcium-channel blockers (e.g. diltiazem and verapamil) may increase plasma levels of tricyclic antidepressants and accompanying toxicity. Antifungals such as fluconazole (CYP2C9 inhibitor) and terbinafine (CYP2D6 inhibitor) have been observed to increase serum levels of amitriptyline and nortriptyline.

*The CYP3A4 and CYP1A2 isozymes* metabolise amitriptyline to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase amitriptyline plasma concentrations and this combination should be avoided. Clinically relevant interactions may be expected with concomitant use of amitriptyline and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir.

*Tricyclic antidepressants and neuroleptics* mutually inhibit the metabolism of each other; this may lead to a lowered convulsion threshold, and seizures. It may be necessary to adjust the dosage of these drugs.

*Cytochrome P450 inducers*: Oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine and St. John's Wort (Hypericum perforatum) may increase the metabolism of tricyclic antidepressants and result in lowered plasma levels of tricyclic antidepressants and reduced antidepressant response.

In the presence of ethanol amitriptyline free plasma concentrations and nortriptyline concentrations were increased.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
For amitriptyline only limited clinical data are available regarding exposed pregnancies.

Animal studies have shown reproductive toxicity (see section 5.3). Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

During chronic use and after administration in the final weeks of pregnancy, neonatal withdrawal symptoms can occur. This may include irritability, hypertonia, tremor, irregular breathing, poor drinking and loud crying and possibly anticholinergic symptoms (urinary retention, constipation).

Breast-feeding
Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from the therapy of this medicinal product taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Amitriptyline reduced the pregnancy rate in rats (see section 5.3).
No data on the effects of amitriptyline on human fertility are available.

## 4.7 Effects on ability to drive and use machines

Amitriptyline is a sedative drug.
Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery. These adverse effects can be potentiated by the concomitant intake of alcohol.

## 4.8 Undesirable effects

Amitriptyline may induce side effects similar to other tricyclic antidepressants. Some of the below mentioned side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressive state improves.

In the listing below the following convention is used:
MedDRA system organ class / preferred term
Very common (> 1/10);
Common (> 1/100, < 1/10);
Uncommon (> 1/1,000, < 1/100);
Rare (> 1/10,000, < 1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

| MedDRA SOC | Frequency | Preferred Term |
|---|---|---|
| Blood and lymphatic system disorders | Rare | Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia. |
| Metabolism and nutrition disorders | Rare | Decreased appetite. |
| Metabolism and nutrition disorders | Not known | Anorexia, elevation or lowering of blood sugar levels. |
| Psychiatric disorders | Very common | Aggression. |
| | Common | Confusional state, libido decreased, agitation. |
| | Uncommon | Hypomania, mania, anxiety, insomnia, nightmare. |
| | Rare | Delirium (in elderly patients), hallucination (in schizophrenic patients), suicidal thoughts or behaviour*. |
| | Not Known | Paranoia. |
| Nervous system disorders | Very common | Somnolence, tremor, dizziness, headache, drowsiness, speech disorder (dysarthria). |
| | Common | Disturbance in attention, dysgeusia. paresthesia, ataxia. |

| | | |
|---|---|---|
| | Uncommon | Convulsion. |
| | Very rare | Akathisia, polyneuropathy. |
| | Not known | Extrapyramidal disorder. |
| Eye disorders | Very common | Accommodation disorder. |
| | Common | Mydriasis. |
| | Very rare | Acute glaucoma. |
| Ear and labyrinth disorders | Uncommon | Tinnitus. |
| Cardiac disorders | Very common | Palpitations, tachycardia. |
| | Common | Atrioventricular block, bundle branch block. |
| | Uncommon | Collapse conditions, worsening of cardiac failure. |
| | Rare | Arrhythmia. |
| | Very rare | Cardiomyopathies, torsades de pointes. |
| | Not known | Hypersensitivity myocarditis. |
| Vascular disorders | Very common | Orthostatic hypotension. |
| | Uncommon | Hypertension. |
| | Not known | Hyperthermia. |
| Respiratory, thoracic, and mediastinal disorders | Very common | Congested nose. |
| | Very rare | Allergic inflammation of the pulmonary alveoli and of the lung tissue, respectively (alveolitis, Löffler's syndrome). |
| Gastrointestinal disorders | Very common | Dry mouth, constipation, nausea. |
| | Uncommon | Diarrhoea, vomiting, tongue oedema. |
| | Rare | Salivary gland enlargement, ileus paralytic. |
| Hepatobiliary disorders | Rare | Jaundice. |
| | Uncommon | Hepatic impairment (e.g. cholestatic liver disease). |
| | Not known | Hepatitis. |
| Skin and subcutaneous tissue disorders | Very common | Hyperhidrosis. |
| | Uncommon | Rash, urticaria, face oedema. |
| | Rare | Alopecia, photosensitivity reaction. |
| Renal and urinary disorders | Common | Micturition disorders. |
| | Uncommon | Urinary retention. |
| Reproductive system and breast disorders | Common | Erectile dysfunction. |
| | Uncommon | Galactorrhoea. |
| | Rare | Gynaecomastia. |
| General disorders and administration site conditions | Common | Fatigue, feeling thirst. |
| | Rare | Pyrexia. |
| | Not known | Injection site reactions. |
| Investigations | Very common | Weight increased. |
| | Common | Electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged, hyponatremia. |
| | Uncommon | Intraocular pressure increased. |
| | Rare | Weight decreased.<br>Liver function test abnormal, blood alkaline phosphatase increased, transaminases increased. |

| | | |
|---|---|---|
| | | |

*Case reports of suicidal thoughts or behaviour were reported during the treatment with or just after conclusion of the treatment with amitriptyline (see section 4.4).

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

Symptoms
*Anticholinergic symptoms:* Mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility. Convulsions, fever. Sudden occurrence of CNS depression. Lowered consciousness progressing into coma. Respiratory depression.
*Cardiac symptoms:* Arrhythmias (ventricular tachyarrhythmias, torsade de pointes, ventricular fibrillation). The ECG characteristically show prolonged PR interval, widening of the QRS-complex, QT prolongation, T-wave flattening or inversion, ST segment depression, and varying degrees of heart block progressing to cardiac arrest. Widening of the QRS-complex usually correlates well with the severity of the toxicity following acute overdoses. Heart failure, hypotension, cardiogenic shock. Metabolic acidosis, hypokalemia.
**The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic**. There is considerably individual variability in response to overdose. Children are especially susceptible to cardiotoxicity and seizures.

During awakening possibly again confusion, agitation and hallucinations and ataxia.

Treatment
1. Admission to hospital (intensive care unit) if required. Treatment is symptomatic and supportive.
2. Assess and treat ABC's (airway, breathing and circulation) as appropriate. Secure an IV access. Close monitoring even in apparently uncomplicated cases.
3. Examine for clinical features. Check urea and electrolytes—look for low potassium and monitor urine output. Check arterial blood gases—look for acidosis. Perform electrocardiograph—look for QRS>0.16 seconds
4. Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.
5. Patency of the airway is maintained by intubation, where required. Treatment in respirator is advised to prevent a possible respiratory arrest. Continuous ECG-monitoring of cardiac function for 3-5 days. Treatment of the following will be decided on a case by case basis:
   - Wide QRS-intervals, cardiac failure and ventricular arrhythmias
   - Circulatory failure
   - Hypotension
   - Hyperthermia
   - Convulsions

   Metabolic acidosis.
6. Unrest and convulsions may be treated with diazepam.
7. Patients who display signs of toxicity should be monitored for a minimum of 12 hours.
8. Monitor for rhabdomyolysis if the patient has been unconscious for a considerable time.
9. Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Deaths by deliberate or accidental overdosage have occurred with this class of medicament.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant)
ATC code: N 06 AA 09

Mechanism of action
Amitriptyline is a tricyclic antidepressant and an analgesic. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiate their action in the brain. This appears to be associated with the antidepressant activity.
Tricyclic antidepressants possess affinity for muscarinic and histamine H1 receptors to varying degrees.

