Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tizanidine 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tizanidine tablets containing 2mg of tizanidine as tizanidine hydrochloride.

Excipients: Each tablet contains 80mg of lactose anhydrous.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

White to off-white, circular, flat bevelled edge tablet. Cross-scored on one side with ‘A’ and ‘592’ 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

Tizanidine is indicated in adults for the treatment of spasticity associated with multiple sclerosis or with spinal cord injury or disease.

4.2 Posology and method of administration

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.

Tizanidine has a narrow therapeutic index and a high inter-patient variability in tizanidine plasma concentrations. 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. In controlled clinical trials efficacy was seen at doses of 8mg and above, though response varies considerably so careful titration is necessary.

Since adverse events are dose-related, treatment should commence with single doses 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 and 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 Undesirable Effects) 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 decreased by up to three fold.

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 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.

Patients with Hepatic Impairment
Tizanidine is contraindicated in patients with significantly impaired hepatic function. Tizanidine should not be used in patients with moderate hepatic impairment unless the potential benefit outweighs the potential risk to the patient. Any treatment should start with the lowest dose and afterwards, dosage increases should be done carefully and according to patient tolerability.

4.3 Contraindications

Hypersensitivity to tizanidine or any other component of the product (see section 6.1 List of excipients).

The use of Tizanidine in patients with significantly impaired hepatic function is contraindicated, because tizanidine is extensively metabolised by the liver (see section 5.2 Pharmacodynamic properties).

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 and section 4.4 Special warnings and special precautions for use).

4.4 Special warnings and precautions for use

Concomitant use of tizanidine with CYP1A2 inhibitors is not recommended (see section 4.3 Contraindications and section 4.5 Interaction with other medicaments and other forms of interaction).

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.

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 (see also section 4.5 Interaction with other medicinal products and other forms of interaction). In extreme cases, rebound hypertension might lead to cerebrovascular accident. Tizanidine should not be stopped abruptly, but rather gradually.

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 Posology and Method of Administration).

Liver Function
Hepatic dysfunction has been reported in association with Tizanidine. 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 be monitored on a monthly basis for the first four months in all patients and in addition, in those patients who develop symptoms suggestive of liver dysfunction such as unexplained nausea, anorexia or tiredness.

If serum levels of SGPT and/or SGOT are three times above the upper limit of normal range in any of these routine

tests, liver function tests should be repeated and if serum levels of SGPT and/or SGOT are persistently above three times the upper limit of normal range, treatment with Tizanidine should be discontinued. Tizanidine should be discontinued in patients with symptoms compatible with hepatitis or where jaundice appears.

Tizanidine should be used with caution in CYP450 1 A2 inhibitors. Concomitant use of tizanidine with fluvoxamine, a potent CYP450 1 A2 inhibitor in man, resulted in a 33-fold increase in the tizanidine AUC by fluvoxamine. (See section 4.5, Interaction with other medicinal products and other forms of interaction).

Tizanidine tablets contain lactose. This medicine is not recommended in patients with rare hereditary problem of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

Tizanidine should be kept out of the reach and sight of children.

4.5 Interaction with other medicinal products and other forms of interaction

Observed interactions resulting in a contraindication
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 (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

Observed interactions resulting in a concomitant use not recommended
Co-administration of tizanidine with other inhibitors of CYP1A2 such as some antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, some fluoroquinolones (enoxacin, norfloxacin) 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 (e.g. amitryptaline and azithromycin) is not recommended.

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 drug-drug interactions have not been reported in clinical trials.

Observed interactions to be considered
Rifampicin
Concomitant administration of Tizanidine with rifampicin results in a 50 % decrease in tizanidine concentrations. Therefore, the therapeutic effects of Tizanidine 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 coadministration is considered a careful dose adjustment (increase) may be required.

Cigarette smoke
Exposure to the polycyclic aromatic hydrocarbons of cigarette smoke leads to induction of CYP1A2. In general, smoking can have a significant impact on the pharmacokinetics of CYP1A2-substrate drugs. Administration of Tizanidine in male smokers (N=53) (>10 cigarettes per day) results in about 30% decrease in tizanidine systemic exposure. Long-term therapy with Tizanidine in heavy smokers may require higher doses than the average doses.

Antiypertensives
As Tizanidine may induce hypotension (see 4.4 Special warnings and precautions for use) it may potentiate the effect

of antihypertensive drugs, including diuretics, and caution should therefore be exercised in patients receiving blood pressure lowering drugs. 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 Special warnings and precautions for use and section 4.8 Undesirable effects).

Alcohol
While on Tizanidine 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 Tizanidine.

