1. Name of the medicinal product

Relezin® 4mg Tablets

2. Qualitative and quantitative composition

Material Name	Function	Amount (mg) / one tablet
Tizanidine Hydrochloride	Active material	4.58*
Core In-active ingredients:-		
Microcrystalline Cellulose	Diluent	94.00
Lactose Anhydrous	Diluent	115.92
Colloidal silicon dioxide	Glidant	1.10
Stearic acid	Lubricant	4.40
Total		220.0

* Equivalent to 4 mg Tizanidine.

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Tablets

Relezin® 4mg Tablets: White to off -white round flat tablets imposed with E15 on one side and crossed on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of spasticity associated with multiple sclerosis or with spinal cord injury or disease.

4.2 Posology and method of administration

Route of administration: Orally.

The effect of tizanidine on spasticity is maximal within 2-3 hours of dosing and it has a relatively short duration of action. The timing and frequency of dosing should therefore be tailored to the individual, and tizanidine should be given in divided doses, up to 3-4 times daily, depending on the patient's needs. There is considerable variation in response

between patients so careful titration is necessary. Care should be taken not to exceed the dose producing the desired therapeutic effect.
It is usual to start with a single dose of 2mg increasing by 2mg increments at no less than half-weekly intervals. The optimum therapeutic response is generally achieved with a daily dose of between 12 and 24mg, administered in 3 or 4 equally spaced doses. Single doses should not exceed 12mg. The total daily dose should not exceed 36mg.
Adverse events may occur at therapeutic doses but these can be minimised by slow titration so that in the large majority of patients they are not a limiting factor.

Discontinuing therapy

If therapy needs to be discontinued, particularly in patients who have been receiving high doses for long periods, the dose should be decreased slowly.

Use in elderly

Experience in the elderly is limited and use of tizanidine is not recommended unless the benefit of treatment clearly outweighs the risk. Pharmacokinetic data suggest that renal clearance in the elderly may in some cases be significantly decreased. Caution is therefore indicated when using tizanidine in elderly patients.

Children and adolescents

Experience with tizanidine in patients under the age of 18 years is limited. Tizanidine is not recommended for use in this population.

Patients with renal impairment

In patients with renal insufficiency (creatinine clearance < 25 ml/min) treatment should be started with 2mg once daily with slow titration to achieve the effective dose. Dosage increases should be in increments of no more than 2mg according to tolerability and effectiveness. If efficacy has to be improved, it is advisable to slowly increase the once-daily dose before increasing the frequency of administration. Renal function should be monitored as appropriate in these patients.

Patients with hepatic impairment

Tizanidine is contraindicated in patients with significantly impaired hepatic function.

4.3 Contraindications

- The use of tizanidine in patients with significantly impaired hepatic function is contraindicated, because tizanidine is extensively metabolised by the liver.
- Concomitant use of tizanidine with strong inhibitors of CYP1A2 such as fluvoxamine or ciprofloxacin is contraindicated.
- 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.

Hypotension

Hypotension may occur during treatment with tizanidine and also as a result of drug

interactions with CYP1A2 inhibitors and/or antihypertensive drugs. 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.

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.

Cardiovascular, hepatic or renal disorders

Caution is required in patients with cardiovascular disorders, coronary artery disease or renal or hepatic disorders. Regular clinical laboratory and ECG monitoring is recommended during treatment with tizanidine.

Hepatic dysfunction

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

This medicinal product contains lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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. Clinically significant and prolonged hypotension may result along with somnolence, dizziness and decreased psychomotor

performance. Coadministration 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.
The increased plasma levels of tizanidine may result in overdose symptoms such as QT(c) prolongation. Concomitant use of tizanidine (in high doses) with other products that could cause QT (c) prolongation is not recommended. Electrocardiographic monitoring may be advisable.

Antihypertensives

As tizanidine may induce hypotension it may potentiate the effect of antihypertensive products, including diuretics, and caution should therefore be exercised in patients receiving blood pressure lowering products. Caution should also be exercised when tizanidine is used concurrently with β-adrenoceptor blocking substances or digoxin as the combination may potentiate hypotension or 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.

