Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tizanidine Dr. Reddy's 4mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg of Tizanidine (as Tizanidine hydrochloride)

Excipient: lactose in the form of lactose, anhydrous 94.42 mg per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off white, oval, flat, bevelled edged tablets embossed with ‘R180’ on one side and quadrisecting score on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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

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 needs. There is considerable variation in response between patients so careful titration is necessary. It is usual to start with a single dose of 2mg increasing by 2mg increments at no less than half-weekly intervals. Care should be taken not to exceed the dose producing the desired therapeutic effect.

Single doses of Tizanidine should not exceed 12mg. The total daily dose should not exceed 36mg, although it is usually not necessary to exceed 24mg daily. Secondary pharmacological effects (see section 4.8) 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.

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

Patients with Renal impairment
In patients with renal insufficiency (creatinine clearance <25ml/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. 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.

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 (see section 4.4).

4.3 Contraindications

Known hypersensitivity to Tizanidine or to any of the excipients.

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 potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Cytochrome P_{450} (CYP) inhibitors

Concomitant use of tizanidine with CYP1A2 inhibitors is not recommended (see sections 4.3 and 4.5)

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

Use in Renal Impairment.
Patients with renal impairment may require to lower doses and therefore caution should be exercised when using Tizanidine in these patients (see section 4.2).

Hypotension
Hypotension may occur during treatment with tizanidine (see section 4.8) and also as a result of drug interactions with CYP1A2 inhibitors and/or antihypertensive drugs (see section 4.5). 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 4.2, 4.5 and 4.8).

Hepatic disorders
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 liver dysfunction such as unexplained nausea, anorexia or tiredness. Treatment with Tizanidine should be discontinued if serum levels of serum glutamic-pyruvic-transaminase (SGPT) and/or serum-glutamic-oxaloacteic transaminase (SGOT) 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.

Renal Insufficiency
Treatment of patients with renal insufficiency should follow the dosage adjustment stated in section 4.2 Posology and method of administration.
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

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). Clinically significant and prolonged hypotension may result along with somnolence, dizziness and decreased psychomotor performance (see section 4.4).

Co-administration of tizanidine with other CYP1A2 inhibitors such as some antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, some
fluoroquinolones (enoxacin, norfloxacin pefloxacin) , rofecoxib, oral contraceptives and ticlopidine is not recommended (see section 4.4).

The increased plasma levels of Tizanidine may result in overdose symptoms such as QT(c) prolongation (see also section 4.9). Concomitant use of tizanidine (in high doses) with other products that could cause QT(c) prolongation is not recommended.

Concomitant use of Tizanidine with antihypertensives including diuretics, may occasionally cause hypotension (see section 4.4 Special warnings and precautions for use) and bradycardia. Caution should also be exercised when Tizanidine is used concurrently with β-adrenoreceptor 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 (see section 4.4 and section 4.8).

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 contraceptives. Although no specific pharmacokinetic study has been conducted to investigate a potential interaction between oral contraceptives and Tizanidine, the possibility of a clinical response and/or adverse effects occurring at lower doses of Tizanidine should not be borne in mind when prescribing Tizanidine to a patient taking the contraceptive pill. Clinically significant interactions have not
been reported in clinical trials.

Alcohol or 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 breast 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 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 (>1/1000 to <1/100), rare (>1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data)

Cardiac disorders

Common: Bradycardia, tachycardia (see sections 4.4 and 4.5)

Not known: QT prolongation has been reported in post-marketing surveillance (see section 4.9)

Nervous system disorders

Common: Drowsiness**, somnolence, dizziness**

Rare: sleep disorders, insomnia

Not known: Headache, ataxia

Eye disorders

Not known: Accommodation disorder

Gastrointestinal disorders

Common: Dry mouth**

Rare: Nausea**, gastrointestinal disorder**

Skin and subcutaneous tissue disorders

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

Musculoskeletal and connective tissue and disorders

Rare: Muscle weakness

Vascular disorders

Common: Hypotention, rebound hypertension (see sections 4.4 and 4.5)

General disorders and administration site conditions

Common: Fatigue **

Not known: absence of appetite

Hepato-biliary disorders

Very rare: Hepatitis, hepatic failure

Psychiatric disorders

Rare: Hallucination*, insomnia, sleep disorder

Not known: Anxiety disorders

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

** With slow upward titration of the dose of tizanidine these effects are usually not severe enough to require discontinuation of treatment.