Clinical efficacy and safety
The efficacy and safety of amitriptyline (as solution for injection) has been demonstrated for the indication Major Depressive Disorder.

The antidepressant effect usually sets in after 2-4 weeks; the sedative action is not delayed.

### 5.2 Pharmacokinetic properties

Absorption
Due to avoiding the first-pass-metabolism in the liver after intravenous administration the drug reaches maximal plasma concentrations very rapidly and completely with a rapid biphasic consequent decline, which reflects generation of the distribution equilibrium between tissue, peripheral and central compartments.

Distribution
The apparent volume of distribution $(V_d)_\beta$ estimated after intravenous administration is 1221±280 l; range 769-1702 l (16±3 l/kg).
The plasma protein binding is about 95%.
Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

In nursing mothers amitriptyline and nortriptyline are excreted in small amounts with the breast milk. The ratio milk concentration/serum concentration in women is around 1:1. The estimated daily infant exposure (amitriptyline + nortriptyline) averages 2% of the corresponding maternal weight related doses of amitriptyline (in mg/kg) (see section 4.6).

Biotransformation
*In vitro* the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are CYP1A2 and CYP2C9. The metabolism is subject to genetic polymorphism. The main active metabolite is the secondary amine, nortriptyline. Nortriptyline is a more potent inhibitor of noradrenaline than of serotonin reuptake, while amitriptyline inhibits the reuptake of noradrenaline and serotonin equally well. Other metabolites such as cis- and trans- 10-hydroxyamitriptyline and cis- and trans- 10-hydroxynortriptyline have the same profile as nortriptyline but are considerably less potent. Demethylnortriptyline and amitriptyline-N-oxide are only present in plasma in minute amounts; the latter is almost inactive. All the metabolites have less anticholinergic activity than amitriptyline and nortriptyline. In plasma the amount of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

Elimination

The elimination half-life from plasma after i.v. administration of 40-60 mg amitriptyline hydrochloride was 10.1-27.8 h and of 15 mg 15.5-19.5 h. In elderly subjects the half-life is prolonged.
The mean systemic clearance ($Cl_s$) is 51.5 ±13.8 l/h, range 25.6-71.8 l/h.
The elimination half-life ($t_{½\,\beta}$) amitriptyline after peroral administration is about 25 hours (24.65±6.31 hours; range 16.49-40.36 hours). The mean systemic clearance ($Cl_s$) is 39.24±10.18 l/h, range 24.53-53.73 l/h.

The excretion proceeds mainly with urine. The renal elimination of unchanged amitriptyline is insignificant (about 2%).

Steady state plasma levels of amitriptyline + nortriptyline are reached within a week for most patients, and in steady state the plasma level comprises approximately equal parts of amitriptyline and nortriptyline around the clock following treatment with conventional tablets 3 times a day.

Elderly patients
Longer half-lives values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function
Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients (see section 4.2).

Reduced renal function
Renal failure has no influence on the kinetics.

Polymorphism
The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19) (see section 4.2).

Pharmacokinetic / Pharmacodynamic relationship
Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.
The therapeutic plasma concentration in major depression is around 80-200 ng/ml (≈ 280-700 nmol/l) (for amitriptyline + nortriptyline). Levels above 300-400 ng/ml are associated with increased risk of disturbance in cardiac conduction in terms of prolonged QRS-complex or AV block.

## 5.3 Preclinical safety data

Amitriptyline inhibited ion channels, which are responsible for cardiac repolarization (hERG channels), in the upper micromolar range of therapeutic plasma concentrations. Therefore, amitriptyline may increase the risk for cardiac arrhythmia (see section 4.4).

The genotoxic potential of amitriptyline has been investigated in various in vitro and in vivo studies. Although these investigations revealed partially contradictory results, particularly a potential to induce chromosome aberrations cannot be excluded. Long-term carcinogenicity studies have not been performed.

In reproductive studies teratogenic effects were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2-40 mg/kg/day (up to 13 times the maximum recommended human amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50-kg patient). However, literature data suggested a risk for malformations and delays in ossification of mice, hamsters, rats and rabbits at 9 33 times the maximum recommended dose. There was a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for the effect on fertility is unknownThere was a possible association with an effect on fertility in rats, namely a lower pregnancy rate. The reason for the effect on fertility is unknown.

# 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

[To be completed nationally]

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

[To be completed nationally]

### 6.4 Special precautions for storage

[To be completed nationally]

### 6.5 Nature and contents of container

[To be completed nationally]

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

# LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**Carton/Label**

## 1. NAME OF THE MEDICINAL PRODUCT

[See Annex I - To be completed nationally]

<[Saroten and associated names 10 mg film-coated tablets; Saroten and associated names 25 mg film-coated tablets; Saroten and associated names 25 mg prolonged-release capsules, hard; Saroten and associated names 50 mg prolonged-release capsules, hard; Saroten and associated names 50 mg film-coated tablets]
Amitriptyline>

<[Saroten and associated names 75 mg, modified release tablets, Saroten and associated names 2 ml, 50 mg solution for injection]
Amitriptyline hydrochloride>

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

## 3. LIST OF EXCIPIENTS

[To be completed nationally]

## 4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
[To be completed nationally]

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**17. UNIQUE IDENTIFIER – 2D BARCODE**

Not applicable.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

Not applicable.

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blisters**

## 1. NAME OF THE MEDICINAL PRODUCT

[See Annex I - To be completed nationally]

<[Saroten and associated names 10 mg film-coated tablets; Saroten and associated names 25 mg film-coated tablets; Saroten and associated names 25 mg prolonged-release capsules, hard; Saroten and associated names 50 mg prolonged-release capsules, hard; Saroten and associated names 50 mg film-coated tablets]
Amitriptyline>

<[Saroten and associated names 75 mg, modified release tablets]
Amitriptyline hydrochloride>

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**AMPOULE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

[See Annex I - To be completed nationally]

Amitriptyline hydrochloride

## 2. METHOD OF ADMINISTRATION

Solution for i.v. infusion and i.m. injection

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

## 6. OTHER

**PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Saroten and associated names (see Annex I) 25 mg prolonged-release capsules, hard**
Amitriptyline
**Saroten and associated names (see Annex I) 50 mg prolonged-release capsules, hard**
Amitriptyline
**Saroten and associated names (see Annex I) 75 mg modified-release tablet**
Amitriptyline hydrochloride

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

**What is in this leaflet**



## 1. What X is and what it is used for

X belongs to a group of medicines known as tricyclic antidepressants.

This medicine is used to treat:
- Depression in adults (major depressive episodes)
- Neuropathic pain in adults
- Chronic tension type headache prophylaxis in adults
- Migraine prophylaxis in adults
- Bed-wetting at night in children aged 6 years and above, only when organic causes, such as spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including muscle relaxants and desmopressin. This medicine should only be prescribed by doctors with expertise in treating patients with persistent bed-wetting.

