1 Trade names

SIRDALUD® tablets: 2 mg, 4 mg

2 Description and composition

Pharmaceutical forms

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

The 2 mg tablets and the 4 mg tablets can be divided in two equal halves [30].

Active substance

Tablets containing 2 mg, 4 mg tizanidine hydrochloride.

Excipients

Tablets

Colloidal anhydrous silica, stearic acid, microcrystalline cellulose, anhydrous lactose.

Information might differ in some countries.

3 Indications

Tablets

Treatment of painful muscle spasms

- associated with static and functional disorders of the spine (cervical and lumbar syndromes) [1,27],
- following surgery, e.g. for herniated intervertebral disc or osteoarthritis of the hip [1,27].

Tablets

Treatment of spasticity due to neurological disorders

- e.g. multiple sclerosis, chronic myelopathy, degenerative spinal cord diseases, cerebrovascular accidents, and cerebral palsy [1,27].

4 Dosage regimen and administration

Sirdalud has a narrow therapeutic index and a high inter-patient variability in tizanidine plasma concentrations which requires individualized dose adjustment [27,28].

A low starting dose of 2 mg three times daily can minimize the risk for adverse effects [27]. The dose should be carefully adjusted upward according to the needs of the individual patient. Sirdalud tablet and Sirdalud MR capsule can be taken with or without food (see section 11 Clinical pharmacology).

Relief of painful muscle spasms

Tablets

The usual dose is 2 to 4 mg three times daily in tablet form. In severe cases, an extra dose of 2 or 4 mg may be taken, preferably at night to minimize sedation.

Spasticity due to neurological disorders

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.

Special populations

Pediatric patients

Experience in patients below 18 years of age is limited and the use of Sirdalud in this population is not recommended.

Geriatric patients (65 years of age or older)

Experience with the use of Sirdalud in the elderly is limited [27,28]. Therefore, it is recommended to start treatment at the lowest dose and increases should be done in small steps according to tolerability and efficacy.

Renal impairment

In patients with creatinine clearance <25 mL/min, it is recommended to start treatment at 2 mg once daily [18]. Increase in dosage should be done in small steps according to tolerability and efficacy. If efficacy has to be improved, it is advisable to first increase the strength of daily dose before increasing the frequency of administration (see section 6 Warnings and precautions).

Hepatic impairment

Use of Sirdalud in patients with severe hepatic impairment is contraindicated (see section 5 Contraindications).

While Sirdalud is extensively metabolized in the liver, limited data are available in this population (see section 11 Clinical pharmacology - Pharmacokinetic properties). Its use has been associated with reversible abnormality in liver function tests (see sections 6 Warnings and precautions and 7 Adverse drug reactions). Sirdalud should be used with caution in patients with moderate hepatic impairment and treatment should be started with the lowest dose. Afterwards, increase in dosage should be done carefully and according to patient tolerability [27].

Discontinuation of treatment

If Sirdalud has to be discontinued, the dosage should be slowly down titrated, particularly in patients who have received high doses for a longer period of time to avoid or minimize the risk of rebound hypertension and tachycardia (see section 6 Warnings and precautions).

5 Contraindications

- Known hypersensitivity to tizanidine or to any of the excipients.
- Severely impaired hepatic function (see section 11 Clinical pharmacology - Pharmacokinetic properties).
- Concomitant use of tizanidine with strong inhibitors of CYP1A2 such as fluvoxamine or ciprofloxacin is contraindicated (see section 8 Interactions) [24,25].

6 Warnings and precautions

CYP inhibitors

The concomitant use of Sirdalud with moderate CYP1A2 inhibitors is not recommended (see section 8 Interactions) [25].

Caution should be exercized when Sirdalud is given with drugs known to increase the QT interval (see section 8 Interactions) [27].

Hypotension

Hypotension may occur during treatment with Sirdalud (see section 7 Adverse drug reactions) and also as a result of drug interactions with CYP1A2 inhibitors and/or antihypertensive drugs (see section 8 Interactions). Severe manifestations of hypotension such as loss of consciousness and circulatory collapse have also been observed [26].

