NOVARTIS

Drug Regulatory Affairs

SIRDALUD® / SIRDALUD® MR

(tizanidine)

2 mg, 4 mg and 6 mg Tablets

6 mg and 12 mg MR Capsules

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

SIRDALUD® tablets: 2 mg, 4 mg and 6 mg

SIRDALUD® MR capsules: 6 mg and 12 mg

2 Qualitative and quantitative composition

Active substance: 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole (= tizanidine).

Tablets containing 2 mg, 4 mg or 6 mg tizanidine hydrochloride.

MR (modified release) capsules containing 6 mg or 12 mg tizanidine hydrochloride.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Tablets (scored and cross-scored) and MR capsules for oral administration.

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

Tablets

Painful muscle spasms

- associated with static and functional disorders of the spine (cervical and lumbar syndromes),
- following surgery, e.g. for herniated intervertebral disc or osteoarthritis of the hip.

Tablets and MR capsules

Spasticity due to neurological disorders

- e.g. multiple sclerosis, chronic myelopathy, degenerative spinal cord diseases, cerebrovascular accidents, and cerebral palsy.

4.2 Posology and method of administration

Relief of painful muscle spasms

2 to 4 mg three times daily in tablet form. In severe cases an extra dose of 2 or 4 mg may be taken at night.

Spasticity due to neurological disorders

The dosage should be adjusted to the needs of the individual patient.

Tablets

The initial daily dose should not exceed 6 mg given in 3 divided doses. It may be increased stepwise at half-weekly or weekly intervals by 2 to 4 mg. The optimum therapeutic response is generally achieved with a daily dose of between 12 and 24 mg, administered in 3 or 4 equally spaced doses. The daily dose of 36 mg should not be exceeded.

MR capsules

The recommended initial dose is 1 capsule of 6 mg once daily; if necessary, the daily dosage may be increased stepwise by 1 capsule of 6 mg at half-weekly or weekly intervals. The usual dosage range is 6 to 24 mg once a day. Clinical experience has shown that 12 mg once daily, given as 2 capsules of 6 mg or 1 capsule of 12 mg, is the optimum dose for the majority of patients and that 24 mg is seldom required.

Use in children

Experience in children is limited and the use of Sirdalud in this patient population is not recommended.

Use in elderly

Experience with the use of Sirdalud in the elderly is limited. Pharmacokinetic data suggest that renal clearance in the elderly may in some cases be significantly decreased. Caution is therefore indicated when using Sirdalud in elderly patients.

4.3 Contraindications

Significantly impaired hepatic function (see section 5.2 Pharmacokinetic properties).

Concomitant use of tizanidine with strong inhibitors of CYP1A2 such as fluvoxamine or ciprofloxacin is contra-indicated (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Known hypersensitivity to tizanidine or to any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

CYP inhibitorsConcomitant use of tizanidine with CYP1A2 inhibitors is not recommended (see section 4.3 Contraindications and section 4.5 Interaction with other medicinal products and other forms of interaction).

Hypotension

Hypotension may occur during treatment with tizanidine (see section 4.8 Undesirable effects) and also as a result of drug interactions with CYP1A2 inhibitors and/or antihypertensive drugs (see section 4.5 Interaction with other medicinal products and other forms of interaction). Severe manifestations of hypotension such as loss of consciousness and circulatory collapse have also been observed.

Withdrawal syndrome

Rebound hypertension and tachycardia have been observed after sudden withdrawal of tizanidine, when it had been used chronically, and/or in high daily dosages, and/or concomitantly with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident. Tizanidine should not be stopped abruptly, but rather gradually (see section 4.5 Interaction with other medicinal products and other forms of interaction and section 4.8 Undesirable effects).

Hepatic dysfunction

Since hepatic dysfunction has been reported in association with tizanidine, but rarely at daily doses up to 12 mg, it is recommended that liver function tests should be monitored monthly for the first four months in patients receiving doses of 12 mg and higher and in patients who develop clinical symptoms suggestive of hepatic dysfunction, such as unexplained nausea, anorexia or tiredness. Treatment with Sirdalud should be discontinued if serum levels of SGPT or SGOT are persistently above three times the upper limit of the normal range.

Renal insufficiency

In patients with renal insufficiency (creatinine clearance < 25 mL/min), it is recommended to start treatment at 2 mg once daily. Dosage increases should be done in small steps according to tolerability and efficacy. If efficacy has to be improved, it is advisable to increase first the once-daily dose before increasing the frequency of administration.

For Sirdalud tablets:

Sirdalud tablets contain lactose. This medicine is not recommended in patients with rare hereditary problem of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

CYP inhibitors

Concomitant administration of drugs known to inhibit the activity of CYP1A2 may increase the plasma levels of tizanidine (see section 5.2 Pharmacokinetic properties).

