NOVARTIS

Drug Regulatory Affairs

SIRDALUD® / SIRDALUD® MR

(Tizanidine)

2 mg, 4 mg and 6 mg Tablets
6 mg and 12 mg MR Capsules

Agreed Core Safety profile

Author(s): Raoof M, Gulati M

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1 NAME OF THE MEDICINAL PRODUCT

Please refer to the local approved SPC.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Please refer to the local approved SPC.

3 PHARMACEUTICAL FORM

Please refer to the local approved SPC.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Please refer to the local approved SPC.

4.2 Posology and method of administration

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.

(Note: For proposed Core Safety Profile common safety related information is included in this section 4.2)

4.3 Contraindications

Significantly impaired hepatic function.

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.

4.4 Special warnings and precautions for use

CYP inhibitors

Concomitant 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.

For Sirdalud MR Capsules:

Sirdalud MR capsules contain sucrose. This medicine is not recommended in patients with rare hereditary problem of fructose intolerance, of sucrase-isomaltase insufficiency 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.

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). Concomitant use of tizanidine (in high doses) with other products that could cause QT (c) prolongation is not recommended.

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.~~ Animal studies indicate increased pre- and perinatal mortality at maternally toxic doses.

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: confusional state, 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

Please refer to the local approved SPC.

6 Pharmaceutical Particulars

Please refer to the local approved SPC.