With low doses, such as those recommended for the relief of painful musclespasms, 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 and section 4.5).

4.9 Overdose

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

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

Treatment:
General supportive measures are indicated and an attempt should be made to remove un-ingested substance from the gastro-intestinal tract using lavage or activated charcoal. The patient should be well hydrated. Forced diuresis is expected to accelerate the elimination of Tizanidine. Further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants centrally acting agents, other centrally acting agents.

ATC code: M03BX02

Tizanidine is a $\alpha_{\square}$-adrenergic receptor agonist within the central nervous system at supra-spinal and spinal levels. This effect results in inhibition of polysnaptic reflex activity. Tizanidine has no direct effect of skeletal muscle, the neuromuscular junction or on monosynaptic spinal reflexes.

In humans, Tizanidine reduces pathologically increased muscle tone, including resistance to passive movements and alleviates spasms and clonus.

5.2 Pharmacokinetic properties

Tizanidine is rapidly absorbed, reaching peak plasma concentrations in approximately I hour. Tizanidine is only about 30% bound to plasma proteins and, in animal studies, was found to readily cross the blood-brain barrier. Although Tizanidine is well absorbed, first pass metabolism limits availability to 34% of that of an intravenous dose.

Tizanidine undergoes rapid and extensive metabolism in the liver and the pattern of biotransformation in animals and humans is qualitatively similar. The metabolites are primarily excreted via the renal route (approximately 70% of the administered dose) and appear to be inactive. Renal excretion of the parent compound is approximately 53% after a single 5mg dose and 66% after dosing with 4mg three times daily. The elimination half-life of Tizanidine from plasma is 2 - 4 hours in patients.

Concomitant food intake has no influence on the pharmacokinetic profile of Tizanidine tablets.

5.3 Preclinical safety data

Acute Toxicity
Tizanidine possesses a low order of acute toxicity. Signs of overdose were seen after single doses >40mg/kg in animals and are related to the pharmacological action of the substance.

Repeat dose toxicity
The toxic effects of Tizanidine are mainly related to its pharmacological action. At doses of 24 and 40mg/kg per day in sub-chronic rodent studies, the α□agonist effects resulted in central nervous system stimulation, eg motor excitation, aggressiveness, tremor and convulsions.

Signs related to centrally mediated muscle relaxation, e.g. sedation and ataxia, were frequently observed at lower dose levels in sub-chronic oral studies with dogs. Such signs, related to myotonolytic activity of the substance, were noted at 1 to 4mg/kg per day in a 13 week dog study, and at 1.5mg/kg per day in a 52 week dog study.

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses of 1.0mg/kg per day and above.

Slight increases in hepatic serum transaminases were observe in a number of toxicity studies at higher dose levels. They were not consistently associated with histopathological changes in the liver.

Mutagenicity
Various *in vitro* assays as well as *in vivo* assays produced no evidence of mutagenic potential of Tizanidine.

Carcinogenicity
No evidence for carcinogenicity was demonstrated in two long-term dietary studies in mice (78 weeks) and rats (104 weeks), at dose levels up to 9 mg/kg per day in rats and up to 16mg/kg per day in mice. At these dose levels, corresponding to the maximum tolerated dose, based on reductions in growth rate, no neoplastic or pre-neoplastic pathology, attributable to treatment, was observed.

Reproductive toxicity
No embryotoxicity or tetraogenicity occurred in pregnant rats and rabbits at dose levels up to 30mg/kg per day of Tizanidine. However, doses of 10 - 100mg/kg per day in rats were maternally toxic and resulted in developmental retardation of fetuses as seen by lower fetal body weights and retarded skeletal ossification.

In female rats, treatment prior to mating through lactation or during late pregnancy until weaning of the young, a dose-dependent (10 and 30mg/kg per day) prolongation of gestation time and dystocia occurred, resulting in an increased fetal mortality and delayed development. These effects were attributed to the pharmacological effect of Tizanidine. No developmental effects occurred at 3 mg/kg per day although sedation was induced in the treated rats. Passage of Tizanidine and/or its metabolites into milk of rodents is known to occur.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Microcrystalline cellulose
Colloidal anhydrous silica
Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVdC - aluminium blisters.

Blister packs of 15, 20, 30, 100 and 120 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Dr**.** Reddy’s Laboratories (UK) Ltd
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Beverley
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HU17 0LD
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8 MARKETING AUTHORISATION NUMBER

PA 1364/2/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 2009

10 DATE OF REVISION OF THE TEXT

August 2011