Concomitant use of tizanidine with fluvoxamine or ciprofloxacin, both CYP450 1A2 inhibitors in man, is contraindicated. Concomitant use of tizanidine with fluvoxamine or ciprofloxacin resulted in a 33-fold and 10-fold increase in tizanidine AUC, respectively (see section 4.3 Contraindications). Clinically significant and prolonged hypotension may result along with somnolence, dizziness and decreased psychomotor performance (see section 4.4 Special warnings and precautions for use). Co-administration of tizanidine with other inhibitors of CYP1A2 such as some antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, some fluoroquinolones (enoxacin, pefloxacin, norfloxacin), rofecoxib, oral contraceptives, and ticlopidine is not recommended (see section 4.4 Special warnings and special precautions for use).

The increased plasma levels of tizanidine may result in overdose symptoms such as QT(c) prolongation (see also section 4.9 Overdose).

Antihypertensives

Concomitant use of tizanidine with antihypertensives, including diuretics, may occasionally cause hypotension (see section 4.4 Special warnings and precautions for use) and bradycardia. In some patients rebound hypertension and tachycardia have been observed upon abrupt discontinuation of tizanidine when concomitantly used with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

Other

Alcohol and sedatives may enhance the sedative action of tizanidine.

4.6 Pregnancy and lactation

Pregnancy

Tizanidine has no teratogenic effects in rats and rabbits. As there have been no controlled studies in pregnant women, however, it should not be used during pregnancy unless the benefit clearly outweighs the risk.

Lactation

Although only small amounts of tizanidine are excreted in animal milk, tizanidine should not be taken by women who are breast-feeding.

4.7 Effects on ability to drive and use machines

Patients experiencing somnolence, dizziness or any signs or symptoms of hypotension should refrain from activities requiring a high degree of alertness, e.g. driving a vehicle or operating machines.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1

Psychiatric disorders		
	Rare:	Hallucination, insomnia, sleep disorder
Nervous system disorders		
	Common:	Somnolence, dizziness
Cardiac disorders		
	Common:	Bradycardia
Vascular disorders		
	Common:	Hypotension
Gastrointestinal disorders		
	Common:	Dry mouth
	Rare:	Nausea, gastrointestinal disorder

Hepatobiliary disorders		
	Very rare:	Hepatitis, hepatic failure
Musculoskeletal and connective tissue disorders		
	Rare:	Muscular weakness
General disorders and administration site conditions		
	Common:	Fatigue
Investigations		
	Common:	Blood pressure decrease
	Rare:	Transaminase increase

With low doses, such as those recommended for the relief of painful muscle spasms, somnolence, fatigue, dizziness, dry mouth, blood pressure decrease, nausea, gastrointestinal disorder and transaminase increase have been reported, usually as mild and transient adverse reactions.

With the higher doses recommended for the treatment of spasticity, the adverse reactions reported with low doses are more frequent and more pronounced, but seldom severe enough to require discontinuation of treatment. In addition, the following adverse reactions may occur: hypotension, bradycardia, muscular weakness, insomnia, sleep disorder, hallucination, hepatitis.

Withdrawal syndrome

Rebound hypertension and tachycardia have been observed after sudden withdrawal of tizanidine, when it had been used chronically, and/or in high daily dosages, and/or concomitantly with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident (see section 4.4 Special warnings and precautions for use and section 4.5 Interaction with other medicinal products and other forms of interaction).

4.9 Overdose

In the few reports of Sirdalud overdosage received, recovery was uneventful, including by a patient who ingested 400 mg Sirdalud.

Symptoms

Nausea, vomiting, hypotension, QT(c) prolongation, dizziness, somnolence, miosis, restlessness, respiratory distress, coma.

Treatment

It is recommended to eliminate the ingested drug by repeated administration of high doses of activated charcoal. Forced diuresis is expected to accelerate the elimination of Sirdalud. Further treatment should be symptomatic.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, other centrally acting agents, ATC code: M03B X02.

Tizanidine is a centrally acting skeletal muscle relaxant. Its principal site of action is the spinal cord, where the evidence suggests that, by stimulating presynaptic alpha$_2$-receptors, it inhibits the release of excitatory aminoacids that stimulate N-methyl-D-aspartate (NMDA) receptors. Polysynaptic signal transmission at spinal interneuron level, which is responsible for excessive muscle tone, is thus inhibited and muscle tone reduced. In addition to its muscle-relaxant properties, tizanidine also exerts a moderate central analgesic effect.

Sirdalud is effective in both acute painful muscle spasms and chronic spasticity of spinal and cerebral origin. It reduces resistance to passive movements, alleviates spasms and clonus, and may improve voluntary strength.

