

**TIZANIDINE 6MG TABLETS  
(TIZANIDINE HYDROCHLORIDE)**

**PL 00289/0704**

**&**

**PL 00289/0705**

**UK Public Assessment Report**

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**TIZANIDINE 6MG TABLETS  
(TIZANIDINE HYDROCHLORIDE)**

**PL 00289/0704 & 0705**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Teva UK Limited Marketing Authorisations (licences) for the medicinal product Tizanidine 6mg Tablets (PL 00289/0704 & 0705) on 14<sup>th</sup> February 2008. This is a prescription-only medicine (POM) used to relieve the stiffness and restriction of muscles resulting from multiple sclerosis, injury or diseases of the spinal cord.

Tizanidine 6mg Tablets contain the active ingredient tizanidine (as tizanidine hydrochloride). Tizanidine belongs to a group of drugs called skeletal muscle relaxants.

Tizanidine 4mg Tablets was considered to be a generic version of the reference product Zanaflex 4mg (PL 21799/0016, Cephalon Limited) based on data submitted by Teva UK Limited. Data from Tizanidine 4mg Tablets were extrapolated to the Marketing Authorisation applied for, Tizanidine 6mg Tablets.

These applications are based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Tizanidine 6mg Tablets outweigh the risk; hence Marketing Authorisations have been granted.

**TIZANIDINE 6MG TABLETS  
(TIZANIDINE HYDROCHLORIDE)**

**PL 00289/0704**

**&**

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**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted Teva UK Limited Marketing Authorisations for the medicinal product Tizanidine 6mg Tablets (PL 00289/0704 & 0705) on 14<sup>th</sup> February 2008. The product is a prescription-only medicine.

These are abridged applications for Tizanidine 6mg Tablets, submitted under Article 10.3 of Directive 2001/83/EC, as amended. The applications refer to the Italian product, Sirdalud 6mg compressa, first licensed on 18<sup>th</sup> June 1993. This product is not marketed in the UK, so the applications refer to the UK-marketed product, Zanaflex 4mg (PL 21799/0016, Cephalon Limited), in the bioequivalence study. Zanaflex 4mg was originally granted a UK licence as PL 14700/0001 on 4<sup>th</sup> June 1997. The reference product has been authorised in the UK since 1997 and so the 10-year period of data exclusivity has expired.

The innovator UK SPC for Zanaflex 4mg states “The timing and frequency of dosing should 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. 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”. As the dosage range of the innovator product includes the dose of 6mg, the application for a 6mg strength tablet is acceptable.

Tizanidine 6mg Tablets contain the active ingredient tizanidine (as tizanidine hydrochloride). Tizanidine is a centrally acting skeletal muscle relaxant. Its principal site of action is the spinal cord, where the evidence suggests that it reduces muscle tone. In addition to its muscle-relaxant properties, tizanidine also exerts a moderate central analgesic effect. The product is used for the treatment of spasticity associated with multiple sclerosis or with spinal cord injury or disease.

These applications depend upon the bioequivalence study presented by the applicant comparing the Teva UK Limited manufactured Tizanidine 4mg Tablets with the reference product Zanaflex 4mg (PL 21799/0016, Cephalon Limited). As the Teva UK Limited test products, Tizanidine 4mg Tablets and Tizanidine 6mg Tablets, were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg strength were extrapolated to the 6mg strength tablets.

These applications for Tizanidine 6mg Tablets were submitted at the same time and both depend on the bioequivalence study presented. All sections of the Scientific Discussion refer to both product licences.

