

## **Public Assessment Report**

**Tizanidine 2mg Tablets**  
**Tizanidine 4mg Tablets**  
**Tizanidine 6mg Tablets**

**PL 14894/0352/58/55**

**PL 14894/0353/56/59**

**PL 14894/0354/57/60**

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### **Lay Summary**

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations (licences) for the medicinal products Tizanidine 2mg, 4mg and 6mg Tablets on 11/07/2008. Tizanidine is a skeletal muscle relaxant and is used to relax muscle contraction which occurs in diseases such as multiple sclerosis or spinal cord injury. The applicant provided data to show that the products were generic medical products of the brand leader Zanaflex Tablets.

## Scientific Discussion

### INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Tizanidine 2mg, 4mg and 6mg Tablets (PL 14894/0352-60) on 11/07/2008. The products are prescription only medicines. The applications are for 3 duplicates of each strength submitted under Article 10.1 of EC directive 2001/83/EC. The applicant provided data to show that the products were generic medical products of the brand leader Zanaflex Tablets, granted to Elan Pharmaceuticals International Limited, UK in March 1999. Tizanidine was first marketed within the EU by Novartis in Denmark in April 1984.

The products contain the active ingredient tizanidine which is indicated in the treatment of spasticity associated with multiple sclerosis or with spinal cord injury or disease. Tizanidine is an  $\alpha_2$  -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.

## PHARMACEUTICAL ASSESSMENT

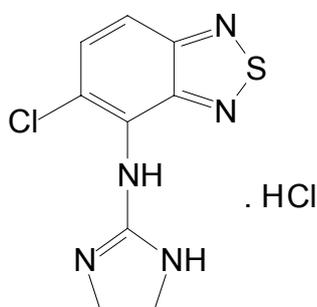
### DRUG SUBSTANCE

#### Nomenclature

rINN, USAN (United States Adopted Name) and common name: tizanidine hydrochloride

Chemical name: 5-Chloro-4-(2-imidazoli-2-ylamino)-2,1,3-benzothiadiazole hydrochloride  
Or 5-Chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,,3 benzothiadiazol-4-amine hydrochloride

#### Structure



#### General Properties

Tizanidine hydrochloride is a white to pale yellowish crystalline powder, with a molecular formula of  $C_9H_8ClN_5S.HCl$  and a molecular weight of 290.21. The molecule has no chiral centres and as such is not optically active. Tizanidine has a melting range of 286-290°C and is soluble in water and methanol, slightly soluble in ethanol, IPA and acetonitrile; practically insoluble in acetone, chloroform, ethyl acetate and ether.

An appropriate specification has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active tizanidine is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 36 months, with no specific storage instructions.

## **DRUG PRODUCT**

### **Description**

All three tablet strengths are described as white to off-white circular tablets with different markings on one side. The 2mg tablet has 'T1' on one side, plain on the other. The 4mg tablet has 'T2' on one side, plain on the other and the 6mg tablet has 'T3' on one side, plain on the other.

### **Other Ingredients**

The other ingredients in the products are

Cellulose, microcrystalline  
Lactose, anhydrous  
Silica, colloidal anhydrous  
Stearic acid

All excipients are Ph. Eur. compendial grade. Typical certificates of analysis are provided from the manufacturer of the finished product for each of the excipients.

A BSE/TSE risk status certificate has been included from all excipient suppliers and indicates that all excipients (except lactose and stearic acid) are either synthetic or of vegetable origin (magnesium stearate – vegetable) and as such pose no BSE/TSE risk. There is a letter from the lactose supplier, stating that the lactose produced by the company is of pharmaceutical grade, in which the BSE-risk is negligible. A TSE certificate of suitability has been provided for the stearic acid.

### **Dissolution and impurity profiles**

Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

### **Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

### **Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

### **Container Closure System**

Tizanidine tablets are packed in both blister packs. Blisters are composed of PVC/PVdC/Aluminium foil (hard tempered heat-sealable). The sources and specifications of blister forming materials are specified and supported by certificates of analysis. Test methods in support of the proposed specifications are provided and are considered satisfactory.

### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, with the following storage conditions, “Store in original packaging” and “Do not store above 25°C”.