5.2 Pharmacokinetic properties

Absorption and bioavailability

Tizanidine is rapidly and almost completely absorbed, reaching peak plasma concentration approximately 1 hour after dosing. Mean absolute bioavailability is about 34% due to extensive first-pass metabolism.

Distribution

Mean steady-state volume of distribution (V_{SS}) following i.v. administration is 2.6 L/kg. Plasma protein binding is 30%. Tizanidine has linear pharmacokinetics over the dose range 4 to 20 mg. The low intraindividual variation in pharmacokinetic parameters (C_{max} and AUC) enables reliable prediction of plasma levels following oral administration. The pharmacokinetic parameters of tizanidine are not affected by gender.

Biotransformation

The drug has been shown to be rapidly and extensively metabolized by the liver. Tizanidine is mainly metabolized by cytochrome P450 1A2 *in vitro*. The metabolites appear to be inactive.

Elimination

Tizanidine is eliminated from the systemic circulation with a mean terminal half-life of 2 to 4 hours. Excretion is primarily via the kidneys (approximately 70% of dose) in the form of metabolites, with unchanged drug accounting for only about 2.7% of urinary recovery.

Modified-release (MR) formulation

Sustained release of tizanidine from Sirdalud MR capsules results in a smoother pharmacokinetic profile by avoiding high initial peaks and maintaining therapeutic plasma concentrations over 24 hours. Maximum mean plasma concentrations are reached within about 8.5 hours, amounting to approximately half those obtained when equal daily amounts of Sirdalud in its tablet form are given in 3 divided doses, whereas the total exposure remains unchanged.

Characteristics in special patient populations

In **patients with renal insufficiency** (creatinine clearance < 25 mL/min), maximal mean plasma levels were found to be twice as high as in normal volunteers, and the terminal half-life was prolonged to approximately 14 hours, resulting in much higher (approximately 6-fold on average) AUC values (see section 4.4 Special warnings and precautions for use).

Effect of food

Concomitant food intake has no relevant influence on the pharmacokinetic profile of tizanidine (given as tablets or capsules). Although C_{max} is about one-third higher, this is not thought to be of any clinical relevance, and absorption (AUC) is not significantly affected.

5.3 Preclinical safety data

Acute toxicity

The acute toxicity of tizanidine is of a low order. After single doses > 40 mg/kg in animals, signs of overdosage were seen related to the drug's pharmacological action.

Chronic and subchronic toxicity

In a 13-week oral toxicity study in rats given average daily doses of 1.7, 8 and 40 mg/kg, the major findings were related to CNS stimulation (e.g. motor excitation, aggressiveness, tremor, and convulsions), and occurred mainly at the highest dose level.

ECG changes and CNS effects were observed at daily doses of 1 mg/kg and higher in dogs in a 13-week study with dose levels of 0.3, 1 and 3 mg/kg/day given as capsules and a 52-week study with 0.15, 0.45 and 1.5 mg/kg/day. These represent exaggerated pharmacological effects. Transient increases in SGPT seen at daily doses of 1 mg/kg and above were not related to histopathological findings but indicate that the liver is a potential target organ.

Mutagenicity

No evidence of mutagenic potential was found in *in vitro*, *in vivo*, or cytogenetic assays.

Carcinogenicity

No indication of carcinogenic potential was seen in rats or mice given doses of up to 9 mg/kg/day and 16 mg/kg/day, respectively, in the feed.

Reproductive toxicity

No embryotoxic or teratogenic effects were observed in pregnant rats and rabbits at dose levels up to 100 mg/kg/day.

Increased prenatal mortality due to prolongation of gestation and dystocia occurred at dose levels of 10 and 30 mg/kg/day in female rats dosed at 3, 10 and 30 mg/kg/day from before mating through to lactation or from late pregnancy until weaning of the young.

6 Pharmaceutical particulars

6.1 List of excipients

Tablets

Silica colloidal anhydrous; stearic acid; cellulose, microcrystalline; lactose, anhydrous.

Information might differ in some countries.

MR capsules

Ethylcellulose; shellac; talc; maize starch; sucrose; iron oxide yellow; titanium dioxide; gelatin; iron oxide black.

Information might differ in some countries.

6.2 Incompatibilities

None known.

6.3 Shelf life

Country specific (climatic zone dependent).

Information might differ in some countries.

6.4 Special precautions for storage

Tablets: Country specific (climatic zone dependent).

MR capsules: Store at room temperature (below 30°C).

Information might differ in some countries.

Sirdalud/Sirdalud MR must be kept out of reach and sight of children.

6.5 Nature and content of container

Country specific.

6.6 Special precautions for disposal

Not applicable.