## PHARMACEUTICAL ASSESSMENT

### ACTIVE SUBSTANCE

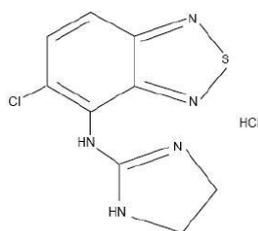
#### Tizanidine hydrochloride

Nomenclature:

INN: Tizanidine hydrochloride

Chemical name: 5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiazol-2-amine hydrochloride

Structure:



Molecular formula:  $C_9H_8ClN_5S.HCl$

Molecular weight: 290.2

CAS No: 51322-75-9

Physical form: White to off white crystalline powder with a melting point of  $290^{\circ}C$ , none hygroscopic and no polymorphism

Tizanidine hydrochloride is not described in the British Pharmacopeia (BP) or European Pharmacopeia (EP).

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin, and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which was set by the DMF (Drug Master File) holder. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for working reference standards used by the active substance manufacturer during validation studies.

Active tizanidine hydrochloride is stored in appropriate packaging. It is packed into polyethylene bags, which are then placed in polyethylene drums for storage and distribution. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active

substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the drug substance and supports a retest period of 36 months when stored in the proposed packaging.

## **DRUG PRODUCT**

### **Description and Composition**

The drug product is presented as white to off-white, biplane, round tablets debossed T6 on one side, and plain on the other. The tablets contain 6mg of the active ingredient tizanidine.

Other ingredients consist of pharmaceutical excipients, namely lactose anhydrous, ProSolv SMCC 50, ProSolv SMCC 90, and stearic acid. Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of ProSolv SMCC 50 and ProSolv SMCC 90 (which comply with suitable in-house specifications). The components of ProSolv SMCC 50 and ProSolv SMCC 90 (microcrystalline cellulose and colloidal silica anhydrous) are stated as complying with the European Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for all excipients.

The stearic acid is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose anhydrous. The applicant has provided a declaration that milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

### **Impurity profiles**

Dissolution profiles for the drug product were comparable to those for the European (Italy and Germany) marketed Tizanidine 6mg tablets equivalent products, as well as to those for the reference product, Zanaflex 4mg.

Impurity profiles for the drug product were found to be similar to those for the products marketed in the EU, and all the impurities are within the specification limits.

### **Pharmaceutical development**

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

### **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 studies have been conducted and 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**

The tablets are packed in aluminium / polyvinylidene chloride / polyvinylchloride blisters, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in carton pack sizes of 10, 14, 20, 30, 50, 50 (hospital pack), 100, and 120 tablets. The MA Holder has stated that not all pack sizes will be marketed and has committed to submitting mock-ups before marketing pack sizes of finished product.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years has been set, with the storage instructions “Do not store above 30 degrees”. This is satisfactory.

**Bioequivalence Study**

A bioequivalence study was submitted comparing the test product, Tizanidine 4mg Tablets, to the reference product, Zanaflex 4mg (PL 21799/0016, Cephalon Limited).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

**Expert Report**

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

**Product Information**

The approved SmPCs, leaflets, and labelling are satisfactory.

**Conclusion**

Considering the bioequivalence, and other quality, data provided, Tizanidine 4mg Tablets has been shown to be a generic medicinal product of Zanaflex 4mg. The results of the bioequivalence study were extrapolated to the 6mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations may be granted.

## **PRECLINICAL ASSESSMENT**

These applications for Tizanidine 6mg Tablets were submitted as abridged applications, according to Article 10.3 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

## **CLINICAL ASSESSMENT**

### **INDICATIONS**

Tizanidine 6mg Tablets are indicated for the treatment of spasticity associated with multiple sclerosis or with spinal cord injury or disease.

The indications are consistent with those for the innovator product and are satisfactory.

### **POSODOLOGY AND METHOD OF ADMINISTRATION**

The posology is consistent with that for the innovator product and is satisfactory.

### **TOXICOLOGY**

No new data has been submitted and none are required for this type of application.

### **CLINICAL PHARMACOLOGY**

#### **Pharmacodynamics**

Tizanidine is a centrally acting skeletal muscle relaxant. Its principal site of action is the spinal cord, where the evidence suggests that, by stimulating presynaptic alpha<sub>2</sub>-receptors, it inhibits the release of excitatory aminoacids that stimulate N-methyl-D-aspartate (NMDA) receptors. Polysynaptic signal transmission at spinal interneuron level, which is responsible for excessive muscle tone, is thus inhibited and muscle tone reduced. In addition to its muscle-relaxant properties, tizanidine also exerts a moderate central analgesic effect.