### **ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY**

Marketing Authorisations were granted.

## **PRE-CLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none are required for an application of this type.

## MEDICAL ASSESSMENT

The products contain the active ingredient tizanidine which is indicated in the treatment of spasticity associated with multiple sclerosis or with spinal cord injury or disease. Tizanidine is an  $\alpha_2$  - adrenergic receptor agonist within the central nervous system at supra-spinal and spinal levels.

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.

### Bioequivalence Study

The applicant has submitted one bioequivalence study. This randomised, single-dose, two-way, crossover study was conducted to compare the relative bioavailability of two formulations of 4 mg tizanidine tablets under fasting conditions. The study was performed in 38 (35 completing) healthy adults. In each study period, a single 4 mg dose was administered to subjects following an overnight fast. The test formulation was Ranbaxy Research Laboratories' 4 mg Tizanidine Tablets and the reference formulation was 4 mg ZANAFLEX™ (Elan Pharma International Ltd.) Tablets. The subjects received the test product in one study period and the reference product in the other period; the order of administration was according to the doing randomization schedule. There was a 7-day interval between treatments.

Blood samples were collected pre-dose and at intervals over 12 hours after each dose. The plasma samples for all subjects who completed both periods of the study were analysed for tizanidine concentration.

Bioequivalence was determined by a statistical comparison of  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{\infty}$  for the test and reference products. Data from a total of 35 subjects were included in the statistical analyses for the valuation of bioequivalence.

Analyses of Variance was performed using the General Linear Model (GLM) procedure of SAS with hypothesis testing for treatment effects at  $\alpha = 0.05$ . The statistical model contained main effects of sequence, subject within Type III mean square term for subjects within sequence. All other main effects were tested against the mean square error term. Least square means for the treatment (LSMEANS statement) and the differences between adjusted treatment means and the standard errors associated with these differences (ESTIMATE statement) were calculated.

The main pharmacokinetic parameters are summarised in table 1 below.

**Table 1: Summary of the main pharmacokinetic parameters of Tizanidine (N=35).**

Parameter	Least Squares Means <sup>1</sup>		Test/Ref. Ratio <sup>2</sup>	90% Confidence Interval <sup>3</sup>	
	Test	Reference		Lower	Upper
<b>AUC 0-t</b> (ng-hr/ml)	9.96	9.92	1.00	0.8874	1.1208
<b>AUCinf</b> (ng-hr/ml)	10.66	10.70	1.00	0.8781	1.1149
<b>Cmax</b> (ng-ml)	3.35	3.72	0.90	0.7586	1.0392
<b>Ke</b> (1/hour)	0.476	0.482	0.99	0.9361	1.0383
<b>Ln-Transformed Data</b>					
<b>AUC 0-t</b> (ng-hr/ml)	5.53	6.0	0.92	0.8242	1.0219
<b>AUCinf</b> (ng-hr/ml)	6.55	7.18	0.91	0.8233	1.0098
<b>Cmax</b> (ng-ml)	2.19	2.47	0.89	0.7950	0.9886

<sup>1</sup> Least squares geometric means for ln-transformed data.

<sup>2</sup> Test/Ref. Ratio calculated as Test mean divided by Reference mean

<sup>3</sup> Confidence interval on the ratio.

When log transformed, the test to reference ratio and the 90% confidence intervals for the major pharmacokinetic parameter [area under the plasma concentration curve (AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>) and the peak plasma concentration (C<sub>max</sub>)] for tizanidine were 0.92 (0.8242 – 1.0219), 0.91 (0.8233 – 1.0098) and 0.89 (0.7950 – 0.9886), respectively.

The results of the study show that the 90% Confidence Intervals for the log-transformed parameters AUC<sub>(0-t)</sub> and AUC<sub>(0-∞)</sub> for Tizanidine were all within the 80-125% acceptable range. These results therefore demonstrate that the test product, Tizanidine (Ranbaxy Ltd) is bioequivalent to the reference formulation Zanaflex™ (Elan Pharma International Ltd). The pharmacokinetics for the innovator product are linear between 2-6mg and therefore the 2mg and 6mg Tablets are considered bioequivalent.