## 2. What you need to know before you take X

**Do not take X:**
- if you are allergic to amitriptyline or any of the other ingredients of this medicine (listed in section 6)
- if you recently have had a heart attack (myocardial infarction)
- if you have heart problems such as disturbances in heart rhythm which are seen on an electrocardiogram (ECG), heart block, or coronary artery disease
- if you are taking medicines known as monoamine oxidase inhibitors (MAOIs)
- if you have taken MAOIs within the last 14 days
- if you have taken moclobemide the day before
- if you have a severe liver disease.

If you are treated with X, you have to stop taking this medicine and wait for 14 days before you start treatment with a MAOI.

This medicine should not be used for children below 6 years of age.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking X.

Heart rhythm disorders and hypotension may occur if you receive a high dosage of amitriptyline. This might also occur in usual doses if you have pre-existing heart disease.

Prolonged QT interval
A heart problem called "prolonged QT interval" (which is shown on your electrocardiogram, ECG) and heart rhythm disorders (rapid or irregular heart beat) have been reported with X. Tell your doctor if you:

- have slow heart rate,
- have or had a problem where your heart cannot pump the blood round your body as well as it should (a condition called heart failure),
- are taking any other medication that may cause heart problems, or
- have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood
- have a surgery planned as it might be necessary to stop the treatment with amitriptyline before you are given anaesthetics. In the case of acute surgery, the anaesthetist should be informed about the treatment of amitriptyline.
- have an over active thyroid gland or receive thyroid medication.

Thoughts of suicide and worsening of your depression
If you are depressed, you can sometimes have thoughts of harming or killing themselves. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (less than 25 years old) with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Episodes of mania
Some patients with manic-depressive illness may enter into a manic phase. This is characterized by profuse and rapidly changing ideas, exaggerated gaiety and excessive physical activity. In such cases, it is important to contact your doctor who probably will change your medication.

Tell your doctor if you have, or have had in the past, any medical problems, especially if you have

- narrow angle glaucoma (loss of vision due to abnormally high pressure in the eye)
- epilepsy, a history of convulsions or fits
- difficulty in passing urine
- enlarged prostate
- thyroid disease
- bipolar disorder

- schizophrenia
- severe liver disease
- severe heart disease
- pylorus stenosis (narrowing of the gastric outlet) and paralytic ileus (blocked intestine)
- diabetes as you might need and adjustment of your antidiabetic medicine.

If you use antidepressants such as Selective Serotonin Re-uptake Inhibitors (SSRIs), your doctor might consider changing the dose of your medicine (see also section 2 Other medicines and X and section 3)

Elderly are more likely to suffer from certain side effects, such as dizziness when you stand up due to low blood pressure (see also section 4 Possible side effects).

**Children and adolescents**

*Depression, neuropathic pain, chronic tension type headache and migraine prophylaxis*
Do not give this medicine to children and adolescents aged below 18 years for these treatments as safety and efficacy have not been established in this age group.

*Bed-wetting at night*
- An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome
- This medicines should not be taking at the same time as an anticholinergic drug (see also section 2 Other medicines and X)
- Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis

**Other medicines and X**
Some medicines may affect the action of other medicines and this can sometimes cause serious side effects.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, such as:
- monoamine oxidase inhibitors (MAOIs) e.g. phenelzine, iproniazid, isocarboxazid, nialamide or tranylcypromine (used to treat depression) or selegiline (used to treat Parkinson's disease). These should not be taken at the same time as X (see section 2 Do not take X)
- adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine (these may be present in cough or cold medicine, and in some anaesthetics)
- medicine to treat high blood pressure for example calcium-channel blockers (e.g. diltiazem and verapamil), guanethidine, betanidine, clonidine reserpine and methyldopa
- anticholinergic drugs such as certain medicines to treat Parkinsons disease and gastrointerstinal disorders (e.g. atropine, hyoscyamine)
- thioridazine (used to treat schizophrenia)
- tramadol (painkiller)
- medicines to treat fungal infections (e.g. fluconazole, terbinafine, ketoconazole, and itraconazole)
- sedatives (e.g. babiturates)
- antidepressants (e.g SSRIs (fluoxetine, paroxetine, fluvoxamine), and bupropion)
- medicines for certain heart conditions (e.g. beta blockers and antiarrhythmics)
- cimetidine (used to treat stomach ulcers)
- methylphenidate (used to treat ADHD)
- ritonavir (used to treat HIV)
- oral contraceptives
- rifampicin (to treat infections)
- phenytoin and carbamazepine (used to treat epilepsy)
- St. John´s Wort (hypericum perforatum) – a herbal remedy used for depression
- thyroid medication.

You should also tell your doctor if you take or have recently taken medicine that may affect the heart´s rhythm. e.g.:

- medicines to treat irregular heartbeats (e.g. quinidine and sotalol)
- astemizole and terfenadine (used to treat allergies and hayfever)
- medicines used to treat some mental illnesses (e.g. pimozide and sertindole)
- cisapride (used to treat certain types of indigestion)
- halofantrine (used to treat malaria)
- methadone (used to treat pain and for detoxification)
- diuretics ("water tablets" e.g. furosemide)

If you are going to have an operation and receive general or local anaesthetics, you should tell your doctor that you are taking this medicine.

Likewise, you should tell your dentist that you take this medicine if you are to receive a local anaesthetic.

**X with alcohol**
It is not advised to drink alcohol during treatment with this medicine as it might increase the sedative effect.

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

Amitriptyline is not recommended during pregnancy unless your doctor considers it clearly necessary and only after careful consideration of the benefit and risk. If you have taken this medicine during the last part of the pregnancy, the newborn may have withdrawal symptoms such as irritability, increased muscle tension, tremor, irregular breathing, poor drinking, loud crying, urinary retention, and constipation.

Your doctor will advise you whether to start/continue/stop breast-feeding, or stop using this medicine taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

**Driving and using machines**
This medicine may cause drowsiness and dizziness, especially in the beginning of the treatment. Do not drive or work with tools or machinery if you are affected.

<[Saroten and associated names prolonged-release capsules, hard]
**X contains sucrose**
If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.>

## 3. How to take X

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

Not all dosage schemes can be achieved with all the pharmaceutical forms/strengths. The appropriate formulation/strength should be selected for the starting doses and any subsequent dose increases.

***Depression***
*Adults*
The recommended initial dose is 50 mg in the evening. Depending on your response to the medicine, your doctor may gradually increase the dose to 150 mg in the evening.

<[Saroten and associated names 75 mg, modified release tablet]

Due to the two score lines the Saroten retard Tabs can be divided into three parts. The dosage therefore can be increased in 25 mg amitriptyline hydrochloride steps. Those parts currently not needed can be stored in the reservoir of the tablet box (under the slide of the closure), until the next administration.>

*Elderly (above 65 years of age) and patients with cardiovascular disease*
The recommended initial dose is 25 mg in the evening. Depending on your response to the medicine, your doctor may increase the dose to 100 mg.
If you receive doses in the range of 100 mg - 150 mg in the evening, your doctor may need to do more frequent follow-up with you.

**Use in children and adolescents**
This medicine should not be given to children or adolescents for treatment of depression. For further information please see section 2.

***Neuropathic pain, chronic tension type headache and migraine prophylaxis***
Your doctor will adjust the medication according to your symptoms and your response to the treatment.

*Adults*
Your doctor will most likely choose to initiate your treatment with Saroten film-coated tablets before starting treatment with X.

The initial dose should be 10 mg - 25 mg in the evening. The recommended doses are 25 mg - 75 mg in the evening.

