Prescribing Information (Summary of Product Characteristics)

1. Name of the medicinal product

International Non-Proprietary Name (INN): Tizanidine Tablets
Trade Name: TIZIGESIC 2

2. Qualitative and quantitative composition

Tizanidine Hydrochloride Ph. Eur 2 mg

Excipients with known effects: Lactose Anhydrous Ph. Eur 100 mg

For full list of excipients, see section 6.1.

3. Pharmaceutical form

Dosage Form: Uncoated Tablets

Description: White, round uncoated tablet with ‘N’ and ‘62’ debossed on one side andplain on the other side.

4. Clinical particulars

1. Therapeutic indications

It is used in symptomatic treatment of painful muscle spasms associated with musculoskeletal conditions.

It is used for symptomatic relief of spasticity associated with spinal cord injury or disease or multiple sclerosis.

2. Posology and method of administration

Adult: Initially 2 mg for 1 dose, then increased in steps of 2 mg/day every 3-4 days in divided doses, adjusted accordingly to response; usual dose up to 24 mg daily in 3-4 divided doses; maximum 36 mg per day.

3. Contraindications

Tizanidine is contraindicated in patients with known hypersensitivity to tizanidine or its ingredients.
Tizanidine is contraindicated in patients with severe hepatic impairment.
Tizanidine is not recommended for use in children below 18 years of age.
Concomitant use of tizanidine with fluvoxamine or with ciprofloxacin, potent inhibitors of CYP1A2, is contraindicated.

4. Special warnings and precautions for useWARNINGS:

Hypotension

Tizanidine is a α_2-adrenergic agonist and can produce hypotension. The hypotensive effect is dose related and has been measured following single doses of ≥ 2 mg. The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to fixed upright position may be at increased risk for hypotension and orthostatic effects.

Risk of liver injury

Tizanidine occasionally causes liver injury, most often hepatocellular in type. In reported controlled clinical studies, patients treated with tizanidine had elevations of liver function tests (ALT/SGPT, AST/SGOT) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated) compared to control patients. Most cases resolved rapidly upon drug withdrawal with no reported residual problems. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. Based upon post marketing experience, death associated with liver failure has been a rare occurrence reported in patients treated with tizanidine.

Sedation

In the multiple dose, reported controlled clinical studies, patients receiving any dose of tizanidine reported sedation as an adverse event. Sedation may interfere with everyday activity. The patients should not drive or operate machinery. The effect appears to be dose related. In the multiple dose studies, the prevalence of patients with sedation peaked following the first week of filtration and then remained stable for the duration of the maintenance phase of the study.

Hallucinosis/Psychotic like symptoms

Tizanidine use has been associated with hallucinations. Visual hallucinations or delusions have been reported in patients in controlled clinical studies. These cases occurred within the first 6 weeks.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

Precautions

Potential interaction with fluvoxamine or ciprofloxacin

In reported pharmacokinetic study, tizanidine serum concentration was significantly increased (Cmax 12-fold, AUC 33-fold) when the drug was given concomitantly with fluvoxamine. Potentiated hypotensive and sedative effects were observed. Fluvoxamine and tizanidine should not be used together.

In a pharmacokinetic study, tizanidine serum concentration was significantly increased (Cmax 7-fold, AUC 10-fold) when the drug was given concomitantly with Ciprofloxacin. Potentiated hypotensive and sedative effects were observed. Ciprofloxacin and Tizanidine should not be used together.

Possible interaction with other CYP1A2 inhibitors

Because of potential drug interactions, concomitant use of Tizanidine with other CYP1A2 inhibitors, such as Zileuton, other fluoroquinolones, antiarrythmics (Amiodarone, Mexiletine, Propafenone, and Verapamil), Cimetidine, Famotidine, Oral contraceptives, Acyclovir and Ticlopidine should ordinarily be avoided. If their use is clinically necessary, they should be used with caution.

Use in Cardiovascular Condition

Additive hypotensive effect is seen when tizanidine is used in patients receiving antihypertensive therapy. Caution is advised when tizanidine is to be used in patients receiving concurrent antihypertensive therapy and should not be used with other α2-adrenergic agonists bradycardia may be enhanced if given with β-blockers or digoxin.

Caution should be exercised when tizanidine is used with drugs known to increase QT interval.

Use in patients with hepatic impairment:
Tizanidine is extensively metabolized in the liver, hepatic impairment would be expected to have significant effects on the pharmacokinetics of tizanidine. Tizanidine should be avoided in patients with severe hepatic impairment. Use in moderate hepatic impairment only if potential benefit out weights risk.

Use in renally impaired patients
Should be used with caution in renally impaired patients. Treatment should be started with equivalent of 2 mg of base once daily; thereafter it advises a slow increase in the once daily dose before increasing frequency of administration.