A total of 41 adverse events were reported in 22 of the 38 subjects during the study. The most common adverse events included sleepiness (25), headaches (2), dizziness (2), and fever (2). All were assessed as mild or moderate in intensity. No serious adverse event was reported.

### **Efficacy**

No new data are submitted or required.

**Safety**

No new data are submitted or required.

**Expert Report**

A brief satisfactory clinical expert report has been submitted with appropriate CV.

**Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL)**

Satisfactory SPC and PIL were provided

**Discussion**

Skeletal muscle relaxants, including Tizanidine, have been marketed in the UK for over ten years. Their use is well established with recognised efficacy and acceptable safety.

**Conclusion**

Marketing Authorisations may be granted.

## **Overall Conclusion and Risk/Benefit Analysis**

### ***Quality***

The important quality characteristics of Tizanidine Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### ***Pre-Clinical***

No new pre-clinical data were submitted and none were required.

### ***Clinical***

Bioequivalence has been demonstrated between the applicant's Tizanidine 4mg Tablets and Zanaflex 4mg Tablets. Given that linear kinetics apply between the 2mg and 6mg tablets of the innovator product, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 2mg and 6mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

### ***Risk/Benefit Analysis***

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. The risk benefit is, therefore, considered to be positive.

**Steps Taken During Assessment**

1	The MHRA received the application on 23/12/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 11/11/2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 14/11/2005 and 16/07/2007 on the medical assessment on 14/11/2005
4	The applicant provided further information in regard to the quality assessment on 27/02/2007 and 12/12/2007 and on the medical assessment on 28/11/2005
5	The application was determined on 11/07/2008.

### **Steps Taken after Assessment**

No non-confidential changes have been made to the marketing authorisations.

## **SUMMARY OF PRODUCT CHARACTERISTICS**

As the SPCs are identical for the duplicates of each strength, only one SPC for each strength has been included in this section.

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Tizanidine 2 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains tizanidine hydrochloride equivalent to 2mg tizanidine.

Each tablet contains 52.86 mg lactose anhydrous. For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet

White to off white circular tablets, debossed with 'T1' on one side and plain on the other side.

### 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 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 decreased by up to three fold.

#### *Children*

Tizanidine is not recommended for use in children below 18 years of age.

#### *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.

### **4.3 Contraindications**

Hypersensitivity to tizanidine or any other component of the product.  
The use of Tizanidine in patients with significantly impaired hepatic function is contraindicated, because tizanidine is extensively metabolised by the liver.

### **4.4 Special warnings and precautions for use**

#### *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**).

#### *Liver Function*

Hepatic dysfunction has been reported in association with Tizanidine. It is recommended that liver function tests should be monitored monthly for the first four months in all patients and in those who develop symptoms suggestive of liver dysfunction such as unexplained nausea, anorexia or tiredness. Treatment with Tizanidine should be discontinued if serum levels of SGPT and/or SGOT are persistently above three times the upper limit of normal range.

Tizanidine should be kept out of the reach of children.

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**

As Tizanidine 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 Tizanidine is used concurrently with  $\beta$  - adrenoceptor blocking drugs or digoxin as the combination may potentiate hypotension or bradycardia.

Caution should be exercised when Tizanidine is prescribed with drugs 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 drug-drug interactions have not been reported in clinical trials.

Alcohol or sedatives may enhance the sedative action of Tizanidine.

#### **4.6 Pregnancy and lactation**

Reproductive studies in rats and rabbits indicate that Tizanidine does not have embryotoxic or teratogenic potential but at maternally toxic doses of 10-100 mg/kg per day Tizanidine can retard foetal development due to its pharmacodynamic effects. Tizanidine and/or its metabolites have been found in the milk of rodents (**see section 5.3**). The safety of Tizanidine in pregnancy has not been established and its safety in breast-fed infants of mothers receiving Tizanidine is not known. Therefore Tizanidine 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 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 Tizanidine include drowsiness, fatigue, dizziness, dry mouth, nausea, gastrointestinal disturbances, and a reduction in blood pressure. With slow upward titration of the dose of Tizanidine 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. antidepressants. 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. 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 Tizanidine, 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

#### Pharmacotherapeutic classification

#### M03B X02 (Muscle relaxant and centrally acting agents)

#### Mode of Action

Tizanidine is an  $\alpha_2$  -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 overdose 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  $\alpha_2$  - 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**

Cellulose, microcrystalline  
Lactose, anhydrous  
Silica, colloidal anhydrous  
Stearic acid

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

Do not store above 25°C. Store in the original package.