Anticipated interactions to be considered
Caution should also be exercised when Tizanidine is used concurrently with Beta -adrenoceptor blocking drugs or digoxin as the combination may potentiate hypotension or bradycardia. Sedatives, hypnotics (e.g. benzodiazepine or baclofen), and other drug such as antihistamines may also enhance the sedative action of tizanidine.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of tizanidine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Tizanidine is not recommended during pregnancy and in women of childbearing potential not using contraception.

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

Fertility
Animal studies have shown no effect on fertility at 10mg/kg/day and 3mg/kg/day in male and female rats, respectively (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients experiencing blurred vision, drowsiness, dizziness or any signs or symptoms of hypotension should be advised against activities requiring a high degree of alertness, e.g. driving a vehicle or operating machinery.

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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports, not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Psychiatric disorders	
Common	Insomnia, sleep disorder
Not known	Hallucination, confusional state
Nervous system disorder	
Very common	Somnolence, drowsiness, dizziness
Not known	Vertigo
Cardiac disorders	

Uncommon	Bradycardia
Vascular disorder	
Common	Hypotension
Not known	Syncope
Gastrointestinal disorders	
Very common	Gastrointestinal disorder, dry mouth
Common	Nausea
Hepatobiliary disorders	
Not known	Hepatitis, hepatic failure
Musculoskeletal and connective tissue disorders	
Very Common	Muscular weakness
General disorders and administration site conditions	
Very common	Fatigue
Not known	Asthenia, withdrawal syndrome
Investigations	
Common	Blood pressure decrease, transaminase increase
Skin and subcutaneous tissue disorder	
Not known	Rash, pruritis
Immune system disorder	
Not known	Allergic reaction
Eye Disorders	
Not known	Vision blurred

With low doses, 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 higher doses, 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.

The hallucinations are self-limiting, without evidence of psychosis, and have invariably occurred in patients concurrently taking potentially hallucinogenic drugs, e.g. anti-depressants. Increases in hepatic serum transaminases, which are reversible on stopping treatment, have occurred.

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 (see also section 4.5 Interaction with other medicinal products and other forms of interaction). In extreme cases, rebound hypertension might lead to cerebrovascular accident.

Reporting of side effects
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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

4.9 Overdose

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, 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

Absorption and distribution
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. Mean steady-state volume of distribution (VSS) following i.v. administration is 2.6 L/kg (CV 21%). Although tizanidine is well absorbed, first pass metabolism limits plasma availability to 34% of that of an intravenous dose. The mean maximum plasma concentration (Cmax) of tizanidine is 12.3 ng/mL (coefficient of variation (CV) 56%) and 15.6 ng/mL (CV 60%) after single and repeated administration of 4 mg doses, respectively. Concomitant food intake has no influence on the pharmacokinetic profile of tizanidine tablets (given as 4 mg tablets). Although Cmax is about one-third higher after administration of the tablet under fed conditions, this is not thought to be of any clinical relevance, and absorption (AUC) is not significantly affected.

Metabolism and elimination
Tizanidine undergoes rapid and extensive (about 95%) metabolism in the liver and the pattern of biotransformation in animals and humans is qualitatively similar. Tizanidine is mainly metabolized by cytochrome P450 1A2 *in vitro*. The metabolites are primarily excreted via the renal route (approximately 70% of the administered dose) and appear to be inactive. Renal excretion (determined by percentage recovery in the urine of the total amount of administrated radioactivity) 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 1 to 20 mg

Special populations

Patients with renal impairment
In patients with renal impairment (creatinine clearance <25 mL/min) the 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 4.2 Posology and Method of Administration).

Patients with hepatic impairment
No specific studies were conducted in patients with hepatic impairment. As tizanidine is extensively metabolized in the liver by CYP1A2 enzyme, hepatic impairment may increase its systemic exposure. Tizanidine is contraindicated in patients with significant hepatic impairment (see section 4.3 Contraindications).

Elderly population
Pharmacokinetic data in the elderly population are limited.

Effect of gender and ethnicity
Gender has no clinically significant effect on the pharmacokinetics of tizanidine and the impact of ethic sensitivity and race on the pharmacokinetics of tizanidine has not been studied.

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 drug.

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 CNS 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 drug, 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 preneoplastic pathology, attributable to treatment, was observed.

Reproductive toxicity
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.

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. Dose levels of 10 and 30 mg/kg/day increased gestation duration in female rats. Prenatal and postnatal pup loss was increased and development retardation occurred. At these doses, dams showed marked signs of muscle relaxation and sedation.

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. At these doses, maternal behavioural effects and clinical signs were observed including marked sedation, weight loss, and ataxia.

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 anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVD/PVDC/Al foil blisters. Carton containing 6 blister strips of 20 tablets to give pack size of 120.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Cephalon UK Limited
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Castleford
West Yorkshire WF10 5HX
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8 MARKETING AUTHORISATION NUMBER

PA0827/009/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 21 December 2008

10 DATE OF REVISION OF THE TEXT

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