Withdrawal syndrome

Rebound hypertension and tachycardia have been observed after sudden withdrawal of Sirdalud, 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. Sirdalud should not be stopped abruptly, but rather gradually down titrated (see sections 4 Dosage regimen and administration and 7 Adverse drug reactions) [26].

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 serum glutamic pyruvic transaminase (SGPT) or serum glutamic-oxaloacetic transaminase (SGOT) are persistently above three times the upper limit of the normal range [2,3,4].

Patients with renal impairment

In patients with creatinine clearance <25 mL/min systemic exposure to tizanidine may increase up to 6 times compared to patient with normal renal function [18]. Therefore, it is recommended to start treatment at 2 mg once daily (see sections 4 Dosage regimen and administration and 11 Clinical pharmacology - Pharmacokinetic properties).

Hypersensitivity reactions

Hypersensitivity reactions including anaphylaxis, angioedema, dermatitis, rash, urticaria, pruritus and erythema have been reported in association with tizanidine. Careful observation of the patient is recommended for one to two days after the first dose is administered. If anaphylaxis or angioedema with anaphylactic shock or difficulty of breathing is observed treatment with Sirdalud should be discontinued immediately and appropriate medical treatment should be instituted [32].

Driving and using 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.

7 Adverse drug reactions

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.

Adverse drug reactions from clinical trials (Table 7-1) are listed according to the system organ class in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness. In addition the corresponding frequency using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions [27]

Psychiatric disorders	
Common	Insomnia, sleep disorder
Nervous system disorders	

Very common:	Somnolence, dizziness
Cardiac disorders	
Uncommon:	Bradycardia
Vascular disorders	
Common:	Hypotension
Gastrointestinal disorders	
Very common:	Gastrointestinal disorder, dry mouth
Common	Nausea
Musculoskeletal and connective tissue disorders	
Very common	Muscular weakness
General disorders and administration site conditions	
Very common:	Fatigue
Investigations	
Common:	Blood pressure decreased, transaminases increased

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been reported during post approval use of Sirdalud via spontaneous reports and literature cases. Since these reactions are reported voluntarily from a population of uncertain size, and are subject to confounding factors, it is not possible to reliably estimate their frequency which is therefore quoted as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders:	Hypersensitivity reactions including anaphylaxis, angioedema and urticaria [32]
Psychiatric disorders:	Hallucination, confusional state [27]
Nervous system disorders:	Vertigo [27]
Vascular disorders:	Syncope [27]
Eye disorders:	Vision blurred [27]
Hepatobiliary disorders:	Hepatitis [4,8], hepatic failure [26]
Skin and subcutaneous tissue disorders:	Rash, erythema, pruritus, dermatitis [32]
General disorders and administration site conditions:	Asthenia, withdrawal syndrome [27]

Withdrawal syndrome

Rebound hypertension and tachycardia have been observed after sudden withdrawal of Sirdalud. In extreme cases, rebound hypertension might lead to cerebrovascular accident (see sections 6 Warnings and precautions and 8 Interactions) [26].

8 Interactions

Concomitant administration of drugs known to inhibit the activity of CYP1A2 may increase the plasma levels of tizanidine (see section 11 Clinical Pharmacology - Pharmacokinetic properties). The increased plasma levels of tizanidine may result in overdose symptoms such as QT(c) prolongation (see also section 10 Overdosage) [26].

Concomitant administration of drugs known to induce the activity of CYP1A2 may decrease the plasma levels of tizanidine (see section 11 Clinical pharmacology - Pharmacokinetic properties). The decreased plasma levels of tizanidine may reduce the therapeutic effect of Sirdalud [28].

Observed interactions resulting in a contraindication

Concomitant use of Sirdalud with fluvoxamine or ciprofloxacin, both CYP1A2 inhibitors, is contraindicated. Concomitant use of Sirdalud with fluvoxamine or ciprofloxacin resulted in a 33-fold and 10-fold increase in tizanidine area under curve (AUC), respectively (see section 5 Contraindications). Clinically significant and prolonged hypotension may result along with somnolence, dizziness and decreased psychomotor performance (see section 6 Warnings and precautions) [24,25]. The increased plasma levels of tizanidine may result in overdose symptoms such as QT(c) prolongation (see also section 10 Overdosage)

Observed interactions resulting in a concomitant use not recommended

Co-administration of Sirdalud with other inhibitors of CYP1A2 such as antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, fluoroquinolones (enoxacin, pefloxacin, norfloxacin), rofecoxib, oral contraceptives, and ticlopidine is not recommended (see section 6 Warnings and precautions) [24,25].