Oral contraceptives

Pharmacokinetic data following single and multiple doses of tizanidine suggested that clearance of tizanidine was reduced by approximately 50% in women who were concurrently taking oral contraceptives. The possibility of a clinical response and/or adverse effects occurring at lower doses of tizanidine should be borne in mind when prescribing tizanidine to a patient taking the contraceptive pill.

Other

Alcohol and sedatives may enhance the sedative action of tizanidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

The adverse effects are classified below by system organ class according to the following convention:
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, including isolated reports (<1/10,000)
Not known (cannot be estimated from the available data)

Psychiatric disorders

Rare:	Hallucinations, insomnia, sleep disorders
Not known:	Anxiety disorders, confusional state

Nervous system disorders

Common:	Somnolence, dizziness
Not known:	Headache, ataxia

Eye disorders

Not known:	Accommodation disorder

Cardiac disorders

Common:	Bradycardia, tachycardia
Not known:	QT prolongation

Vascular disorders

Common:	Hypotension,, rebound hypertension

Gastrointestinal disorders

Common:	Dry mouth
Rare:	Nausea, gastrointestinal disorder

Hepato-biliary disorders

Rare:	Increases in hepatic serum transaminases
Very rare:	Hepatitis, hepatic failure

Skin and subcutaneous tissue disorders

Rare:	Allergic reactions (e.g. pruritus and rash)

Musculoskeletal, connective tissue disorders

Rare:	Muscular weakness

General disorders and administration site conditions

Common	Fatigue
Not known:	Absence of appetite

Investigations

Common:	Blood pressure decrease
Rare:	Transaminase increase

* The hallucinations are self-limiting, without evidence of psychosis, and have invariably occurred in patients concurrently taking potentially hallucinogenic substances, e.g. anti-depressants.

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.

4.9 Overdose

Symptoms

Nausea, vomiting, hypotension, bradycardia, QT prolongation, dizziness, miosis, respiratory distress, coma, restlessness, somnolence.

Treatment

General supportive measures are indicated and an attempt should be made to remove ingested substance from the gastro-intestinal tract using gastric lavage or by repeated administration of high doses of activated charcoal. The patient should be well hydrated as forced diuresis is expected to accelerate the elimination of tizanidine. Further treatment should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Musculo-skeletal system; muscle relaxants; centrally acting agents; 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 alpha2-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. Tizanidine has no direct effect on skeletal muscle, the neuromuscular junction or on monosynaptic spinal reflexes. In addition to its muscle-relaxant properties, tizanidine also exerts a moderate central analgesic effect.
In humans, tizanidine reduces pathologically increased muscle tone, including resistance to passive movements and alleviates painful spasms and clonus.

5.2 Pharmacokinetic properties

Absorption
Tizanidine is rapidly absorbed, reaching peak plasma concentration in approximately 1 hour after dosing.
Distribution
Tizanidine is only about 30% bound to plasma proteins. Mean steady-state volume of distribution (VSS) following I.V. administration is 2.6 L/kg.
Metabolism
Although tizanidine is well absorbed, first pass metabolism limits plasma availability to 34% of that of an intravenous dose. Tizanidine undergoes rapid and extensive metabolism in the liver. Tizanidine is mainly metabolized by cytochrome P450 1A2 *in vitro*.
Elimination
The metabolites are primarily excreted via the renal route (approximately 70% of the administered dose) and appear to be inactive. The elimination half-life of tizanidine from plasma is 2-4 hours in patients.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

- Microcrystalline cellulose
- Lactose Anhydrous
- Colloidal silicon dioxide
- Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Relezin® Tablets are packed in PVC/PVDC /Aluminum blister then packed in cardboard cartons with a multi folded leaflet.

Pack size: 30 Tablets/pack

6.6 Special precautions for disposal and other handling

Any unused product or waste should be disposed of in accordance with local requirements.

7. Marketing authorization holder

The United Pharmaceutical Mfg. Co. Ltd.
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Tel: + 962 (6) 416 2901
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8. Marketing authorization number(s)

Authorization number: 2-16-6-39812

9. Date of first authorization/renewal of the authorization

Date of first Authorization: 07/08/1991
Date of renewal of the authorization: 03/12/2012

10. Date of revision of the text

November, 2012.