Depending on your response to the medicine, your doctor may gradually increase the dose. If you receive doses above 100 mg daily, your doctor may need to do more frequent follow-up with you.

*Elderly (above 65 years of age) and patients with cardiovascular disease*
A starting dose of 10 mg - 25 mg in the evening is recommended. Depending on your response to the medicine, your doctor may gradually increase the dose.
If you receive doses above 75 mg daily, your doctor may need to do more frequent follow-up with you.

**Use in children and adolescents**
This medicine should not be given to children or adolescents for treatments of neuropathic pain, chronic tension type headache prophylaxis and migraine prophylaxis. For further information please see section 2.

***Bed-wetting at night***
**Use in children and adolescents**
The recommended doses for children:

- aged below 6 years: see section 2 Do not take X
- aged 6 to 10 years: 10 mg - 20 mg daily. A more suitable dosage form should be used for this age group.
- aged 11 years and above: 25 mg – 50 mg.

The dose should be increased gradually.
Take this medicine 1-1½ hours before bedtime.

Before starting treatment, your doctor will conduct an ECG of your heart to check for sign of unusual heartbeat.

Your doctor will re-evaluate your treatment after 3 months and if needed perform a new ECG.

Do not stop the treatment without consulting your doctor first.

***Patients with special risks***

Patients with liver diseases or people known as “poor metabolisers” usually receive lower doses.
Your doctor may take blood samples to determine the level of amitriptyline in the blood (see also section 2).

**How and when to take X**
This medicine is taken every evening as a single daily dose.
This medicine can be taken with or without food.

<[Saroten and associated names prolonged-release capsules, hard]
Swallow the capsules with a drink of water.
If you have difficulty in swallowing the capsules, you can open them and put the pellets in e.g. yoghurt or a cold drink. Do not chew the pellets.>

<[Saroten and associated names 75 mg, modified release tablets]
The score line facilitates breaking of the retard tablet into 3 equal doses. Those parts currently not needed can be stored in the reservoir of the tablet box.
X can be taken with or without food.
The tablets are swallowed with water independent of meals.>

**Duration of treatment**
Do not change the dose of the medicine or stop taking the medicine without consulting your doctor first.

***Depression***
As with other medicines for the treatment of depression it may take a few weeks before you feel any improvement.

In treating depression the duration of treatment is individual, and is usually at least 6 months. The duration of treatment is decided by your doctor.

Continue to take this medicine for as long as your doctor recommends.

The underlying illness may persist for a long time. If you stop your treatment too soon, your symptoms may return.

***Neuropathic pain, chronic tension type headache and migraine prophylaxis***
It might take a few weeks before your feel any improvement of your pain.

Talk to your doctor about the duration of your treatment and continue to take this medicine for as long as your doctor recommends.

***Bed-wetting at night***
Your doctor will evaluate if the treatment should be continued after 3 months.

**If you take more X than you should**
Contact your doctor or nearest hospital casualty department immediately. Do this even if there are no signs of discomfort or poisoning. Take the container of this medicine with you if you go to a doctor or hospital.

Symptoms of overdose include:
- dilated pupils
- fast or irregular heartbeats
- difficulties passing water
- dry mouth and tongue
- intestinal blockage
- fits

- fever
- agitation
- confusion
- hallucinations
- uncontrolled movements
- low blood pressure, weak pulse, pallor
- difficulty breathing
- blue discolouration of the skin
- decreased heart rate
- drowsiness
- loss of consciousness
- coma
- various cardiac symptoms such as heart block, heart failure, hypotension, cardiogenic shock, metabolic acidosis, hypokalemia.

**If you forget to take X**
Take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

**If you stop taking X**
Your doctor will decide when and how to stop your treatment to avoid any unpleasant symptoms that might occur if it is stopped abruptly (e.g. headache, feeling unwell, sleeplessness and irritability).

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

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following symptoms you should see your doctor immediately:

- Attacks of intermittent blurring of vision, rainbow vision, and eye pain.
  You should immediately have an eye examination before the treatment with this medicine can be continued. This condition may be signs of acute glaucoma. Very rare side effect, may affect up to 1 in 10,000 people.

- A heart problem called "prolonged QT interval" (which is shown on your electrocardiogram, ECG). Common side effect, may affect up to 1 in 10 people.

- Bad constipation, a swollen stomach, fever and vomiting.
  These symptoms may be due to parts of the intestine becoming paralysed. Rare side effect, may affect up to 1 in 1,000 people.

- Any yellowing of the skin and the white in the eyes (jaundice).
  Your liver may be affected. Rare side effect, may affect up to 1 in 1,000 people.

- Bruising, bleeding, pallor or persistent sore throat and fever.
  These symptoms can be the first signs that your blood or bone marrow may be affected.
  Effects on the blood could be a decrease in the number of red cells (which carry oxygen around the body), white cells (which help to fight infection) and platelets (which help with clotting). Rare side effect, may affect up to 1 in 1,000 people.

- Suicidal thoughts or behaviour. Rare side effect, may affect up to 1 in 1,000 people.

Side effects listed below have been reported in the following frequencies:

Very common: may affect more than 1 in 10 people

- sleepiness/drowsiness
- shakiness of hands or other body parts
- dizziness
- headache
- irregular, hard, or rapid heartbeat
- dizziness when you stand up due to low blood pressure (orthostatic hypotension)
- dry mouth
- constipation
- nausea
- excessive sweating
- weight gain
- slurred or slow speech
- aggression
- congested nose.

Common: may affect up to 1 in 10 people

- confusion
- sexual disturbances (decreased sex-drive, problems with erection)
- disturbance in attention
- changes in taste
- numbness or tingling in the arms or legs
- disturbed coordination
- dilated pupils
- heart block
- fatigue
- low sodium concentration in the blood
- agitation
- urination disorders
- feeling thirsty.

Uncommon: may affect up to 1 in 100 people

- excitement, anxiety, difficulties sleeping, nightmares
- convulsions
- tinnitus
- increased blood pressure
- diarrhoea, vomiting
- skin rash, nettle rash (urticarial), swelling of the face and tongue
- difficulties passing urine
- increased production of breast milk or breast milk outflow without breast feeding
- increased pressure in the eye ball
- collapse conditions
- worsening of cardiac failure
- liver function impairment (e.g. cholestatic liver disease).

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

- decreased appetite
- delirium (especially in elderly patients), hallucinations (especially in patients with schizophrenia),
- abnormality in the heart's rhythm, or heartbeat pattern
- swelling of the salivary glands
- hair loss
- increased sensitivity to sunlight
- breast enlargement in men
- fever

- weight loss
- abnormal results of liver function tests.

Very rare: may affect up to 1 in 10,000 people
- heart muscle disease
- feeling of inner restlessness and a compelling need to be in constant motion
- disorder of the peripheral nerves
- acute increase of pressure in the eye
- particular forms of abnormal heart rhythm (so called torsades de pointes)
- allergic inflammation of the lung alveoli and of the lung tissue.

Not known: frequency cannot be estimated from the available data
- absent sensation of appetite
- elevation or lowering of blood sugar levels
- paranoia
- movement disorders (involuntary movements or decreased movements)
- hypersensitivity inflammation of heart muscle
- hepatitis
- hot flush.

An increased risk of bone fractures has been observed in patients taking this type of medicines.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store X

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

Do not use this medicine after the expiry date which is stated on the label afterr EXP. The expiry date refers to the last day of that month.

