NOVARTIS

Sirdalud® / Sirdalud® MR

Composition

Active substance
Tizanidine, as the hydrochloride

Excipients
Tablets: Tableting excipients
Capsules: Capsule excipients

Pharmaceutical form and quantity of active substance per unit

Scored tablets containing 2 or 4 mg tizanidine hydrochloride

MR capsules containing 6 or 12 mg tizanidine hydrochloride (with sustained active substance release)

Indications / Potential uses

- Painful muscle spasms
- Spasticity due to multiple sclerosis
- Spasticity due to spinal injury
- Spasticity due to brain injury

Dosage and Administration

Adults

Relief of painful muscle spasms
2–4 mg three times daily in tablet form. In severe cases an additional dose of 2 or 4 mg may be taken at bedtime.

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 three divided doses. It may be increased stepwise by 2–4 mg at half-weekly or weekly intervals. The optimum therapeutic response is generally achieved with a daily dose of between 12 and 24 mg, given in three or four divided doses. A total daily dose of 36 mg should not be exceeded.

MR capsules
The recommended starting dose is one 6 mg capsule once daily; if necessary, it may be increased stepwise by one 6 mg capsule at half-weekly or weekly intervals. The standard dose is 6–24 mg once daily. Clinical experience has shown the optimum dose in most patients to be 12 mg once daily, 24 mg/day only being required in rare cases. One 12 mg capsule may be given instead of two 6 mg capsules.

Special patient populations

Use in children
Experience in children is limited and use of Sirdalud is therefore not recommended in this patient group.

Use in the elderly
Experience in elderly patients is limited. Pharmacokinetic data indicate that renal clearance may be significantly reduced in some elderly patients. Caution is therefore indicated when using Sirdalud in this patient group.

Contraindications

Hypersensitivity to the active substance.
Significant impairment of liver function.
Concomitant administration of tizanidine with fluvoxamine or ciprofloxacin is contraindicated (see **Interactions** and **Warnings and Precautions**).

Warnings and Precautions

Concomitant administration of CYP1A2 inhibitors with tizanidine is not recommended (see **Interactions** and **Contraindications**).

Liver function impairment has been reported in association with tizanidine, although rarely in patients receiving daily doses up to 12 mg. Monitoring of liver function is therefore recommended at monthly intervals during the first four months of therapy in patients receiving doses of 12 mg or more and in patients with clinical symptoms indicating liver function impairment (e.g. unexplained nausea, appetite loss or fatigue). Sirdalud therapy should be discontinued if serum ALT (SGPT) or AST (SGOT) remain at more than three times the normal level over a prolonged period.

In patients with impaired kidney function (creatinine clearance < 25 ml/minute) the recommended starting dose is 2 mg once daily. The dosage should subsequently be increased in small steps depending on efficacy and tolerability. To achieve enhanced efficacy it is advisable to increase the size of the once-daily dose first before increasing the frequency of administration.

Experience in children is limited and use of Sirdalud is therefore not recommended in this patient group.

Caution is indicated when using Sirdalud in elderly patients.

Sirdalud tablets contain lactose. Patients with rare hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Sirdalud tablets.

Interactions

Concomitant administration of tizanidine with fluvoxamine or ciprofloxacin, which are both potent CYP1A2 inhibitors in man, is contraindicated (see **Contraindications**). Concomitant administration of tizanidine with fluvoxamine resulted in a 33-fold increase in the AUC of tizanidine, while concomitant administration of tizanidine with ciprofloxacin resulted in a 10-fold increase in the AUC of tizanidine. This may lead to a clinically significant and prolonged drop in blood pressure, accompanied by drowsiness, light-headedness and decreased psychomotor performance (see **Contraindications**). Concomitant administration of other CYP1A2 inhibitors – such as some antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, some fluoroquinolones (enoxacin, pefloxacin, norfloxacin), rofecoxib, oral contraceptives and ticlopidine – is not recommended.

Concomitant use of Sirdalud with antihypertensive agents, including diuretics, can occasionally cause hypotension and bradycardia.

Sirdalud may potentiate the effects of alcohol and sedatives.

Pregnancy and Lactation

No clinical data are available on use in pregnant women. Sirdalud should therefore not be used during pregnancy unless clearly necessary.

Sirdalud has no teratogenic effects in rats and rabbits.

In animals small amounts of tizanidine are excreted in milk. Tizanidine should therefore not be taken by women who are breastfeeding.

Effects on ability to drive and use machines

Patients experiencing drowsiness or dizziness should refrain from activities requiring a high degree of alertness (e.g. driving, using machines).