Observed interactions to be considered

Caution should be exercised when Sirdalud is given with drugs known to prolong the QT interval (including but not limited to cisapride, amytriptyline and azithromycin) (see section 6 Warnings and precautions) [28].

Antihypertensives

Concomitant use of Sirdalud with antihypertensives, including diuretics, may occasionally cause hypotension (see section 6 Warnings and precautions) and bradycardia. In some patients rebound hypertension and tachycardia have been observed upon abrupt discontinuation of Sirdalud when concomitantly used with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident (see sections 6 Warnings and precautions and 7 Adverse drug reactions) [26].

Rifampicin

Concomitant administration of Sirdalud with rifampicin results in 50% decrease in tizanidine concentrations. Therefore, the therapeutic effects of Sirdalud may be reduced during treatment with rifampicin, which may be of clinical significance in some patients. Long term co-

administration should be avoided and if co-administration is considered a careful dose adjustment (increase) may be required [28].

Cigarette smoke

Administration of Sirdalud in smokers (>10 cigarettes per day) results in about 30% decrease in tizanidine systemic exposure. Long-term therapy with Sirdalud in heavy smokers may require higher doses than the average doses [28].

Alcohol

While on Sirdalud therapy, alcohol consumption should be minimized or avoided as it may increase the potential for adverse events (e.g. sedation and hypotension). The central nervous system depressant effects of alcohol may be enhanced by Sirdalud [28].

Anticipated interactions to be considered

Sedatives, hypnotics (e.g. benzodiazepine or baclofen), and other drug such as antihistamines may enhance the sedative action of tizanidine [28].

Sirdalud should be avoided when using with other alpha-2 adrenergic agonists (such as clonidine) because of their potential additive hypotensive effect [28].

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

As there is limited experience with the use of Sirdalud in pregnant women, it should not be used during pregnancy unless the benefit clearly outweighs the risk.

Animal data

Reproduction studies performed in rats at a dose of 3 mg/kg/day and in rabbits at 30 mg/kg/day did not show evidence of teratogenicity. In female rats, dose levels of 10 and 30 mg/kg/day increased the duration of gestation. Prenatal and postnatal pup loss was increased and development retardation occurred. At these doses, dams showed marked signs of muscle relaxation and sedation. Based on body surface area (BSA), these doses were 2.2 and 6.7 times the maximum recommended human dose of 0.72 mg/kg/day.

9.2 Lactation

Risk summary

Small amounts of tizanidine are excreted in rat milk [6]. Since no human data are available Sirdalud should not be given to women who are breast-feeding.

9.3 Females and males of reproductive potential

Pregnancy testing

Sexually-active females of reproductive potential are recommended to have a pregnancy test prior to starting treatment with Sirdalud.

Contraception - Females

Females of reproductive potential should be advised that animal studies have been performed showing Sirdalud to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) when using Sirdalud during treatment and for 1 day after stopping treatment with Sirdalud tablet and for 2 days after stopping treatment with Sirdalud MR capsule [33,34].

InfertilityThere is no data on the effect of Sirdalud on human fertility.

No impairment of fertility was observed in male rats at a dose of 10 mg/kg/day, and in female rats at a dose of 3 mg/kg/day. Fertility was reduced in male rats receiving 30 mg/kg/day and in female rats receiving 10 mg/kg/day. Based on body surface area, these doses were 6.7 and 2.2 times the maximum recommended human dose of 0.72 mg/kg. At these doses, behavioral effects and clinical signs including marked sedation, weight loss and ataxia were observed in rats. [22,29,31,33].

10 Overdosage

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.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

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 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 reduced. In addition to its muscle-relaxant properties, tizanidine also exerts a moderate central analgesic effect [9,10,11,12].

Pharmacodynamics (PD)

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.

The antispastic activity (measured by the Ashworth score and pendulum test) and adverse effects (heart rate and blood pressure) of Sirdalud are related to plasma tizanidine concentrations [28].