Use in women taking oral contraceptives
Reported evidence suggests that mean peak plasma concentrations after a single 4 mg dose of tizanidine were 3 times greater in 15 women taking oral contraceptives. The effect appears to be due to inhibition of cytochrome p450 isoenzyme CYP1A2, resultingin reduces presystemic metabolism of tizanidine. Because therapeutic range of tizanidine is narrow, care should be excercised if it is given to patients taking oral contraceptives.

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 to minimize the risk of withdrawal and rebound hypertension, tachycardia and hypertonia.

5. Interaction with other medicinal products and other forms of interaction
In vitro studies of cytochrome P450 isoenzymes using human liver microsomes indicate that neither Tizanidine nor the major metabolites are likely to affect the metabolism of other drugs metabolized by cytochrome P450 isoenzymes.

Fluvoxamine
The effect of Fluvoxamine on the pharmacokinetics of a single 4 mg dose of Tizanidine was studied in 10 healthy subjects. The Cmax, AUC, and half-life of Tizanidineincreased by 12-fold, 33-fold, and 3-fold, respectively. These changes resulted in significantly decreased blood pressure, increased drowsiness, and increased psychomotorimpairment.

Phenytoin
An increase in serum concentration of phenytoin has been reported when tizanidine wasadded to therapy.

Ciprofloxacin
The effect of Ciprofloxacin on the pharmacokinetics of a single 4 mg dose of Tizanidine was studied in 10 healthy subjects. The Cmax and AUC of Tizanidine increased by 7-fold and 10-fold, respectively. These changes resulted in significantly decreased blood pressure, increased drowsiness, and increased psychomotor impairment.

CYP1A2 inhibitors
The interaction between Tizanidine and either Fluvoxamine or Ciprofloxacin is most likely due to inhibition of CYP1A2 by Fluvoxamine or Ciprofloxacin. Although there have been no clinical studies evaluating the effects of other CYP1A2 inhibitors on Tizanidine, other CYP1A2 inhibitors, including Zileuton, other fluroquinolones, antiarrythmics (Amiodarone, Mexiletine, Propafenone, and Verapamil), Cimetidine and Famotidine, Oral contraceptives, Acyclovir, and Ticlopidine may also lead to substantial increases in Tizanidine blood concentrations.

Acetaminophen
Tizanidine delayed the Tmax of Acetaminophen by 16 minutes. Acetaminophen did not affect the pharmacokinetics of Tizanidine.

Alcohol
Alcohol increased the AUC of Tizanidine by approximately 20%, while also increasing its Cmax by approximately 15%. This was associated with an increase in side effects of Tizanidine. The CNS depressant effects of Tizanidine and alcohol are additive.

Oral Contraceptives
Reported evidence suggests that mean peak plasma concentrations after a single 4 mg dose of tizanidine were 3 times greater in women taking oral contraceptives. The effect appears to be due to inhibition of cytochrome p450 isoenzyme CYP1A2, resulting in reduced presystemic metabolism of tizanidine.

6. Fertility Pregnancy and lactation

Pregnancy: Avoid tizanidine use in pregnancy (toxicity in animal studies).

Breast Feeding: Avoid tizanidine use in breast feeding women (present in milk in animal studies)

Geriatric Use: Tizanidine should be used with caution in elderly patients because clearance is decreased four-fold.

Pediatric Use: There are no adequate and well-controlled studies to document the safety efficacy of tizanidine in children.

4.7 Effects on ability to drive and use machines
Patients experiencing 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.

8. Undesirable effects

Common adverse events leading to discontinuation
Reported evidence suggests that adverse events most frequently leading to withdrawal of Tizanidine treated patients were asthenia (weakness, fatigue and/or tiredness), somnolence, dry mouth, increased spasm or tone, and dizziness.

In patients with spasticity, the most frequent adverse effects were dry mouth, somnolence/ sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. Three- quarters of the patients rated the events as mild to moderate and one-quarter of the patients rated the events as being severe. These events appeared to be dose related.

Adverse events reported in controlled studies
Common or very common: Altered liver enzymes, dizziness, drowsiness, dry mouth,fatigue. gastro intestinal disturbance, hypotension, nausea.

Uncommon: Bradycardia
Frequency not known: Asthenia, blurred vision, Confusion, Convulsions, Hallucinations, hepatitis, insomnia, liver failure, syncope.

9. Overdose
The reported clinical manifestations of tizanidine overdose were consistent with its known pharmacology. When overdose occur, basic steps to ensure the adequacy of an airway and the monitoring of cardiovascular and respiratory systems should be undertaken. In general, symptoms resolve within one to three days following discontinuation of tizanidine and administration of appropriate therapy. Due to the similar mechanism of action, symptoms and management of tizanidine overdose are similar to those following clonidine overdose. For the most recent information concerning the management of overdose, contact a poison control center.

