Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zanaflex 4 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zanaflex tablets containing 4 mg of tizanidine as hydrochloride.
Contains Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Product imported from Greece:
White to off-white, circular, flat tablets, cross-scored on one side and embossed with ‘R’ and ‘L’.

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

For oral administration.
The effect of Zanaflex 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 Zanaflex 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 8 mg and above, though response varies considerably so careful titration is necessary. Since adverse events are dose-related, treatment should commence with single doses of 2 mg increasing by 2 mg 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 Zanaflex should not exceed 12 mg 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 Zanaflex 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 Zanaflex in patients under the age of 18 years is limited. Zanaflex 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
Zanaflex is contraindicated in patients with significantly impaired hepatic function.

4.3 Contraindications

Hypersensitivity to tizanidine or any other component of the product (see section 6.1 List of Excipients).
The use of Zanaflex 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 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). Use in Renal Impairment
Patients with renal impairment may require lower doses and therefore caution should be exercised when using Zanaflex in these patients (see section 4.2 Posology and Method of Administration).
Liver Function
Hepatic dysfunction has been reported in association with Zanaflex. 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 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 Zanaflex should be discontinued. Zanaflex should be discontinued in patients with symptoms compatible with hepatitis or where jaundice appears.
Tizanidine should be used in caution with CYP450 1A2 inhibitors. Concomitant use of tizanidine with fluvoxamine, a potent CYP450 1A2 inhibitor in man, resulted in a 33-fold increase in the tizanidine AUC by fluvoxamine. (See Drug Interaction section).
Zanaflex 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.
Zanaflex should be kept out of the reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

As Zanaflex may induce hypotension it may potentiate the effect of antihypertensive drugs, including diuretics, and caution should therefore be exercised in patients receiving blood pressure lowering drugs. Caution should also be exercised when Zanaflex is used concurrently with β-adrenoceptor blocking drugs or digoxin as the combination may potentiate hypotension or bradycardia.
Caution should be exercised when Zanaflex is prescribed with drugs known to increase the QT interval.
Concomitant use of tizanidine with fluvoxamine or ciprofloxacin, both CYP1A2 inhibitors in man, is contraindicated. Concomitant use of tizanidine with fluvoxamine or ciprofloxacin resulted in a 33-fold and a 10-fold increase in tizanidine AUC, respectively. Clinically significant and prolonged hypotension may result along somnolence, dizziness and decreased psychomotor performance (see section 4.3 Contraindications). Co-administration of tizanidine with other inhibitors of CYP1A2 such as 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).

Pharmacokinetic data following single and multiple doses of Zanaflex suggested that clearance of Zanaflex 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 Zanaflex, the possibility of a clinical response and/or adverse effects occurring at lower doses of Zanaflex should be borne in mind when prescribing Zanaflex to a patient taking the contraceptive pill. Clinically significant drug-drug interactions have not been reported in clinical trials.
Alcohol or sedatives may enhance the sedative action of Zanaflex.

4.6 Fertility, pregnancy and lactation

Reproductive studies in rats and rabbits indicate that Zanaflex does not have embryotoxic or teratogenic potential but at maternally toxic doses of 10-100 mg/kg per day Zanaflex can retard foetal development due to its pharmacodynamic effects. Zanaflex and/or its metabolites have been found in the milk of rodents (see section 5.3 preclinical safety data). The safety of Zanaflex in pregnancy has not been established and its safety in breast-fed infants of mothers receiving Zanaflex is not known. Therefore Zanaflex should not be used in pregnant or nursing mothers unless the likely benefit clearly outweighs the risk.

4.7 Effects on ability to drive and use machines

Patients experiencing drowsiness and dizziness should be advised against activities requiring a high degree of alertness, e.g. driving a vehicle or operating machinery.

4.8 Undesirable effects

The most frequently reported adverse events occurring in association with Zanaflex include drowsiness, fatigue, dizziness, dry mouth, nausea, gastrointestinal disturbances, and a reduction in blood pressure. With slow upward titration of the dose of Zanaflex these effects are usually not severe enough to require discontinuation of treatment. Insomnia, bradycardia and hallucinations have also been reported. 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. Infrequent cases of acute hepatitis have been reported. Muscle weakness has been reported infrequently, although in controlled clinical trials it was clearly demonstrated that Zanaflex does not adversely affect muscle strength. Allergic reactions (e.g. pruritus and rash) have rarely been reported.

4.9 Overdose

Clinical experience is limited. In one adult case, who ingested 400mg Zanaflex, recovery was uneventful. This patient received mannitol and frusemide.
Symptoms: nausea, vomiting, hypotension, 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. The patient should be well hydrated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 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 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 3mg/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 anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

4 mg tablets:

Carton containing 3 blister strips of 10 tablets to give pack size of 30.

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 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Limited,
Ballymurray,
Co. Roscommon,
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1447/26/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 26th September 2008

10 DATE OF REVISION OF THE TEXT