[To be completed nationally]

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

## 6. Contents of the pack and other information

**What X contains**
<[Saroten and associated names prolonged-release capsules, hard ]
The active substance is amitriptyline.>

<[Saroten and associated names 75 mg, modified release tablets]
The active substance is amitriptyline hydrochloride.>

[To be completed nationally]

**What X looks like and contents of the pack**
[To be completed nationally].

**Marketing Authorisation Holder and Manufacturer**
[See Annex I - To be completed nationally]

**This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>**.
[To be completed nationally]

**Package leaflet: Information for the patient**

**Saroten and associated names (see Annex I) 10 mg film-coated tablets**
**Saroten and associated names (see Annex I) 25 mg film-coated tablets**
**Saroten and associated names (see Annex I) 50 mg film-coated tablets**
Amitriptyline

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

**What is in this leaflet**



## 1. What X is and what it is used for

X belongs to a group of medicines known as tricyclic antidepressants.

This medicine is used to treat:
- Depression in adults (major depressive episodes)
- Neuropathic pain in adults
- Chronic tension type headache prophylaxis in adults
- Migraine prophylaxis in adults
- Bed-wetting at night in children aged 6 years and above, only when organic causes, such as spina bifida and related disorders, have been excluded and no response has been achieved to all other non-drug and drug treatments, including muscle relaxants and desmopressin. This medicine should only be prescribed by doctors with expertise in treating patients with persistent bed-wetting.

## 2. What you need to know before you take X

**Do not take X:**
- if you are allergic to amitriptyline or any of the other ingredients of this medicine (listed in section 6)
- if you recently have had a heart attack (myocardial infarction)
- if you have heart problems such as disturbances in heart rhythm which are seen on an electrocardiogram (ECG), heart block, or coronary artery disease
- if you are taking medicines known as monoamine oxidase inhibitors (MAOIs)
- if you have taken MAOIs within the last 14 days
- if you have taken moclobemide the day before
- if you have a severe liver disease.

If you are treated with X, you have to stop taking this medicine and wait for 14 days before you start treatment with a MAOI.

This medicine should not be used for children below 6 years of age.

**Warnings and precautions**
Talk to your doctor or pharmacist before taking X.

Heart rhythm disorders and hypotension may occur if you receive a high dosage of amitriptyline. This might also occur in usual doses if you have pre-existing heart disease.

Prolonged QT interval
A heart problem called "prolonged QT interval" (which is shown on your electrocardiogram, ECG) and heart rhythm disorders (rapid or irregular heart beat) have been reported with X. Tell your doctor if you:
- have slow heart rate,
- have or had a problem where your heart cannot pump the blood round your body as well as it should (a condition called heart failure),
- are taking any other medication that may cause heart problems, or
- have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood
- have a surgery planned as it might be necessary to stop the treatment with amitriptyline before you are given anaesthetics. In the case of acute surgery, the anaesthetist should be informed about the treatment of amitriptyline.
- have an over active thyroid gland or receive thyroid medication.

Thoughts of suicide and worsening of your depression
If you are depressed, you can sometimes have thoughts of harming or killing themselves. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:
- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (less than 25 years old) with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

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Some patients with manic-depressive illness may enter into a manic phase. This is characterized by profuse and rapidly changing ideas, exaggerated gaiety and excessive physical activity. In such cases, it is important to contact your doctor who probably will change your medication.

Tell your doctor if you have, or have had in the past, any medical problems, especially if you have
- narrow angle glaucoma (loss of vision due to abnormally high pressure in the eye)
- epilepsy, a history of convulsions or fits
- difficulty in passing urine
- enlarged prostate
- thyroid disease
- bipolar disorder
- schizophrenia

- severe liver disease
- severe heart disease
- pylorus stenosis (narrowing of the gastric outlet) and paralytic ileus (blocked intestine)
- diabetes as you might need and adjustment of your antidiabetic medicine.

If you use antidepressants such as SSRIs, your doctor might consider changing the dose of your medicine (see also section 2 Other medicines and X and section 3)

Elderly are more likely to suffer from certain side effects, such as dizziness when you stand up due to low blood pressure (see also section 4 Possible side effects).

**Children and adolescents**

*Depression, neuropathic pain, chronic tension type headache and migraine prophylaxis*
Do not give this medicine to children and adolescents aged below 18 years for these treatments as safety and efficacy have not been established in this age group.

*Bed-wetting at night*
- An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome
- This medicines should not be taking at the same time as an anticholinergic drug (see also section 2 Other medicines and X)
- Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed when treating patients with depression should therefore be followed when treating patients with enuresis

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Some medicines may affect the action of other medicines and this can sometimes cause serious side effects.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, such as:
- monoamine oxidase inhibitors (MAOIs) e.g. phenelzine, iproniazid, isocarboxazid, nialamide or tranylcypromine (used to treat depression) or selegiline (used to treat Parkinson's disease). These should not be taken at the same time as X (see section 2 Do not take X)
- adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine (these may be present in cough or cold medicine, and in some anaesthetics)
- medicine to treat high blood pressure for example calcium-channel blockers (e.g. diltiazem and verapamil), guanethidine, betanidine, clonidine reserpine and methyldopa
- Anticholinergic drugs such as certain medicines to treat Parkinsons disease and gastrointerstinal disorders (e.g. atropine, hyoscyamine)
- thioridazine (used to treat schizophrenia)
- tramadol (painkiller)
- medicines to treat fungal infections (e.g. fluconazole, terbinafine, ketoconazole, and itraconazole)
- sedatives (e.g. babiturates)
- antidepressants (e.g SSRIs (fluoxetine, paroxetine, fluvoxamine), and bupropion)
- medicines for certain heart conditions (e.g. beta blockers and antiarrhythmics)
- cimetidine (used to treat stomach ulcers)
- methylphenidate (used to treat ADHD)
- ritonavir (used to treat HIV)
- oral contraceptives
- rifampicin (to treat infections)
- phenytoin and carbamazepine (used to treat epilepsy)
- St. John´s Wort (hypericum perforatum) – a herbal remedy used for depression
- thyroid medication.

You should also tell your doctor if you take or have recently taken medicine that may affect the heart´s rhythm. e.g.:

- medicines to treat irregular heartbeats (e.g. quinidine and sotalol)
- astemizole and terfenadine (used to treat allergies and hayfever)
- medicines used to treat some mental illnesses (e.g. pimozide and sertindole)
- cisapride (used to treat certain types of indigestion)
- halofantrine (used to treat malaria)
- methadone (used to treat pain and for detoxification)
- diuretics ("water tablets" e.g. furosemide)

If you are going to have an operation and receive general or local anaesthetics, you should tell your doctor that you are taking this medicine.

Likewise, you should tell your dentist that you take this medicine if you are to receive a local anaesthetic.

**X with alcohol**
It is not advised to drink alcohol during treatment with this medicine as it might increase the sedative effect.

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

Amitriptyline is not recommended during pregnancy unless your doctor considers it clearly necessary and only after careful consideration of the benefit and risk. If you have taken this medicine during the last part of the pregnancy, the newborn may have withdrawal symptoms such as irritability, increased muscle tension, tremor, irregular breathing, poor drinking, loud crying, urinary retention, and constipation.

Your doctor will advise you whether to start/continue/ stop breast-feeding, or stop using this medicine taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

**Driving and using machines**
This medicine may cause drowsiness and dizziness, especially in the beginning of the treatment. Do not drive or work with tools or machinery if you are affected.