In humans, tizanidine reduces pathologically increased muscle tone, including resistance to passive movements and alleviates painful spasms and clonus.

#### **Pharmacokinetics**

Tizanidine is rapidly absorbed, reaching peak plasma concentration in approximately 1 hour after dosing. 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. The metabolites are primarily excreted via the renal route (approximately 70% of the administered dose). The elimination half-life of tizanidine from plasma is 2-4 hours in patients. Tizanidine has linear pharmacokinetics over the dose range 4 to 20 mg.

#### **Pharmacokinetics - Bioequivalence studies**

The applicant presented a single bioequivalence study comparing the test product, Tizanidine 4mg Tablets, to the reference product, Zanaflex 4mg (PL 21799/0016, Cephalon Limited) in fasting healthy subjects. This was a randomised, single-dose, open-label, crossover, two-period study conducted in 32 subjects, with 30 completing the study.

Each subject received 1 x 4mg tizanidine tablet (test) or 1 x 4mg Zanaflex tablet (reference). Treatment periods 1 and 2 were separated by 14 days for wash out purposes. Blood samples were taken over 10 hours as per protocol and analysed by a validated HPLC method.

The results of the main pharmacokinetic parameters are presented below.

<b>Parameter</b>	<b>Test</b>	<b>Reference</b>	<b>Point estimate (90% CI)</b>
$C_{max}$ (ng/ml)	4.986	4.771	Lower 90% CI: 85.48% Upper 90% CI: 116.49%
$AUC_{0-t}$ (ng.hr/ml)	12.98	12.22	Lower 90% CI: 89.62% Upper 90% CI: 117.16%
$AUC_{\infty}$ (ng.hr/ml)	13.93	13.28	Lower 90% CI: 90.33% Upper 90% CI: 117.32%

The 90% confidence intervals are all within the acceptable range of 80% to 125% specified for bioequivalence between products, and the test product can be considered to be bioequivalent to the reference product.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg strength were extrapolated to the 6mg strength product.

### **EFFICACY**

No new data are submitted and none are required for applications of this type.

Efficacy is reviewed in the clinical overview. The reference product is established and the applications depend upon the bioequivalence study.

### **SAFETY**

No new data are submitted and none are required for applications of this type.

Safety is reviewed in the clinical overview. The reference product is established and the applications depend upon the bioequivalence study.

### **EXPERT REPORT**

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

### **PRODUCT INFORMATION:**

#### **Summary of Product Characteristics (SmPC)**

The approved SmPCs are consistent with that for the reference product and are acceptable.

#### **Patient Information Leaflet (PIL)**

The PILs are in line with the approved SmPCs and are satisfactory.

### **Labelling**

Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

### **CONCLUSIONS**

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Tizanidine 4mg Tablets) and reference (Zanaflex 4mg) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 4mg strength were extrapolated to the 6mg strength product.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations may be granted on medical grounds.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Tizanidine 6mg 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.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

Bioequivalence has been demonstrated between the applicant's Tizanidine 4mg Tablets, and the reference product Zanaflex 4mg (PL 21799/0016, Cephalon Limited).

As Teva UK manufactured Tizanidine 4mg Tablets and Tizanidine 6mg Tablets were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg strength were extrapolated to the 6mg tablet strength, and no separate bioequivalence studies were necessary.

No new or unexpected safety concerns arise from these applications.

### **PRODUCT LITERATURE**

The SmPCs, PILs and labelling are satisfactory and consistent with those for the innovator product.