5. Pharmacological properties

(ATC) Classification: M03B X02: Muscle relaxants, other centrally acting agents
Distribution Category: Prescription Preparation

1. Pharmacodynamics properties

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, Tizanidine has no direct effects on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of Tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitations of spinal motor neurons. The imidazoline chemical structure of Tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists.

2. Pharmacokinetics properties

Reported evidence suggests that following oral administration, tizanidine is essentially completely absorbed. The absolute oral bioavailability of Tizanidine is approximately 40% due to extensive first pass hepatic metabolism. Tizanidine is extensively distributed throughout the body with a mean steady state volume of distribution of 2.4 L/Kg (CV =21%) following intravenous administration in healthy adult volunteers. Tizanidine is approximately 30% bound to plasma proteins.

Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg. Tizanidine has a half-life of approximately 2.5 hours. Approximately 95% of an administered dose is metabolized. The primary cytochrome P450 isoenzyme involved in Tizandine metabolism is CYP1A2. Tizanidine metabolites are not known to be active, their half- lives range from 20 to 40 hours.

Reported evidence suggests following single and multiple oral dosing of 14C-Tizanidine, an average of 60% and 20% of total radioactivity was recovered in the urine and feces, respectively.

Special populationsAge effects

No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data following single dose administration of 6 mg Tizanidine showed that younger subjects cleared the drug four times faster than the elderly subjects. Tizanidine has not been evaluated in children.

Hepatic impairment

Monitor liver function monthly for first 4 months and in those who develop unexplained nausea, anorexia or fatigue. Treatment should be stopped if liver enzymes are persistently elevated. Avoid in severe hepatic impairment.

Renal impairment
Should be used with caution in renally impaired patients. Treatment should be started with equivalent of 2 mg of base once daily; thereafter it advices a slow increase in the once daily dose before increasing frequency of administration.

Gender effects
No specific pharmacokinetic study was conducted to investigate gender effects. Retrospective analysis of pharmacokinetic data, however, following single and multiple dose administration of 4 mg Tizanidine showed that gender had no effect on the pharmacokinetics of Tizanidine.

Race effects
Pharmacokinetic differences due to race have not been studied.

3. Preclinical safety data
No evidence for carcinogenicity was seen in two dietary studies in rodents. Tizanidine was not mutagenic or clastogenic in the following in vitro assays: the bacterial Ames testand the mammalian gene mutation test and chromosomal aberration test in Chinese hamster cells. It was also negative in the following in vivo assays: the bone marrow micronucleus test in mice, the bone marrow micronucleus and cytogenicity test in Chinese hamsters, the dominant lethal mutagenicity test in mice, and the unscheduled DNA synthesis (UDS) test in mice.

Reported evidence suggests that tizanidine did not affect fertility in male rats at doses of10 mg/kg, approximately 2.7 times the maximum recommended human dose on a mg/m2basis, and in females at doses of 3 mg/kg, approximately equal to the maximum recommended human dose on a mg/m2 basis; fertility was reduced in males receiving 30 mg/kg (8 times the maximum recommended human dose on a mg/m2 basis) and in females receiving 10 mg/kg (2.7 times the maximum recommended human dose on a mg/m2 basis). At these doses, maternal behavioral effects and clinical signs were observed including marked sedation, weight loss and ataxia.

6.1 Pharmaceutical particulars
6.1 List of excipients
Microcrystalline Cellulose Ph. Eur./BP (Avicel PH 112)
Lactose Anhydrous Ph. Eur./BP (Pharmatose DCL 21)
Colloidal Anhydrous Silica Ph. Eur./BP
Stearic Acid Ph. Eur./BP

6.2 Incompatibilities
None

3. Shelf Life
36. months from the date of manufacture

4. Special precautions for storage
Store below 30°C.

5. Nature and contents of container
Blister of white opaque PVC film coated with PVdC on the inner side with a backing of aluminium foil.

Each carton contains 3 Aluminium blisters of 10 tablets along with Pack Insert.

6. Special precautions for disposal and other handling
No special requirements

6. Marketing Authorization Holder
Unichem Laboratories Limited
Unichem Bhavan,Prabhat Estate,
S. V. Road, Jogeshwari (West), Mumbai – 400 102
India.
Phone: 91-22-66888333
Fax: 91-22-26785198/4391

7. Marketing Authorization Number(s)
TAN 22 HM 0121

8. Date of first registration/renewal of the registration
11/04/2022

9. Date of revision of the Text