**X contains lactose**
If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take X

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

Not all dosage schemes can be achieved with all the pharmaceutical forms/strengths. The appropriate formulation/strength should be selected for the starting doses and any subsequent dose increases.

***Depression***
*Adults*
The recommended initial dose is 25 mg two times daily.

Depending on the response to the medicine, your doctor may gradually increase the dose to 150 mg per day divided in two doses.

*Elderly (above 65 years of age) and patients with cardiovascular disease*

The recommended initial dose is 10 mg – 25 mg daily.
Depending on your response to the medicine, your doctor may gradually increase the dose to a total daily dose of 100 mg divided in two doses. If you receive doses in the range of 100 mg – 150 mg, your doctor may need to do more frequent follow-up with you.

*Use in children and adolescents*
This medicine should not be given to children or adolescents for treatment of depression. For further information please see section 2.

***Neuropathic pain, chronic tension type headache and migraine prophylaxis***
Your doctor will adjust the medication according to your symptoms and your response to the treatment.

*Adults*
The recommended initial dose is 10 mg - 25 mg in the evening.

The recommended daily dose is 25 mg - 75 mg.

Depending on your response to the medicine, your doctor may gradually increase the dose. If you receive doses above 100 mg daily, your doctor may need to do more frequent follow-up with you. Your doctor will instruct you whether to take the doses once daily or divide into two doses.

*Elderly (above 65 years of age) and patients with cardiovascular disease*
The recommended initial dose is 10 mg – 25 mg in the evening.

Depending on your response to the medicine, your doctor may gradually increase the dose. If you receive doses above 75 mg daily, your doctor may need to do more frequent follow-up with you.

*Use in children and adolescents*
This medicine should not be given to children or adolescents for treatments of neuropathic pain, chronic tension type headache prophylaxis and migraine prophylaxis. For further information please see section 2.

***Bed-wetting at night***
*Use in children and adolescents*
The recommended doses for children:
- aged below 6 years:  see section 2 Do not take X
- aged 6 to 10 years: 10 mg – 20 mg daily. A suitable dosage form should be used for this age group.
- aged 11 years and above: 25 mg – 50 mg.

The dose should be increased gradually.

Take this medicine 1-1½ hours before bedtime.

Before starting treatment, your doctor will conduct an ECG of your heart to check for sign of unusual heartbeat.

Your doctor will re-evaluate your treatment after 3 months and if needed perform a new ECG.

Do not stop the treatment without consulting your doctor first.

***Patients with special risks***
Patients with liver diseases or people known as “poor metabolisers” usually receive lower doses.
Your doctor may take blood samples to determine the level of amitriptyline in the blood (see also section 2).

**How and when to take X**

This medicine can be taken with or without food.

<[Saroten and associated names 50 mg film-coated tablets]
X are dividable tablets with three score lines. The score line facilitates breaking of the tablet into 4 equal doses. Those parts currently not needed can be stored in the reservoir of the tablet box (under the slide of the closure), until the next administration.>

Swallow the tablets with a drink of water. Do not chew them.

**Duration of treatment**
Do not change the dose of the medicine or stop taking the medicine without consulting your doctor first.

***Depression***
As with other medicines for the treatment of depression it may take a few weeks before you feel any improvement.

In treating depression the duration of treatment is individual, and is usually at least 6 months. The duration of treatment is decided by your doctor.

Continue to take this medicine for as long as your doctor recommends.

The underlying illness may persist for a long time. If you stop your treatment too soon, your symptoms may return.

***Neuropathic pain, chronic tension type headache and migraine prophylaxis***
It might take a few weeks before your feel any improvement of your pain.

Talk to your doctor about the duration of your treatment and continue to take this medicine for as long as your doctor recommends.

***Bed-wetting at night***
Your doctor will evaluate if the treatment should be continued after 3 months.

**If you take more X than you should**
Contact your doctor or nearest hospital casualty department immediately. Do this even if there are no signs of discomfort or poisoning. Take the container of this medicine with you if you go to a doctor or hospital.

Symptoms of overdose include:
- dilated pupils
- fast or irregular heartbeats
- difficulties passing water
- dry mouth and tongue
- intestinal blockage
- fits
- fever
- agitation
- confusion
- hallucinations
- uncontrolled movements
- low blood pressure, weak pulse, pallor
- difficulty breathing
- blue discolouration of the skin
- decreased heart rate
- drowsiness

- loss of consciousness
- coma
- various cardiac symptoms such as heart block, heart failure, hypotension, cardiogenic shock, metabolic acidosis, hypokalemia.

**If you forget to take X**
Take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

**If you stop taking X**
Your doctor will decide when and how to stop your treatment to avoid any unpleasant symptoms that might occur if it is stopped abruptly (e.g. headache, feeling unwell, sleeplessness and irritability).

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

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following symptoms you should see your doctor immediately:

- Attacks of intermittent blurring of vision, rainbow vision, and eye pain.
  You should immediately have an eye examination before the treatment with this medicine can be continued. This condition may be signs of acute glaucoma. Very rare side effect, may affect up to 1 in 10,000 people.

- A heart problem called "prolonged QT interval" (which is shown on your electrocardiogram, ECG). Common side effect, may affect up to 1 in 10 people.

- Bad constipation, a swollen stomach, fever and vomiting.
  These symptoms may be due to parts of the intestine becoming paralysed. Rare side effect, may affect up to 1 in 1,000 people.

- Any yellowing of the skin and the white in the eyes (jaundice).
  Your liver may be affected. Rare side effect, may affect up to 1 in 1,000 people.

- Bruising, bleeding, pallor or persistent sore throat and fever.
  These symptoms can be the first signs that your blood or bone marrow may be affected.
  Effects on the blood could be a decrease in the number of red cells (which carry oxygen around the body), white cells (which help to fight infection) and platelets (which help with clotting). Rare side effect, may affect up to 1 in 1,000 people.

- Suicidal thoughts or behaviour. Rare side effect, may affect up to 1 in 1,000 people.

Side effects listed below have been reported in the following frequencies:

Very common: may affect more than 1 in 10 people
- sleepiness/drowsiness
- shakiness of hands or other body parts
- dizziness
- headache
- irregular, hard, or rapid heartbeat
- dizziness when you stand up due to low blood pressure (orthostatic hypotension)
- dry mouth
- constipation

- nausea
- excessive sweating
- weight gain
- slurred or slow speech
- aggression
- congested nose.

Common: may affect up to 1 in 10 people
- confusion
- sexual disturbances (decreased sex-drive, problems with erection)
- disturbance in attention
- changes in taste
- numbness or tingling in the arms or legs
- disturbed coordination
- dilated pupils
- heart block
- fatigue
- low sodium concentration in the blood
- agitation
- urination disorders
- feeling thirsty.

Uncommon: may affect up to 1 in 100 people
- excitement, anxiety, difficulties sleeping, nightmares
- convulsions
- tinnitus
- increased blood pressure
- diarrhoea, vomiting
- skin rash, nettle rash (urticarial), swelling of the face and tongue
- difficulties passing urine
- increased production of breast milk or breast milk outflow without breast feeding
- increased pressure in the eye ball
- collapse conditions
- worsening of cardiac failure
- liver function impairment (e.g. cholestatic liver disease).

Rare: may affect up to 1 in 1,000 people
- decreased appetite
- delirium (especially in elderly patients), hallucinations (especially in patients with schizophrenia),
- abnormality in the heart's rhythm, or heartbeat pattern
- swelling of the salivary glands
- hair loss
- increased sensitivity to sunlight
- breast enlargement in men
- fever
- weight loss
- abnormal results of liver function tests.