Package leaflets have been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflets contain.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

### **RISK BENEFIT ASSESSMENT**

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study, and the valid extrapolation of its results and conclusions, support the claim that Tizanidine 6mg Tablets are a hybrid version of Zanaflex 4mg. Extensive clinical experience with tizanidine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

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**STEPS TAKEN FOR ASSESSMENT**

- 1 The MHRA received the marketing authorisation applications on 1<sup>st</sup> July 2004
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 29<sup>th</sup> July 2004
- 3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 25<sup>th</sup> April 2005
- 4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 20<sup>th</sup> July 2005
- 5 Following assessment of the response the MHRA requested further information relating to the quality sections on 19<sup>th</sup> April 2006
- 6 The applicant responded to the MHRA's request, providing further information for the quality sections on 21<sup>st</sup> October 2006
- 7 The applications were determined on 14<sup>th</sup> February 2008

## SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Tizanidine 6mg Tablets (PL 00289/0704 and 0705) is as follows:

### 1 NAME OF THE MEDICINAL PRODUCT

Tizanidine 6 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 6 mg of tizanidine (as hydrochloride).

#### Excipients:

Each tablet contains 113.53 mg of lactose, anhydrous.

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet.

White to off-white, biplane, round tablets, 9 mm in diameter,, debossed "T6" on one side, plain on the other.

### 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 use

The effect of tizanidine on spasticity is maximal within 2-3 hours of dosing and it has a relatively short duration of action. The timing and frequency of dosing should therefore be tailored to the individual, and tizanidine should be given in divided doses, up to 3-4 times daily, depending on the patient's needs. There is considerable variation in response between patients so careful titration is necessary. Care should be taken not to exceed the dose producing the desired therapeutic effect. It is usual to start with a single dose of 2 mg increasing by 2 mg increments at no less than half-weekly intervals. The optimum therapeutic response is generally achieved with a daily dose of between 12 and 24 mg, administered in 3 or 4 equally spaced doses. Single doses should not exceed 12 mg. The total daily dose should not exceed 36 mg.

Adverse events (see section 4.8) may occur at therapeutic doses but these can be minimised by slow titration so that in the large majority of patients they are not a limiting factor.

#### *Discontinuing therapy*

If therapy needs to be discontinued, particularly in patients who have been receiving high doses for long periods, the dose should be decreased slowly (see section 4.4).

#### *Elderly*

Experience in the elderly is limited and use of tizanidine is not recommended unless the benefit of treatment clearly outweighs the risk. Pharmacokinetic data suggest that renal clearance in the elderly may be decreased by up to three fold.

#### *Children and adolescents*

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

*Patients with Renal impairment*

In patients with renal insufficiency (creatinine clearance < 25 ml/min) treatment should be started with 2 mg once daily with slow titration to achieve the effective dose. Dosage increases should be in increments of no more than 2 mg according to tolerability and effectiveness. It is advisable to slowly increase the once-daily dose before increasing the frequency of administration. Renal function should be monitored as appropriate in these patients (see section 4.4).

*Patients with Hepatic Impairment*

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

**4.3 CONTRAINDICATIONS**

The use of tizanidine in patients with significantly impaired hepatic function is contraindicated, because tizanidine is extensively metabolised by the liver.

Concomitant use of tizanidine with strong inhibitors of CYP1A2 such as fluvoxamine or ciprofloxacin is contra-indicated (see sections 4.4 and 4.5).

Hypersensitivity to tizanidine or to any of the excipients.

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE***Cytochrome P450 (CYP) inhibitors*

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

*Hypotension*

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

*Withdrawal syndrome*

Rebound hypertension and tachycardia have been observed after sudden withdrawal of tizanidine, when it had been used chronically, and/or in high daily dosages, and/or concomitantly with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident. Tizanidine should not be stopped abruptly, but rather gradually (see sections 4.2, 4.5 and 4.8).

*Use in Renal Impairment*

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

*Cardiovascular, hepatic or renal disorders*

Caution is required in patients with cardiovascular disorders, coronary artery disease or renal or hepatic disorders. Regular clinical laboratory and ECG monitoring is recommended during treatment with tizanidine.