Adverse effects

Adverse effects – such as drowsiness, fatigue, light-headedness, dry mouth, reduced blood pressure, nausea, gastrointestinal disorders and elevated serum transaminases – are usually mild and transient in patients using low doses, such as those recommended for treatment of painful muscle spasms.

With higher doses, such as those recommended for the treatment of spasticity, the above-mentioned reactions are more frequent and more pronounced, but seldom severe enough to require discontinuation of treatment. The following adverse effects may also occur: hypotension, bradycardia, muscle weakness, insomnia, sleep disorders, hallucinations and hepatitis.

Frequency
Very common (> 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to < 1/100), rare (> 1/10 000 to < 1/1000), very rare (< 1/10 000).

Psychiatric disorders
Rare: Hallucinations, insomnia, sleep disturbances.

Nervous system disorders
Common: Drowsiness, light-headedness, dizziness.

Heart
Common: Bradycardia.

Vascular disorders
Common: Hypotension.

Gastrointestinal disorders
Common: Dry mouth.
Rare: Nausea, gastrointestinal disturbances.

Hepatobiliary disorders
Rare: Elevated serum transaminases.
Very rare: Acute hepatitis.

Musculoskeletal system
Rare: Muscle weakness.

General disorders
Common: Fatigue.

Overdose

Very few reports of Sirdalud overdosage have been received. In all patients reported to have taken overdoses of Sirdalud alone, including one patient who had ingested 400 mg Sirdalud, recovery was uneventful.

Signs and symptoms
Nausea, vomiting, hypotension, dizziness, miosis, respiratory depression, coma, restlessness, drowsiness.

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

Properties and Actions

ATC code: M03BX02

Mechanism of action
Sirdalud is a centrally acting muscle relaxant / antispasticity agent. Its principal site of action is the spinal cord.

Evidence suggests that by stimulating presynaptic alpha$_2$-receptors, it inhibits the release of excitatory amino acids 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 is reduced.

Pharmacodynamics
Sirdalud is effective in both acute painful muscle spasms and chronic spasticity of spinal and cerebral origin. It reduces resistance to passive movement, alleviates spasm and clonus, and improves voluntary strength.

Sustained release of the active ingredient from Sirdalud MR capsules (MR = modified release) means that high initial peaks are avoided and therapeutic plasma concentrations maintained over 24 hours.

Pharmacokinetics

Tablets

Absorption and distribution
Tizanidine is rapidly absorbed. Peak plasma concentration is attained approx. 1 hour after administration. Mean absolute bioavailability is 34%. Mean steady-state volume of distribution (V_{SS}) following intravenous administration is 160 litres. Plasma protein binding is 30%. Within-patient variation in pharmacokinetic parameters (C_{max} and AUC) is relatively low, enabling reliable prediction of plasma levels following oral administration.

Metabolism / Elimination
The drug has been shown to be rapidly and extensively metabolized by the liver. Tizanidine is mainly metabolized by CYP1A2 *in vitro*. The metabolites appear to be inactive. Their excretion is primarily via the kidneys (70%). Excretion of total radioactivity (i.e. unchanged substance plus metabolites) is biphasic, with a rapid initial phase ($t_{½}$ = 2.5 hours) and a slower elimination phase ($t_{½}$ = 22 hours). Only small amounts of unchanged substance (approx. 2.7%) are excreted renally. The mean elimination half-life of the unchanged substance is 2–4 hours.

MR capsules
Sustained release of tizanidine from Sirdalud MR capsules results in a smoother pharmacokinetic profile by avoiding high initial peaks in the plasma. Under steady-state conditions, peak plasma concentrations are attained within approx. 6 hours; they correspond to approx. 40% of the peak plasma concentrations attained after the same daily doses of Sirdalud in tablet form are given in three divided doses. Therapeutic plasma levels are maintained for 24 hours.

Concomitant food intake has no effect on the pharmacokinetic profile of Sirdalud tablets or capsules.

Preclinical data

Mutagenicity
No evidence of mutagenic potential was found in a number of different *in vitro* and *in vivo* studies.

Carcinogenicity
In studies in rats and mice, there was no evidence of carcinogenic potential.

Reproductive toxicity
There were no embryotoxic or teratogenic effects in pregnant rats and rabbits following administration of doses of up to 100 mg/kg.
In studies, female rats were given daily doses of 3, 10 and 30 mg/kg from before mating through to lactation or from late pregnancy until weaning of the young. Administration of 10 and 30 mg/kg daily caused both prolonged gestation and dystocia, resulting in an increase in prenatal mortality.

Other information

Shelf-life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
See folding box

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box.

Information last revised

December 2005

Approval date (text)

14 December 2005

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacis

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