Very rare: may affect up to 1 in 10,000 people
- heart muscle disease
- feeling of inner restlessness and a compelling need to be in constant motion
- disorder of the peripheral nerves
- acute increase of pressure in the eye
- particular forms of abnormal heart rhythm (so called torsades de pointes)
- allergic inflammation of the lung alveoli and of the lung tissue.

Not known: frequency cannot be estimated from the available data

- absent sensation of appetite
- elevation or lowering of blood sugar levels
- paranoia
- movement disorders (involuntary movements or decreased movements)
- hypersensitivity inflammation of heart muscle
- hepatitis
- hot flush.

An increased risk of bone fractures has been observed in patients taking this type of medicines.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store X

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

Do not use this medicine after the expiry date which is stated on the label afterr EXP. The expiry date refers to the last day of that month.

[To be completed nationally]

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

## 6. Contents of the pack and other information

**What X contains**
The active substance is amitriptyline.
[To be completed nationally]

**What X looks like and contents of the pack**
[To be completed nationally].

**Marketing Authorisation Holder and Manufacturer**
[See Annex I - To be completed nationally]

**This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.**
[To be completed nationally]

**Package leaflet: Information for the patient**

**Saroten and associated names 2 ml, 50 mg solution for injection**
Amitriptyline hydrochloride

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

**What is in this leaflet**


## 1. What X is and what it is used for

X belongs to a group of medicines known as tricyclic antidepressants.

X is used for the in-hospital treatment of depression in adults (major depressive episodes).

## 2. What you need to know before you are given X

**You will not be given X:**
- if you are allergic to amitriptyline or any of the other ingredients of this medicine (listed in section 6).
- if you recently have had a heart attack (myocardial infarction).
- if you have heart problems such as disturbances in heart rhythm which are seen on an electrocardiogram (ECG), heart block, or coronary artery disease
- if you are taking medicines known as monoamine oxidase inhibitors (MAOIs)
- if you have taken MAOIs within the last 14 days
- if you have taken moclobemide the day before
- if you have a severe liver disease.

If you are treated with X, you have to stop taking this medicine and wait for 14 days before you start treatment with a MAOI.

**Warnings and precautions**
Talk to your doctor before X is administered

Heart rhythm disorders and hypotension may occur if you receive a high dosage of amitriptyline. This might also occur in usual doses if you have pre-existing heart disease.

Prolonged QT interval

A heart problem called “prolonged QT interval” (which is shown on your electrocardiogram, ECG) and heart rhythm disorders (rapid or irregular heart beat) have been reported with X. Tell your doctor if you:
- have slow heart rate,
- have or had a problem where your heart cannot pump the blood round your body as well as it should (a condition called heart failure),
- are taking any other medication that may cause heart problems, or
- have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood.
- have a surgery planned as it might be necessary to stop the treatment with amitriptyline before you are given anaesthetics. In the case of acute surgery, the anaesthetist should be informed about the treatment of amitriptyline.
- have an overactive thyroid gland or receive thyroid medication

Thoughts of suicide and worsening of your depression
If you are depressed, you can sometimes have thoughts of harming or killing themselves. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.
You may be more likely to think like this:
- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (less than 25 years old) with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Episodes of mania
Some patients with manic-depressive illness may enter into a manic phase. This is characterized by profuse and rapidly changing ideas, exaggerated gaiety and excessive physical activity. In such cases, it is important to contact your doctor who probably will change your medication.

Tell your doctor if you have, or have had in the past, any medical problems, especially if you have
- narrow angle glaucoma (loss of vision due to abnormally high pressure in the eye)
- epilepsy, a history of convulsions or fits
- difficulty in passing urine
- enlarged prostate
- thyroid disease
- bipolar disorder
- schizophrenia
- severe liver disease
- severe heart disease
- pylorus stenosis (narrowing of the gastric outlet) and paralytic ileus (blocked intestine)
- diabetes as you might need and adjustment of your antidiabetic medicine

If you use antidepressants such as Selective Serotonin Re-uptake Inhibitors (SSRIs), your doctor might consider to changing the dose of your medicine (see also section 2 Other medicines and X and section 3)

Elderly are more likely to suffer from certain side effects, such as dizziness when you stand up due to low blood pressure (see also section 4, Possible side effects).

**Children and adolescents**

Do not give this medicine to children and adolescents aged below 18 years for these treatments, as safety and efficacy have not been established in this age group.

**Other medicines and Saroten solution for injection**
Some medicines may affect the action of other medicines and this can sometimes cause serious side effects.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, such as:
- monoamine oxidase inhibitors (MAOIs) e.g. phenelzine, iproniazid, isocarboxazid, nialamide or tranylcypromine (used to treat depression) or selegiline (used to treat Parkinson's disease). These should not be taken at the same time as Saroten Retard (see section 2 Do not take X) adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine (these may be present in cough or cold medicine, and in some anaesthetics)
- medicine to treat high blood pressure for example calcium-channel blockers (e.g. diltiazem and verapamil), guanethidine, betanidine, clonidine reserpine and methyldopa
- anticholinergics such as certain medicines to treat Parkinsons disease and gastrointerstinal disorders (e.g. atropine, hyoscyamine)
- thioridazine (used to treat schizophrenia)
- tramadol (painkiller)
- medicines to treat fungal infections (e.g. fluconazole, terbinafine, ketoconazole, and itraconazole)
- sedatives (e.g. babiturates)
- antidepressants (e.g SSRIs fluoxetine, paroxetine, fluvoxamine and bupropion)
- medicines for certain heart conditions (e.g. beta blockers and antiarrhythmics)
- cimetidine (used to treat stomach ulcers)
- methylphenidate (used to treat ADHD)
- ritonavir (used to treat HIV)
- oral contraceptives
- rifampicin (to treat infections)
- phenytoin and carbamazepine (used to treat epilepsy)
- St. John´s Wort (hypericum perforatum) – a herbal remedy used for depression
- thyroid medication

You should also tell your doctor, if you take or have recently taken medicine that may affect the heart´s rhythm. e.g.:
- medicines to treat irregular heartbeats (e.g. quinidine and sotalol)
- astemizole and terfenadine (used to treat allergies and hayfever)
- medicines used to treat some mental illnesses (e.g. pimozide and sertindole)
- cisapride (used to treat certain types of indigestion)
- halofantrine (used to treat malaria)methadone (used to treat pain and for detoxification)
- diuretics (“water tablets” e.g. furosemide)

If you are going to have an operation and receive general or local anaesthetics you should tell your doctor that you are taking this medicine.

Likewise, you should tell your dentist that you take this medicine if you are to receive a local anaesthetic.

**X with alcohol**

It is not advised to drink alcohol during treatment with X as it might increase the sedative effect.

**Pregnancy, breast-feeding and fertility**

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

Amitriptyline is not recommended during pregnancy unless your doctor considers it clearly necessary and only after careful consideration of the benefit and risk. If you have taken this medicine during the last part of the pregnancy, the newborn may have withdrawal symptoms such as irritability, increased muscle tension, tremor, irregular breathing, poor drinking, loud crying, urinary retention, and constipation.

Your doctor will advise you whether to start/continue/ stop breast-feeding, or stop using this medicine taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

**Driving and using machines**
This medicine may cause drowsiness and dizziness, especially in the beginning of the treatment.Do not drive or work with tools or machinery if you are affected.