*Hepatic dysfunction*

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

This medicinal product contains lactose monohydrate. 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**

##### *CYP inhibitors*

Concomitant administration of agents known to inhibit the activity of CYP1A2 may increase the plasma levels of tizanidine (see section 5.2). Concomitant use of tizanidine with fluvoxamine or ciprofloxacin, both CYP1A2 inhibitors in man, is contraindicated (see section 4.3), as it resulted in a 33-fold and 10-fold increase in tizanidine AUC, respectively. Clinically significant and prolonged hypotension may result along with somnolence, dizziness and decreased psychomotor performance (see section 4.4). Coadministration of tizanidine with other inhibitors of CYP1A2 such as some antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, some fluoroquinolones (enoxacin, pefloxacin, norfloxacin), rofecoxib, oral contraceptives, and ticlopidine is not recommended (see section 4.4).

Caution should be exercised when tizanidine is prescribed with substances known to increase the QT interval. Electrocardiographic monitoring may be advisable.

##### *Antihypertensives*

As tizanidine may induce hypotension it may potentiate the effect of antihypertensive products, including diuretics, and caution should therefore be exercised in patients receiving blood pressure lowering products. Caution should also be exercised when tizanidine is used concurrently with  $\beta$ -adrenoceptor blocking substances or digoxin as the combination may potentiate hypotension or bradycardia. In some patients rebound hypertension and tachycardia have been observed upon abrupt discontinuation of tizanidine when concomitantly used with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident (see sections 4.4 and 4.8).

Pharmacokinetic data following single and multiple doses of tizanidine suggested that clearance of tizanidine was reduced by approximately 50% in women who were concurrently taking oral contraceptives. Although no specific pharmacokinetic study has been conducted to investigate a potential interaction between oral contraceptives and tizanidine, the possibility of a clinical response and/or adverse effects occurring at lower doses of tizanidine should be borne in mind when prescribing tizanidine to a patient taking the contraceptive pill. Clinically significant interactions have not been reported in clinical trials.

Alcohol or centrally-acting agents may enhance the sedative action of tizanidine.

#### **4.6 PREGNANCY AND LACTATION**

##### *Pregnancy*

Animal studies did not indicate embryotoxic and teratogenic effects in animals. As there have been no controlled studies in pregnant women, however, it should not be used during pregnancy unless the benefit clearly outweighs the risk.

##### *Lactation*

Although only small amounts of tizanidine are excreted in animal milk, tizanidine should not be taken by women who are breast-feeding.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

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

#### 4.8 UNDESIRABLE EFFECTS

The adverse effects are classified below by system organ class according to the following convention:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $\leq 1/100$ )

Rare ( $\geq 1/10,000$  to  $\leq 1/1,000$ )

Very rare, including isolated reports ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

##### *Cardiac disorders*

Common: bradycardia, tachycardia (see sections 4.4 and 4.5)

Not known: QT prolongation has been reported in post-marketing surveillance (see section 4.9)

##### *Nervous system disorders*

Common: drowsiness\*\*, fatigue\*\*, dizziness\*\*

Rare: sleep disorders, insomnia

Not known: headache, ataxia

##### *Eye disorders*

Not known: accommodation disorder

##### *Gastrointestinal disorders*

Common: dry mouth\*\*, nausea\*\*, gastrointestinal disturbances\*\*

##### *Skin and subcutaneous tissue disorders*

Rare: Allergic reactions (e.g. pruritus and rash)

##### *Musculoskeletal, connective tissue and bone disorders*

Rare: Muscle weakness

##### *Vascular disorders*

Common: reduction in blood pressure\*\*, rebound hypertension (see sections 4.4 and 4.5)

##### *General disorders and administration site conditions*

Not known: absence of appetite

##### *Hepato-biliary disorders*

Rare: increases in hepatic serum transaminases

Very rare: hepatitis, hepatic failure

##### *Psychiatric disorders*

Rare: hallucinations\*

Not known: anxiety disorders

- \* The hallucinations are self-limiting, without evidence of psychosis, and have invariably occurred in patients concurrently taking potentially hallucinogenic substances, e.g. anti-depressants.
- \*\* With slow upward titration of the dose of tizanidine these effects are usually not severe enough to require discontinuation of treatment.

