SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tizanidine 2 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of tizanidine (as 2.290 mg tizanidine hydrochloride).

Excipient(s) with known effect:
Each tablet contains 57.910 mg of lactose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White to off-white, biconvex, round, tablets, debossed "T2" on one side and scoreline on the other.

The scoreline 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

Posology

For oral 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'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 2 mg increasing by 2 mg increments at no less than half-weekly intervals.

The total daily dose should not exceed 36 mg, although it is usually not necessary to exceed 24 mg 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 be in some cases significantly decreased by up to three fold. 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.

Renal impairment

In patients with renal insufficiency (creatinine clearance < 25 ml/min) treatment should be started with 2 mg once daily with slow titration to achieve the effective dose. Dosage increases should be in increments of no more than 2 mg 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.

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 contra-indicated (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Hypersensitivity to the active substance(s) or to any excipients listed in section 6.1.

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 Tizanidine should be discontinued if serum levels of SGPT (serum glutamic-pyruvic transaminase)or SGOT (serum glutamic-oxaloacteic transaminase) 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.

Tizanidine should be kept out of the reach of children.

This medicinal product contains lactose. 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 (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

As tizanidine may induce hypotension it may potentiate the effect of antihypertensive products. 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. Caution should therefore be exercised in patients receiving blood pressure lowering products. 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).

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.

Caution should be exercised when tizanidine is prescribed with substances known to increase the QT interval.

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. 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 be borne in mind when prescribing tizanidine to a patient taking the contraceptive pill. Clinically significant interactions have not been reported in clinical trials.

Other

Alcohol or sedatives may enhance the sedative action of tizanidine.

4.6 Fertility, pregnancy and lactation

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 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000). Not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1

Immune system disorders

not known: hypersensitivity reactions

Psychiatric disorders

Rare: hallucinations*, insomnia, sleep disorder

Nervous system disorders

Common: drowsiness** , somnolence, dizziness**
not known: Dysarthria

Cardiac disorders

Common: bradycardia

Vascular disorders

Common: hypotension

Gastrointestinal disorders

Common: dry mouth**
Rare: nausea**, gastrointestinal disorder**
not known: abdominal pain, vomiting

Hepatobiliary disorders

Very rare: acute hepatitis, hepatic failure

Skin and subcutaneous tissue disorders

not known: pruritus, rash

Musculoskeletal and connective tissue disorders

Rare: Muscle weakness***

General disorders and administration site conditions

Common: fatigue**

Investigations

Common: blood pressure decrease**

Rare: Increases in hepatic serum transaminases (reversible on stopping treatment)

* 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 slow upward titration of the dose of tizanidine these effects are usually not severe enough to require discontinuation of treatment.
*** In controlled clinical trials it was clearly demonstrated that tizanidine does not adversely affect muscle strength.

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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Clinical experience is limited. In one adult case, who ingested 400 mg tizanidine, recovery was uneventful. This patient received mannitol and furosemide.

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

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 tizanidine. Further treatment should be symptomatic. The patient should be well hydrated

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 an α_2-adrenergic receptor agonist within the central nervous system at supra-spinal and spinal levels. This effect results in inhibition of spinal polysynaptic reflex activity. Tizanidine has no direct effect on 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 painful spasms and clonus.

5.2 Pharmacokinetic properties

Tizanidine is rapidly absorbed, reaching peak plasma concentration in approximately 1 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 plasma 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 5 mg dose and 66% after dosing with 4 mg 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 overdosage were seen after single doses > 40 mg/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 40 mg/kg per day in subchronic and chronic rodent studies, the α_2-agonist effects resulted in central nervous system stimulation, e.g. 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 subchronic and chronic oral studies with dogs. Such signs, related to the myotonolytic activity of the substance, were noted at 1 to 4 mg/kg per day in a 13 week dog study, and at 1.5 mg/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 1.0 mg/kg per day and above.

Slight increases in hepatic serum transaminases were observed 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 16 mg/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 teratogenicity occurred in pregnant rats and rabbits at dose levels up to 30 mg/kg per day of tizanidine. However, doses of 10-100 mg/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, treated prior to mating through lactation or during late pregnancy until weaning of the young, a dose-dependent (10 and 30 mg/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 dams.

Passage of tizanidine and/or its metabolites into milk of rodents is known to occur.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Cellulose, microcrystalline

Silica, colloidal anhydrous
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, 30,50, 100, 120 and clinical pack 500 (10x50) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point, Whistler Drive,
Castleford, WF10 5HX,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER

PL 00289/0648

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 December 2006

10. DATE OF REVISION OF THE TEXT

21/10/2021