**6.5 Nature and contents of container**

Blister strip of white opaque PVC film coated with PVdC on the inner side with a backing of aluminium foil (coated with heat seal lacquer).

Pack size of 120 Tablets.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Ranbaxy (UK) Limited  
20, Balderton Street  
London  
W1K 6TL  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 14894/0352

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

11/07/2008

**10 DATE OF REVISION OF THE TEXT**

11/07/2008

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Tizanidine 4 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains tizanidine hydrochloride equivalent to 4mg tizanidine.

Each tablet contains 105.71mg lactose anhydrous. For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet

White to off white circular tablets, debossed with 'T2' on one side and plain on the other side.

### 4 CLINICAL PARTICULARS

#### 4.2 *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 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 decreased by up to three fold.

#### *Children*

Tizanidine is not recommended for use in children below 18 years of age.

#### *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.

### **4.3 Contraindications**

Hypersensitivity to tizanidine or any other component of the product.  
The use of Tizanidine in patients with significantly impaired hepatic function is contraindicated, because tizanidine is extensively metabolised by the liver.

### **4.4 Special warnings and precautions for use**

#### *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**).

#### *Liver Function*

Hepatic dysfunction has been reported in association with Tizanidine. It is recommended that liver function tests should be monitored monthly for the first four months in all patients and in those who develop symptoms suggestive of liver dysfunction such as unexplained nausea, anorexia or tiredness. Treatment with Tizanidine should be discontinued if serum levels of SGPT and/or SGOT are persistently above three times the upper limit of normal range.

Tizanidine should be kept out of the reach of children.

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***

As Tizanidine 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 Tizanidine is used concurrently with  $\beta$  - adrenoceptor blocking drugs or digoxin as the combination may potentiate hypotension or bradycardia.

Caution should be exercised when Tizanidine is prescribed with drugs 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 drug-drug interactions have not been reported in clinical trials.

Alcohol or sedatives may enhance the sedative action of Tizanidine.

#### **4.6 *Pregnancy and lactation***

Reproductive studies in rats and rabbits indicate that Tizanidine does not have embryotoxic or teratogenic potential but at maternally toxic doses of 10-100 mg/kg per day Tizanidine can retard foetal development due to its pharmacodynamic effects. Tizanidine and/or its metabolites have been found in the milk of rodents (**see section 5.3**). The safety of Tizanidine in pregnancy has not been established and its safety in breast-fed infants of mothers receiving Tizanidine is not known. Therefore Tizanidine 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 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 Tizanidine include drowsiness, fatigue, dizziness, dry mouth, nausea, gastrointestinal disturbances, and a reduction in blood pressure. With slow upward titration of the dose of Tizanidine 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. 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 Tizanidine, 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*

#### **Pharmacotherapeutic classification**

#### **M03B X02 (Muscle relaxant and centrally acting agents)**

#### **Mode of Action**

Tizanidine is an  $\alpha_2$  -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  $\alpha_2$  - 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***

Cellulose, microcrystalline  
Lactose, anhydrous  
Silica, colloidal anhydrous  
Stearic acid

### **6.2 *Incompatibilities***

Not applicable

### **6.3 *Shelf life***

2 years

### **6.4 *Special precautions for storage***

Do not store above 25°C. Store in the original package.

### **6.5 *Nature and contents of container***

Blister strip of white opaque PVC film coated with PVdC on the inner side with a backing of aluminium foil (coated with heat seal lacquer).

Pack size of 120 Tablets.

**6.6** *Special precautions for disposal*

No special requirements.

**7** **MARKETING AUTHORISATION HOLDER**

Ranbaxy (UK) Limited  
20, Balderton Street  
London  
W1K 6TL  
United Kingdom

**8** **MARKETING AUTHORISATION NUMBER(S)**

PL 14894/0353

**9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

11/07/2008

**10** **DATE OF REVISION OF THE TEXT**

11/07/2008

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Tizanidine 6 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains tizanidine hydrochloride equivalent to 6mg tizanidine.