#### 4.9 OVERDOSE

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

*Symptoms:* Nausea, vomiting, hypotension, bradycardia, QT prolongation, dizziness, miosis, respiratory distress, coma, restlessness, somnolence.

*Treatment:* General supportive measures are indicated and an attempt should be made to remove uningested substance from the gastro-intestinal tract using gastric lavage by repeated administration of high doses of activated charcoal. The patient should be well hydrated. Further treatment should be symptomatic.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

*Pharmacotherapeutic group:* Musculo-skeletal system; muscle relaxants; centrally acting agents; other centrally acting agents

*ATC code:* M03B X02

Tizanidine is a centrally acting skeletal muscle relaxant. Its principal site of action is the spinal cord, where the evidence suggests that, by stimulating presynaptic alpha<sub>2</sub>-receptors, it inhibits the release of excitatory aminoacids that stimulate N-methyl-D-aspartate (NMDA) receptors. Polysynaptic signal transmission at spinal interneuron level, which is responsible for excessive muscle tone, is thus inhibited and muscle tone reduced. Tizanidine has no direct effect on skeletal muscle, the neuromuscular junction or on monosynaptic spinal reflexes. In addition to its muscle-relaxant properties, tizanidine also exerts a moderate central analgesic effect.

In humans, tizanidine reduces pathologically increased muscle tone, including resistance to passive movements and alleviates painful spasms and clonus.

#### 5.2 PHARMACOKINETIC PROPERTIES

##### *Absorption*

Tizanidine is rapidly absorbed, reaching peak plasma concentration in approximately 1 hour after dosing.

##### *Distribution*

Tizanidine is only about 30% bound to plasma proteins and, in animal studies, was found to readily cross the blood-brain barrier. Mean steady-state volume of distribution (VSS) following i.v. administration is 2.6 L/kg.

##### *Metabolism*

Although tizanidine is well absorbed, first pass metabolism limits plasma availability to 34% of that of an intravenous dose. Tizanidine undergoes rapid and extensive metabolism in the liver. Tizanidine is mainly metabolized by cytochrome P450 1A2 in vitro.

##### *Elimination*

The metabolites are primarily excreted via the renal route (approximately 70% of the administered dose) and appear to be inactive. Renal excretion of the parent compound is approximately 53% after a single 5 mg dose and 66% after dosing with 4 mg three times daily. The elimination half-life of tizanidine from plasma is 2-4 hours in patients.

#### *Linearity*

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

#### *Characteristics in special patient populations*

The pharmacokinetic parameters of tizanidine are not affected by gender.

In patients with renal insufficiency (creatinine clearance < 25 mL/min), maximal mean plasma levels were found to be twice as high as in normal volunteers, and the terminal half-life was prolonged to approximately 14 hours, resulting in much higher (approximately 6-fold on average) AUC values (see section 4.4).

#### *Effect of food*

Concomitant food intake has no clinically significant influence on the pharmacokinetic profile of tizanidine tablets.

### **5.3 PRECLINICAL SAFETY DATA**

#### Acute toxicity

Tizanidine possesses a low order of acute toxicity. Signs of overdose were seen after single doses > 40 mg/kg in animals and are related to the pharmacological action of the substance.

#### Repeat dose toxicity

The toxic effects of tizanidine are mainly related to its pharmacological action. At doses of 24 and 40 mg/kg per day in subchronic and chronic rodent studies, the  $\alpha_2$ -agonist effects resulted in central nervous system stimulation, e.g. motor excitation, aggressiveness, tremor and convulsions.

