Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Sympramol
50 mg coated tablets

Opipramol Dihydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 50 mg opipramol dihydrochloride.

Excipients:
lactose 45.6 mg
sucrose 81.3 mg
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Coated tablet
Reddish and round coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Generalised anxiety disorders and somatoform disorders.

4.2 Posology and method of administration

The treatment must always be under medical supervision.

The dosage in adults is usually 50 mg opipramol dihydrochloride in the morning and at midday and 100 mg opipramol dihydrochloride at night.
Depending on efficacy and tolerability, the dose can be reduced to 50 mg - 100 mg opipramol dihydrochloride once daily, preferably at night, or increased to 100 mg opipramol dihydrochloride up to 3 times a day.

Children over 6 years are given 3 mg opipramol dihydrochloride/kg body weight. As experiences with opipramol are limited in paediatrics, this dosage recommendation is for guidance only.

Opipramol Dihydrochloride 50 mg coated tablets should be taken with some liquid (water, fruit juice).

As the effect of opipramol is not apparent suddenly and the overall alteration in mood occurs gradually, this medicinal product should be taken regularly for at least 2 weeks.
An average treatment period of 1-2 months is advisable.

4.3 Contraindications

- hypersensitivity to opipramol dihydrochloride, tricyclic antidepressants or to any of the excipients
- acute alcohol, hypnotic, analgesic and psychotropic intoxication
- acute urinary retention
- acute delirium
- untreated narrow-angle glaucoma
- prostatic hypertrophy with residual urine
- paralytic ileus
- pre-existing higher-degree AV block or diffuse supraventricular or ventricular conduction disorders
- combination with monoaminoxidase (MAO) inhibitors (see section 4.5)

4.4 Special warnings and precautions for use

Opipramol should not be used with prostatic hypertrophy without residual urine, manifest hepatic and renal disease, increased tendency to seizures (e.g. with brain damage of various aetiology, epilepsy, alcoholism), cerebrovascular insufficiency and previous cardiac damage, particularly conduction disorders. Patients with pre-existing first-degree AV block or other conduction disorders should be treated only with frequent ECG monitoring (for higher-degree AV block, see section 4.3).

As alterations in the blood count (neutropenia, agranulocytosis) can occur very rarely, the blood count should be measured during treatment with opipramol, particularly if fever, flu-like infections and sore throat occur.

Opipramol can cause hypersensitivity reactions, including delayed reactions. If allergic skin reactions occur, opipramol must be discontinued.

During prolonged treatment, it is advisable to measure the liver function tests.

Patients with the rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption, fructose intolerance or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Treatment with opipramol does not preclude additional therapy with neuroleptics, hypnotics and tranquilizers (e.g. benzodiazepines). It should be noted that a few specific effects, particularly centrally depressant effects, can be intensified with combined medication. The same applies for sedation after systemic anaesthetics.

The effect particularly of strong anticholinergics, such as antiparkinson agents and phenotiazines, can be intensified.
Concomitant treatment with serotonin reuptake inhibitors and opipramol can lead to additive effects on the serotoninergic system. With fluoxetine and fluvoxamine there can be an increase in the plasma concentrations of tricyclic psychotropic substances and an associated intensification of the undesirable effects. If necessary, the dose of opipramol should be reduced.

Combination with alcohol can lead to drowsiness.

MAO inhibitors should be stopped at least 14 days before treatment with opipramol. The same applies for opipramol when MAO inhibitors are given afterwards.

Concomitant use of beta-blockers (e.g. propanolol), class Ic antiarrhythmics and substances from the group of the tricyclic antidepressants and preparations that affect the microsomal enzyme system of the liver can lead to a change in the plasma concentration of these substances and of opipramol. Barbiturates and anticonvulsants can reduce the plasma concentration of opipramol and thus diminish the therapeutic effect. Concomitant administration of neuroleptics (e.g. haloperidol, risperidone) can increase the plasma concentration of opipramol. If necessary, appropriate dose adjustments should be made.

4.6 Pregnancy and lactation

There are no data on exposed pregnant women for opipramol.
Animal studies do not permit conclusions on harmful effects of opipramol on embryonic development or fertility (see section 5.3). Opipramol should be prescribed during pregnancy, particularly the first trimester, only if strictly indicated.
Opipramol should not be used during the lactation period as the active substance passes into breast milk in small amounts. If strictly indicated, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

The ability to react can be altered with correct use of opipramol dihydrochloride so that the ability to drive or use machines is impaired, particularly in combination with alcohol.

4.8 Undesirable effects

Rates of incidence:
common (≥1/100, <1/10); uncommon (≥1/1,000, ≤1/100); rare (≥1/10,000, ≤1/1,000); very rare (≤1/10,000)

	common	uncommon	rare	very rare
Blood and the lymphatic system disorders			Blood count changes, especially leucopenia	Agranulocytosis
Nervous system disorders	Particularly at the start of treatment fatigue, dry mouth, blocked nose	Vertigo, drowsiness, disorders of micturition, disorders of accommodation, tremor, weight gain, sensation of thirst	Excitation states, headache, paraesthesias, particularly in elderly patients, confusional states and delirium, particularly with sudden discontinuation of more prolonged high-dose therapy, agitation, sweating and sleep disorders	Cerebral seizures, motor disorders (akathisia, dyskinesias), ataxia, polyneuropathies, sudden glaucoma, anxiety states
Cardiac disorders	Particularly at the start of treatment hypotension and orthostatic dysregulation	Tachycardia, palpitations	Collapse states, conduction disorders, intensification of existing heart failure	
Gastrointestinal disorders		Constipation	Gastrointestinal disorders, taste disorders, paralytic ileus, particularly with sudden discontinuation of more prolonged high-dose therapy, nausea and vomiting	
Hepato-biliary disorders		Temporary rises in liver enzyme activity		Severe liver function disorders, after long-term treatment icterus and chronic liver damage
Skin and subcutaneous tissue disorders		Allergic skin reactions (exanthem, urticaria)	Oedema	Hair loss
Renal and urinary disorders			Urinary retention	
Reproductive system and breast disorders		Ejaculation disorders, erectile impotence	Galactorrhoea	

