Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tizaflex 4 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 mg tablet contains:
4 mg tizanidine (as 4.576 mg tizanidine hydrochloride)
Excipient with known effect
200 mg of lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Tizaflex tablets are white, round tablets.
Tizaflex 4 mg tablets are scored and marked 'N 63' on the other side.

The 4 mg tablet can be divided 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

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 optimum therapeutic response is generally achieved with a daily dose of between 12 and 24 mg, administered in 3 or 4 equally spaced doses. Single doses should not exceed 12 mg. The total daily dose should not exceed 36 mg.

Adverse events (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.

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).

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 Tizaflex in elderly patients.

Paediatric population

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

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. 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 (see section 4.4).

Hepatic impairment
Tizanidine is contraindicated in patients with significantly impaired hepatic function (see sections 4.3 and 4.4)

Method of administration
For oral use.

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 (see sections 4.4 and 4.5).

Hypersensitivity to the active substance or to any of the excipients listed in 6.1.

4.4 Special warnings and precautions for use

Cytochrome P450 (CYP) inhibitors
Concomitant use of tizanidine with CYP1A2 inhibitors is not recommended (see sections 4.3 and 4.5).

Hypotension
Hypotension may occur during treatment with tizanidine (see section 4.8) and also as a result of interactions with CYP1A2 inhibitors and/or antihypertensive agents (see section 4.5). Severe manifestations of hypotension such as loss of consciousness and circulatory collapse have 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).

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

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
Hepatic dysfunction has been reported in association with tizanidine, but rarely at daily doses up to 12 mg. It is recommended in all patients that before beginning therapy, liver function tests should be performed in order to establish a baseline and to exclude pre-existing liver disease or significantly impaired hepatic function. Liver function tests should then be monitored monthly for thefirst four months of treatment in patients receiving doses of 12 mg and higherand in those 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 SGPT (serum glutamic-pyruvic transaminase) and/or SGOT (serum glutamic-oxaloacetic transaminase) are persistently above three times the upper limit of normal range. Tizanidine should be discontinued in patients with symptoms compatible with hepatitis or where jaundice occurs.

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 interactions

CYP inhibitors
Concomitant administration of drugs known to inhibit the activity of CYP1A2 may increase the plasma levels of tizanidine (see section 5.2). Concomitant use of tizanidine with fluvoxamine or ciprofloxacin, both CYP450 1A2 inhibitors in man, is contraindicated (see section 4.3). 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 (see section 4.4). 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).

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. 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 antihypertensive products, 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 (see sections 4.4 and 4.8).

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. 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 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.

Breast-feeding
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

Tizanidine has minor or moderate influence on the ability to drive and use machines: patients experiencing drowsiness or dizziness or any signs or symptoms of hypotension should be advised against activities requiring a high degree of alertness.

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)

Immune system disorders
Not known: Hypersensitivity reactions

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

Nervous system disorders
Common: Somnolence**, dizziness**
Not known: Headache, ataxia, dysarthria

Eye disorders
Not known: Accommodation disorder

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)

Vascular disorders
Common: Hypotension**, rebound hypertension (see sections 4.4 and 4.5)

Gastrointestinal disorders
Common: Dry mouth**
Rare: Nausea**, gastrointestinal disturbances**
Not known: Abdominal pain, vomiting

Hepatobiliary disorders
Rare: Increases in hepatic serum transaminases
Very rare: 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**
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 of tizanidine, such as those recommended for the relief of painful muscle spasms, somlonence, fatigue, dizziness, dry mouth, blood pressure decrease, nausea, gastrointestinal disorder and transaminase increase have been reported, but 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.

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).

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 HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

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

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 and, in animal studies, was found to readily cross the bloodbrain barrier. Mean steady-state volume of distribution (VSS) following i.v. administration is 2.6 L/kg.

Biotransformation
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. 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.

Linearity
Tizanidine has linear pharmacokinetics over the dose range 4 to 20 mg. The low intraindividual variation in pharmacokinetic parameters (C^{max} and AUC) enables reliable prediction of plasma levels following oral administration.

Characteristics in special patient populations
The pharmacokinetic parameters of tizanidine are not affected by gender.
In patients with renal insufficiency (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 4.4).

Effect of food
Concomitant food intake has no clinically significant 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 > 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.

Retinal atrophy and corneal opacity have been observed in chronic toxicity studies in the rat. The no observed adverse effect load in the rat was below 1 mg/kg/day.

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 foetuses as seen by lower foetal 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 foetal 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

Colloidal anhydrous silica
Stearic acid
Microcrystalline cellulose
Lactose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

White PVC/PVdC-aluminium blisters containing 10, 28, 30, 34, 60, 84, 90, 91, 98, 100, 105 or 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
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Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/051/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 May 2009
Date of last renewal: 19th November 2012

10 DATE OF REVISION OF THE TEXT

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