**X contains sodium**
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

## 3. How you will be given Saroten solution for injection

Your doctor will give you Saroten solution for injection.

X can be added to an infusion or injected into a big muscle. The solution for injection prepared with sodium chloride solution 0.9% must be used immediately.
Wrongly administered injections (subcutaneous, paravenous or intra-arterial injection) must be avoided due to the risk of considerable tissue injury.
Dosage and duration of treatment will be determined by you physician based on the severity of your disease and your clinical response. The solution for injection should mainly be used for acute treatment. After 1-2 weeks the oral formulations should be used for further treatment. The general duration of treatment will be decided by the treating physician on an individual basis.
After reduction of the depressive symptoms the treatment with amitriptyline should be continued for up to 6 month.

Talk with your physician in case you have the impression that the effect of X is too strong or weak.

In case of sufficient effect, the dose should be as low as possible. If required, the available dose range can be exploited.
At the start of treatment, the dose should be gradually increased, when treatment is discontinued, it must be reduced gradually.

The recommended dose is:
Saroten injectable solution is used in hospitalized patients especially for the initial treatment of depressive disorders. Usually the X is added to a solution for infusion. The daily dosage is in general between 1and 3 ampoules of 2 ml (equivalent to 50-150 mg amitriptyline hydrochloride/day). If a dose increase is required this should be done stepwise within 3 to 7 days. After about 1 to 2 weeks a stepwise reduction together with a change to the oral formulations for further treatment can be initiated.
Unless prescribed otherwise, adult patients receive 1 ampoule Saroten 2 ml (50 mg amitriptyline hydrochloride) in 250 to 500 ml sodium chloride solution 0.9% for 2-3 hours as a drip infusion under control of blood pressure and ECG.

X can also be injected into a big muscle (i,m. injection). Unless prescribed otherwise adults will receive half an ampoule up to 2 ampoules (1 to 4 ml solution for injection, equivalent to 25 to 100 mg amitriptyline hydrochloride per day) in several single injections of no more than 25 mg amitriptyline hydrochloride.

*Elderly patients (above 65 years of age) and patients with cardiovascular disease*
Elderly often require a considerably lower dose and often show at half the daily dose a satisfying success of treatment. Doses above 100 mg should be used with caution and your doctor might choose to follow you more closely.

*Patients with special risks*
Weakened patients with cerebral or cardiac impairment, as well as patients with poor circulation, breathing problems, impaired liver function or advanced renal impairment a dose reduction is recommended.

Patients known as “poor metabolisers” usually receive lower doses. Your doctor may take blood samples to determine the level this medicine in the blood (see also section 2).

**Use in children and adolescents**
X should not be given to children or adolescents.

**If you were given more X then you should**

Contact your doctor immediately. Do this even if there are no signs of discomfort or poisoning.

Symptoms of overdose include:
- dilated pupils
- fast or irregular heartbeats
- difficulties passing water
- dry mouth and tongue
- intestinal blockage
- fits
- fever
- agitation
- confusion
- hallucinations
- uncontrolled movements
- low blood pressure, weak pulse, pallor
- difficulty breathing
- blue discolouration of the skin
- decreased heart rate
- drowsiness
- loss of consciousness
- coma
- various cardiac symptoms such as heart block, heart failure, hypotension, cardiogenic shock, metabolic acidosis, hypokalemia.

**If a dose of X is missed**
Make a new appointment for an injection with your physician.

**Stopping treatment with Saroten solution for injection**
Your doctor will decide when and how to stop your treatment to avoid any unpleasant symptoms that might occur if it is stopped abruptly (e.g. headache, feeling unwell, sleeplessness and irritability).

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

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following symptoms you should see your doctor immediately:

- Attacks of intermittent blurring of vision, rainbow vision, and eye pain.
  You should immediately have an eye examination before the treatment with this medicine can be continued. This condition may be signs of acute glaucoma. Very rare side effect, may affect up to 1 in 10,000 people.
- A heart problem called "prolonged QT interval" (which is shown on your electrocardiogram, ECG). Common side effect, may affect up to 1 in 10 people.
- Bad constipation, a swollen stomach, fever and vomiting.
  These symptoms may be due to parts of the intestine becoming paralysed. Rare side effect, may affect up to 1 in 1,000 people.
- Any yellowing of the skin and the white in the eyes (jaundice). Your liver may be affected. Rare side effect, may affect up to 1 in 1,000 people.
- Bruising, bleeding, pallor or persistent sore throat and fever.
  These symptoms can be the first signs that your blood or bone marrow may be affected.
  Effects on the blood could be a decrease in the number of red cells (which carry oxygen around the body), white cells (which help to fight infection) and platelets (which help with clotting). Rare side effect, may affect up to 1 in 1,000 people.
- Suicidal thoughts or behaviour. Rare side effect, may affect up to 1 in 1,000 people.

Side effects listed below have been reported in the following frequencies:

*Very common: may affect more than 1 in 10 people*
- sleepiness/drowsiness
- shakiness of hands or other body parts
- dizziness
- headache
- irregular, hard or rapid heartbeat
- dizziness when you stand up due to low blood pressure (orthostatic hypotension)
- dry mouth
- constipation
- nausea
- excessive sweating
- weight gain
- slurred or slow speech
- aggression
- congested nose

Common: may affect up to 1 in 10 people
- confusion
- sexual disturbances (decreased sex-drive, problems with erection)
- disturbance in attention
- changes in taste
- numbness or tingling in the arms or legs
- disturbed coordination
- dilated pupils
- heart block
- fatigue
- low sodium concentration in the blood
- agitation
- urination disorders
- feeling thirsty

Uncommon: may affect up to 1 in 100 people,

- excitement, anxiety, difficulties sleeping, nightmares
- convulsions
- tinnitus
- increased blood pressure
- diarrhoea, vomiting
- skin rash, nettle rash (urticarial), swelling of the face and tongue
- difficulties passing urine
- increased production of breast milk or breast milk outflow without breast feeding
- increased pressure in the eye ball
- collapse conditions
- worsening of cardiac failure
- liver function impairment (e.g. cholestatic liver disease)

Rare: may affect up to 1 in 1,000 people
- decreased appetite
- delirium (especially in elderly patients), hallucinations (especially in patients with schizophrenia),
- abnormality in the heart's rhythm, or heartbeat pattern
- swelling of the salivary glands
- hair loss
- increased sensitivity to sunlight
- breast enlargement in men
- fever
- weight loss
- abnormal results of liver function tests

Very rare: may affect up to 1 in 10,000 people
- heart muscle disease
- feeling of inner restlessness and a compelling need to be in constant motion
- disorder of the peripheral nerves
- acute increase of pressure in the eye
- particular forms of abnormal heart rhythm (so called torsades de pointes)
- allergic inflammation of the lung alveoli and of the lung tissue

Not known: frequency cannot be estimated from the available data
- absent sensation of appetite
- elevation or lowering of blood sugar levels
- paranoia
- movement disorders (involuntary movements or decreased movements)
- hypersensitivity inflammation of heart muscle
- hepatitis
- hot flush
- injection site reactions

An increased risk of bone fractures has been observed in patients taking this type of medicines.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.* By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Saroten solution for injection
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the card box and ampoule. The expiry date refers to the last day of that month.

[To be completed nationally]

## 6. Contents of the pack and other information

### What X contains

The active substance is amitriptyline hydrochloride
[To be completed nationally]

### What X looks like and contents of the pack

[To be completed nationally]

### Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

**This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.**

[To be completed nationally]