Each tablet contains 158.58mg lactose anhydrous. For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet

White to off white circular tablets, debossed with 'T3' on one side and plain on other side.

### 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 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 decreased by up to three fold.

*Children*

Tizanidine is not recommended for use in children below 18 years of age.

*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.

**4.3 Contraindications**

Hypersensitivity to tizanidine or any other component of the product.  
The use of Tizanidine in patients with significantly impaired hepatic function is contraindicated, because tizanidine is extensively metabolised by the liver.

**4.4 Special warnings and precautions for use***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).

*Liver Function*

Hepatic dysfunction has been reported in association with Tizanidine. It is recommended that liver function tests should be monitored monthly for the first four months in all patients and in those who develop symptoms suggestive of liver dysfunction such as unexplained nausea, anorexia or tiredness. Treatment with Tizanidine should be discontinued if serum levels of SGPT and/or SGOT are persistently above three times the upper limit of normal range.

Tizanidine should be kept out of the reach of children.

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**

As Tizanidine 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 Tizanidine is used concurrently with  $\beta$  - adrenoceptor blocking drugs or digoxin as the combination may potentiate hypotension or bradycardia.

Caution should be exercised when Tizanidine is prescribed with drugs 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 drug-drug interactions have not been reported in clinical trials.

Alcohol or sedatives may enhance the sedative action of Tizanidine.

**4.6 Pregnancy and lactation**

Reproductive studies in rats and rabbits indicate that Tizanidine does not have embryotoxic or teratogenic potential but at maternally toxic doses of 10-100 mg/kg per day Tizanidine can retard foetal development due to its pharmacodynamic effects. Tizanidine and/or its metabolites have been found in the milk of rodents (see section 5.3). The safety of Tizanidine in pregnancy has not been established and its safety in breast-fed infants of mothers receiving Tizanidine is not known. Therefore Tizanidine 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 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 Tizanidine include drowsiness, fatigue, dizziness, dry mouth, nausea, gastrointestinal disturbances, and a reduction in blood pressure. With slow upward titration of the dose of Tizanidine 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. Allergic reactions (e.g. pruritus and rash) have rarely been reported.

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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.

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

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Cellulose, microcrystalline  
Lactose, anhydrous  
Silica, colloidal anhydrous  
Stearic acid

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

Do not store above 25°C. Store in the original package.

### **6.5 Nature and contents of container**

Blister strip of white opaque PVC film coated with PVdC on the inner side with a backing of aluminium foil (coated with heat seal lacquer).

Pack size of 120 Tablets.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Ranbaxy (UK) Limited  
20 Balderton Street  
London  
W1K 6TL  
United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 14894/0354

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

11/07/2008

**10 DATE OF REVISION OF THE TEXT**

11/07/2008

## Labels and Leaflet

PACKAGE LEAFLET : INFORMATION FOR THE USE

**TIZANIDINE**  
**2/4/6 MG TABLETS**

(Tizanidine Hydrochloride)

**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Tizanidine tablets are and what they are used for
2. Before you take Tizanidine tablets
3. How to take Tizanidine tablets
4. Possible side effects
5. How to store Tizanidine tablets
6. Further information

**1. WHAT TIZANIDINE TABLETS ARE AND WHAT THEY ARE USED FOR**

Tizanidine belongs to the class of medicines called muscle relaxant and centrally acting agents.