Pharmacokinetics (PK)

Absorption

Tizanidine is rapidly and almost completely absorbed, reaching peak plasma concentration approximately 1 hour after dosing [13-16]. Mean absolute bioavailability from the tablet formulation is about 34% (coefficient of variation - CV 38%) due to extensive first-pass metabolism [13]. The mean maximum plasma concentration (Cmax) of tizanidine is 12.3 ng/mL (CV 10%) and 15.6 ng/mL (CV 13%) after single and repeated administration of 4 mg doses, respectively [17].

Concomitant food intake has no relevant influence on the pharmacokinetic profile of tizanidine (given as 4 mg tablets or 12 mg MR capsules). Although Cmax is about one-third higher after administration of the tablet under fed conditions, this is not considered to be of any clinical relevance, and absorption (AUC) is not significantly affected [19,20].

Distribution

Mean steady-state volume of distribution (VSS) following i.v. administration is 2.6 L/kg (CV 21%) [13]. Plasma protein binding is 30%.

Biotransformation/metabolism

The drug has been shown to be rapidly and extensively (about 95%) metabolized by the liver [28]. Tizanidine is mainly metabolized by cytochrome P450 1A2 *in vitro* [24]. 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 after Sirdalud tablet administration [13-16] and 8 to 9 hours after Sirdalud MR capsule administration [34]. Excretion is primarily via the kidneys (approximately 70% of dose) in the

form of metabolites, with unchanged drug accounting for only about 4.5% of urinary recovery [28].

Linearity

Tizanidine has linear pharmacokinetics over the dose range 1 to 20 mg [28].

Bioavailability of modified-release (MR) formulation

Administration of the sustained release formulation, Sirdalud MR 12 mg capsules, results in a smoother pharmacokinetic profile by avoiding high initial peaks and maintaining therapeutic plasma concentrations over 24 hours compared with Sirdalud 4 mg tablet given 3 times daily. Following administration of the Sirdalud MR 12 mg capsule the maximum mean plasma concentrations are reached within about 8.5 hours, amounting to approximately half (6.6 ng/mL, CV 5%) those obtained when Sirdalud 4 mg tablet is given 3 times daily (see absorption), whereas the total daily systemic exposure remains unchanged [17].

Special populations

Renal impairment

In patients with 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 6 Warnings and precautions) [18].

Hepatic impairment

No specific studies were conducted in this population. As tizanidine is extensively metabolized in the liver by the CYP1A2 enzyme, hepatic impairment may increase its systemic exposure [28]. Sirdalud is contraindicated in patients with severe hepatic impairment (see section 5 Contraindications).

Geriatric patients (65 years of age or above)

Pharmacokinetic data in this population are limited [28].

Gender

Gender has no clinically significant effect on the pharmacokinetics of tizanidine [15].

Ethnicity

Impact of ethnic sensitivity and race on the pharmacokinetics of tizanidine has not been studied.

12 Clinical studies

No recent clinical data regarding the approved indications for Sirdalud are available.

13 Non-clinical safety data

Preclinical data reveal no special hazard for humans at the recommended therapeutic dose based on conventional studies of repeated dose toxicity, mutagenicity and carcinogenic potential. [21,22,29,31]

Acute toxicity

The acute toxicity of tizanidine is of a low order. Signs of overdosage were seen related to the drug's pharmacological action.

Repeat dose 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 central nervous system (CNS) stimulation (e.g. motor excitation, aggressiveness, tremor, and convulsions), and occurred mainly at the highest dose level.

Electrocardiogram (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.

Carcinogenicity and Mutagenicity

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

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

For reproductive toxicity, please see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities

None known.

Storage Condition

Do not store above 30°C/Store below 30°C

Sirdalud must be kept out of the sight and reach of children [23].

Instructions for use and handling

Country specific.

Shelf Life

24 Months

15 Marketing Authorization Holder

Sirdalud 2mg Tablet- NAFDAC Reg No.: 04-0816

Sirdalud 4mg Tablet- NAFDAC Reg No.: A4-1452

Novartis Nigeria Limited

Landmark House,

Plot 52-54 Isaac John Street,

Ikeja GRA, Lagos.

Nigeria

Tel: +234 1 7009911