4.9 Overdose

Symptoms of intoxication
Drowsiness, insomnia, dizziness, agitation, coma, stupor, temporary confusional states, increased anxiety, ataxia, convulsions, oliguria, anuria, tachy-/bradycardia, arrhythmia, AV block, hypotension, shock, respiratory depression, rarely cardiac arrest.

Treatment of intoxication
A specific antidote is not available. The harmful agent should be removed by vomiting and/or gastric lavage. The patient should be admitted to hospital with vital functions protected. Cardiovascular monitoring should be continued for at least 48 hours.
In the case of overdose, the following measures should be instituted:
- Respiratory insufficiency: intubation and artificial ventilation
- Severe hypotension: appropriate positioning, plasma expanders, dopamine or dobutamine as drip infusion.
- Cardiac arrhythmias: individual treatment; if necessary cardiac pacemaker, correction of low potassium levels and possible acidosis.
- Convulsions: injection of diazepam intravenously or a different anticonvulsant agent such as phenobarbital or paraldehyde (caution: possible intensification of existing respiratory insufficiency, hypotension or coma by these substances).
- Dialysis and haemodialysis are of hardly any benefit.

As children react much more sensitively to acute overdoses of tricyclic antidepressants/anxiolytics than adults and as serious incidents have been reported, all possible measures should be taken to prevent overdose; if they occur nevertheless, the symptoms of overdose must be taken seriously and treated carefully.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Sedative/Anxiolytic

Mechanism of action
Opipramol has high affinity for the sigma binding sites (type 1 and type 2) and has an antagonistic effect at the type 1 histamine receptors. The affinity for the type 2A serotonin receptors, type 2 dopamine receptors and the α-adrenergic receptors is lower. In contrast to the structurally related tricyclic antidepressants, opipramol has only slight anticholinergic activity and does not inhibit the reuptake of serotonin or noradrenaline.

Opipramol has a modulating effect on the NMDA system through the sigma receptors; protective effects against neuron loss due to ischaemia in the hippocampus region were demonstrated in animal experiments.

The dopamine turnover is increased. Similar modulating effects are described for sigma ligands in the serotoninergic and noradrenergic system also. Opipramol, like other more selective sigma ligands, is active in pharmacologic behavioural models, which are indicative of anxiolysis, and has comparatively lower activity in the swimming test in the rat, which is used as a screening method for potential antidepressants.

In humans, opipramol has sedating, anxiolytic and slight mood-elevating effects.

5.2 Pharmacokinetic properties

Following oral ingestion, opipramol is absorbed rapidly and completely. Partial metabolism to dehydroxyethyl-opipramol takes place during its passage through the liver. The plasma protein binding is about 91%, the distribution volume is approx. 10 l/kg and the elimination half-life is about 11 hours.

Opipramol is essentially metabolised by the CYP2D6 isoenzyme. In patients with CYP2D6 deficiency (“poor metabolisers“) the maximum plasma concentration of opipramol can be up to 2.5 times higher than with normal metabolism. However, the elimination half-life is not prolongated with chronic use, so that accumulation of opipramol is not to be expected even in slow metabolisers.

5.3 Preclinical safety data

The acute toxicity is relatively low. Intoxication symptoms affect the CNS predominantly (see section 4.9).
Subchronic and chronic administration of very high doses causes CNS symptoms, liver and lung damage, skin and coat changes and cataract formation in certain species.
In vitro and *in vivo* studies gave no evidence of mutagenic potential. Animal experiments yielded no evidence of an impairment of fertility by opipramol. In embryotoxicity studies no teratogenic effects occurred but embryotoxic effects were observed in the maternal toxic dose range. Studies of peri- and postnatal toxicity were not performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Maize starch
Lactose monohydrate
Povidone K 30
Microcrystalline cellulose
Talcum
Magnesium stearate

Tablet coating:
Shellac
Talcum
Calcium carbonate
Sucrose
Kaolin white (white clay)
Acacia (gum arabic)
Titanium dioxide (E171)
Iron-(III)-oxide (E172)
Opaglos 6000 NS
made of yellow carnauba wax
and white beeswax
Sodium benzoate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Usunięto: 18 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/PVC/PVDC blister
Pack sizes: 20,40, 50, 60, 90,100, 120
Hospital pack: 30 x 20
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

SymPhar Sp. z o.o.
ul.Włoska 1
00-777 Warsaw

Sformatowano: Angielski (Stany Zjednoczone)

Poland

8. MARKETING AUTHORISATION NUMBER(S)

12777

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

06.04.2007

10. DATE OF REVISION OF THE TEXT

04/2013