Tizanidine tablets are used for one or more of the following:

- Muscle spasticity/rigidity associated with multiple sclerosis
- Spinal cord injury
- Spinal cord disease

**2. BEFORE YOU TAKE TIZANIDINE TABLETS**

Do not take Tizanidine tablets

- if you are allergic (hypersensitive) to Tizanidine or any of the other ingredients of Tizanidine tablets (An allergic reaction may include rash, itching, swelling of face, lips, or hands/feet or breathing difficulties). See section 6 for a list of ingredients
- if you are pregnant or planning to become pregnant or are breast-feeding
- if you have a condition known as angioneurotic oedema that manifests with swelling of face, lips, hands/feet, or breathing difficulties
- if you have been diagnosed as having a condition known as renal artery stenosis (narrowing of the arteries)
- if you have low blood pressure (hypotension)
- if you are under 18 years old or elderly and frail

**Take special care with Tizanidine tablets**

- if you have problems with your heart, kidneys and/or liver. Your doctor may reduce the dose of the tablets
- if you are on haemodialysis (where the blood is cleaned)
- if you have been diagnosed to have conditions known as lupus erythematosus or scleroderma (diseases that affect your immune system)
- if you are taking diuretics (water tablets) and/or are on a low salt diet, or have had diarrhoea and/or vomiting recently

If you need to undergo an operation or need an anaesthetic, tell the doctor or

dentist about your medicine.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking, or have recently taken any other medicines, including medicines obtained without a prescription.

Care is needed:

- if you are taking water tablets, especially the ones that prevent loss of potassium in urine (e.g. spironolactone, amiloride, triamterene)
- if you are taking other high blood pressure medicines (e.g. beta blockers)
- if you are taking insulin or oral anti-diabetic medicines (e.g. glibenclamide, metformin)
- if you are taking pain relievers known as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (e.g. ibuprofen)
- if you are taking lithium (used in treatment of certain mental illnesses)
- if you are taking all oporinol (used for treatment of gout) or corticosteroids or other medicines that depress the immune system
- if you are taking a medicine called digoxin (for controlling fast or irregular heart beat)
- if you are taking the oral contraceptive pill

**Taking Tizanidine with food and drink**

Tizanidine tablets can be taken any time of the day before, with or after food.

**Pregnancy and breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine. Do not take Tizanidine tablets if you are pregnant or planning to become pregnant. Tizanidine tablets should not be taken if you are breast-feeding.

**Driving and using machines**

Tizanidine may affect the ability to drive or operate machinery in some people. This occurs especially after the first dose, or after the dose is increased and if taking alcohol at the same time. Make sure you know how you react to Tizanidine before you drive, use machines, or engage in any other activity that could be dangerous if you are not alert.

**Important information about some of the ingredients of Tizanidine tablets**

Your medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

**3. HOW TO TAKE TIZANIDINE TABLETS**

Always take Tizanidine tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The starting dose of Tizanidine is 2 mg once a day. This will be gradually increased by your doctor depending

on the benefit you get from the tablets. You should not increase the dose more often than every three to four days. As you increase the dose of Tizanidine your doctor will instruct you how to space the doses out during the day you will normally take the tablets three to four times a day. Most patients take a maximum dose of 24 mg per day, occasionally some patients will require higher doses of up to 36 mg a day.

If you have been diagnosed as suffering from renal problems, your doctor might start your treatment at 2 mg once a day and if required, your dose might be increased more slowly than normal to achieve the desired effect.

Swallow the tablet(s) whole with a glass of water. The tablets can be taken before, with or after food. To help you remember to take your medicine, try to get into the habit of taking it at the same time each day.

If you have the impression that the effect of Tizanidine tablets is too strong or too weak, talk to your doctor or pharmacist.

#### If you take more Tizanidine tablets than you should,

Consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so your doctor will know what you have taken.

#### If you forget to take Tizanidine tablets,

Take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten dose.

#### If you stop taking Tizanidine tablets

Take your tablets as directed and for as long as directed. Do not stop taking them, even if you feel better, as otherwise the symptoms may return.

#### If you have any further questions on the use of this product, ask your doctor or pharmacist.

#### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Tizanidine tablets can cause side effects, although not everybody gets them. Side effects observed with Tizanidine tablets are generally mild and transient. The most frequently reported side effects are nausea (feeling sick), dizziness and headache, drowsiness.

**If any of the following happen, stop taking Tizanidine tablets and tell your doctor immediately or go to the casualty department at your nearest hospital.**

- Rashes, hives, itching, chest constriction, shortness of breath or swelling of face, lips, hands/feet, fainting, high temperature

These are very serious side effects. If you have them you may have had a serious allergic reaction or other type of reaction to Tizanidine. You may need urgent medical attention or hospitalisation.

**Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:**

- Dizziness or light headedness, weakness, or fainting (especially after the first dose or after the dose is increased)

**Tell your doctor if you notice any of the following:**

- Nausea (feeling sick) or vomiting (being sick), indigestion, pain in the belly, diarrhoea or loose stools, constipation, dry mouth, inflammation of mouth, loss of appetite, runny or stuffy nose
- Fatigue (tiredness), muscle weakness or drowsiness
- You may also experience slow pulse rate
- Dry mouth
- Headache, disturbances of balance, restlessness, tremors (uncontrolled shaking), confusion, sleep disorders (difficulty in sleeping or excessive), nervousness, muscle cramps, anxiety, hallucinations or muscle weakness.

There may be changes in the results of certain laboratory tests

- Abnormal liver function tests (notify your doctor if you experience any nausea, reduced appetite, excessive tiredness or jaundice yellow skin discolouration as you may need to have a blood test).

Other side effects not listed above may also occur in some patients.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### 5. HOW TO STORE TIZANIDINE TABLETS

Keep out of the reach and sight of children.

Do not take Tizanidine tablets after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

#### 6. FURTHER INFORMATION

##### What Tizanidine tablets contain

The active substance is tizanidine hydrochloride equivalent to 2 mg, 4 mg or 6 mg tizanidine.

The other ingredients are cellulose microcrystalline, lactose anhydrous, silica colloidal anhydrous and stearic acid.

##### What Tizanidine tablets look like and contents of the pack

Tizanidine tablets are available in three strengths: 2 mg, 4 mg or 6 mg.

Tizanidine 2 mg Tablets are white to off white circular tablets, imprinted with 'T1' on one side and plain on the other side.

Tizanidine 4 mg Tablets are white to off white circular tablets, imprinted with 'T2' on one side and plain on the other side.

Tizanidine 6 mg Tablets are white to off white circular tablets, imprinted with 'T3' on one side and plain on the other side.

Tizanidine tablets are available in pack size of 120 tablets only.

**Marketing Authorisation Holder:** Ranbaxy (UK) Ltd., 20 Balderton Street, London W1K 6TL, United Kingdom.

**Manufacturer:** Ranbaxy Ireland Ltd., Spafield, Cork Road, Cashel, Co-Tipperary, Republic of Ireland.

This leaflet was approved in

**RANBAXY**

There is one pack design for each strength and so the labels are shown only once.

<p style="writing-mode: vertical-rl; transform: rotate(180deg);">2 mg 120 TABLETS BN EDC</p>	<p><b>Tizanidine 2 mg Tablets</b></p> <p>Each tablet contains tizanidine hydrochloride equivalent to 2 mg tizanidine. The tablets also contain lactose. Use as directed by a physician. For oral use only. Do not exceed the stated dose. Do not store above 25°C. Store in the original package.</p> <p><b>2 mg</b> 120 TABLETS</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. POM</p>	<p>Tizanidine Tabs 2 mg 120's Pack</p> <p>Size : 88 x 52 x 38 mm, CAG Market : UK Proof : 11-11-04, 16-11-04, 23-11-04 7-12-06, 14-2-07, 11-12-07</p> <p>.Z1104/08, K106/08</p> <p>Braille Text: Tizanidine 2 mg Tablets</p>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);">2 mg 120 TABLETS BN EDC</p>	<p>120 TABLETS</p> <p><b>RANBAXY</b></p> <p><b>Tizanidine</b> 2 mg Tablets</p> <p><b>2 mg</b></p> <p>Please read the enclosed leaflet carefully with this medicine</p>	<p>5 015525 201110</p>
<p style="writing-mode: vertical-rl; transform: rotate(180deg);">2 mg 120 TABLETS BN EDC</p>	<p><b>RANBAXY</b></p> <p><b>Tizanidine 2 mg Tablets</b></p> <p>PL No. 14894/0352</p> <p>MA Holder: <b>Ranbaxy (UK) Limited</b>, 20 Balderton Street, London W1K 6TL, UK.</p> <p>CODE No. MPDRUGS0504/83</p>	<p><b>2 mg</b> 120 TABLETS</p>

**For further information for more information see:**

<b>RANBAXY</b> Tizanidine 2 mg Tablets	<b>RANBAXY</b> Tizanidine 4 mg Tablets	<b>RANBAXY</b> Tizanidine 6 mg Tablets
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Presented through the fol from the other side.

CODE No. MPDRUGS0504/83

<p><b>Tizanidine 4 mg Tablets</b></p> <p>Each tablet contains tizanidine hydrochloride equivalent to 4 mg tizanidine. The tablets also contain lactose. Use as directed by a physician. For oral use only. Do not exceed the stated dose. Do not store above 25°C. Store in the original package.</p> <p><b>4 mg</b> 120 TABLETS</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p>POM</p> <p>BN EPC</p>	
<p>All's pharmaceutical label:</p> 	<p>Tizanidine Tabs 4 mg 120's Pack</p> <p>Size : 96 x 52 x 42 mm, CAG Market : UK Prod : 11-11-04, 16-11-04, 23-11-04 7-12-06, 14-2-07, 11-12-07</p> <p>J21/04/08, K10/W08</p> <p>Braille Text: Tizanidine 4 mg Tablets</p> 
<p><b>RANBAXY</b> Tizanidine 4 mg Tablets</p> <p><b>4 mg</b> 120 TABLETS</p>	<p>120 TABLETS</p> <p><b>RANBAXY</b></p> <p><b>Tizanidine</b> 4 mg Tablets</p> <p><b>4 mg</b></p> <p>Please refer to enclosed leaflet for use and storage of this medicine</p>
	<p><b>RANBAXY</b></p> <p><b>Tizanidine 4 mg Tablets</b></p> <p><b>4 mg</b> 120 TABLETS</p> <p>PL No. 14894/0353 MA Holder: <b>Ranbaxy (UK) Limited</b>, 20 Balderton Street, London W1K 6TL, UK.</p> <p>CODE No: WFRU65252483</p>

Press tablet through perforation from the other side.

**RANBAXY** **RANBAXY** **RANBAXY**  
Tizanidine Tizanidine Tizanidine

**4 mg** **4 mg** **4 mg**

Tablets Tablets Tablets  
Ranbaxy (UK) Limited Ranbaxy (UK) Limited Ranbaxy (UK) Limited

Press tablet through the foil from the other side.

**RANBAXY** **RANBAXY** **RANBAXY**  
Tizanidine Tizanidine Tizanidine

**4 mg** **4 mg** **4 mg**

Tablets Tablets Tablets  
Ranbaxy (UK) Limited Ranbaxy (UK) Limited Ranbaxy (UK) Limited

CODE No: WFRU65252483 CODE No: WFRU65252483

<p style="writing-mode: vertical-rl; transform: rotate(180deg);">                 6 mg                  TIZANIDINE                  TABLETS             </p>	<p><b>RANBAXY</b>  <b>Tizanidine 6 mg Tablets</b></p> <p>Each tablet contains tizanidine hydrochloride equivalent to 6 mg tizanidine.                  The tablets also contain lactose.                  Use as directed by a physician.                  For oral use only.                  Do not exceed the stated dose.                  Do not store above 25°C.                  Store in the original package.</p> <p style="text-align: right;"> <b>6 mg</b>                  120 TABLETS                  KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.                  POM             </p>	<p>BN                  EP</p>
<p>After pharmacist label:</p> 		
<p style="text-align: center;"> <b>RANBAXY</b>  <b>Tizanidine</b>  <b>6 mg Tablets</b> </p> <p style="text-align: right;"> <b>6 mg</b>                  120 TABLETS             </p> <p style="text-align: right; font-size: small;">Please read the enclosed leaflet before taking this medicine</p>		
<p><b>RANBAXY</b>  <b>Tizanidine 6 mg Tablets</b></p> <p style="text-align: right;"> <b>6 mg</b>                  120 TABLETS             </p> <p>PL No. 14894/0354                  MA Holder:                  Ranbaxy (UK) Limited,                  20 Balderton Street,                  London W1K 6TL, UK.                  CODE No. NPNR0326A10</p>		

Braille Text:  
 Tizanidine  
 6 mg Tablets