Signs related to centrally mediated muscle relaxation, e.g. sedation and ataxia, were frequently observed at lower dose levels in subchronic and chronic oral studies with dogs. Such signs, related to the myotonolytic activity of the substance, were noted at 1 to 4 mg/kg per day in a 13 week dog study, and at 1.5 mg/kg per day in a 52-week dog study.

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses of 1.0 mg/kg per day and above.

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

Slight increases in hepatic serum transaminases were observed in a number of toxicity studies at higher dose levels. They were not consistently associated with histopathological changes in the liver.

#### Mutagenicity

Various in vitro assays as well as in vivo assays produced no evidence of mutagenic potential of tizanidine.

#### Carcinogenicity

No evidence for carcinogenicity was demonstrated in two long-term dietary studies in mice (78 weeks) and rats (104 weeks), at dose levels up to 9 mg/kg per day in rats and up to 16 mg/kg per day in mice. At these dose levels, corresponding to the maximum tolerated dose, based on reductions in growth rate, no neoplastic or pre-neoplastic pathology, attributable to treatment, was observed.

#### Reproductive toxicity

No embryotoxicity or teratogenicity occurred in pregnant rats and rabbits at dose levels up to 30 mg/kg per day of tizanidine. However, doses of 10-100 mg/kg per day in rats were maternally toxic and resulted in developmental retardation of fetuses as seen by lower foetal body weights and retarded skeletal ossification.

In female rats, treated prior to mating through lactation or during late pregnancy until weaning of the young, a dose-dependent (10 and 30 mg/kg per day) prolongation of gestation time and dystocia occurred, resulting in an increased foetal mortality and delayed development. These effects were attributed to the pharmacological effect of tizanidine. No developmental effects occurred at 3 mg/kg per day although sedation was induced in the treated dams.

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

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

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

### **6.2 INCOMPATIBILITIES**

Not applicable

### **6.3 SHELF LIFE**

3 years

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Do not store above 30°C

### **6.5 NATURE AND CONTENTS OF CONTAINER**

PVC/PVdC-aluminium blisters.

Blister packs of 10, 20, 30, 50, 50 (hospital pack), 100 and 120 tablets.

Not all pack sizes may be marketed.

### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements

## **7 MARKETING AUTHORISATION HOLDER**

Teva UK Ltd  
Brampton Road, Hampden Park  
Eastbourne, BN22 9AG  
England

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

PL 00289/0704  
PL 00289/0705

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

14/02/2008

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

14/02/2008

## PATIENT INFORMATION LEAFLET

## Tizanidine 6mg Tablets – PL 00289/0704

**TIZANIDINE 6 mg TABLETS**  
tizanidine hydrochloride**PACKAGE LEAFLET: INFORMATION FOR THE USER**

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 any further questions, ask your doctor or 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 get 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 is and what it is used for
2. Before you take Tizanidine
3. How to take Tizanidine
4. Possible side effects
5. How to store Tizanidine
6. Further information

**1 WHAT TIZANIDINE IS AND WHAT IT IS USED FOR**

- Tizanidine belongs to a group of medicines called skeletal muscle relaxants.
- Your medicine is used to relieve the stiffness and restriction of muscles resulting from multiple sclerosis, injury or diseases of the spinal cord.

**2 BEFORE YOU TAKE TIZANIDINE**

**Do NOT take Tizanidine if you:**

- Are allergic (hypersensitive) to tizanidine or any of the ingredients in your medicine
- Have liver problems
- Are taking medicines such as fluvoxamine (for depression) or ciprofloxacin (an antibiotic) (see also 'Taking other medicines', below)

**Take special care with Tizanidine**

Tell your doctor before taking Tizanidine if you:

- have kidney problems
- have heart problems
- have liver problems

**Taking other medicines**

Tizanidine must not be taken at the same time as fluvoxamine (to treat depression) ciprofloxacin (an antibiotic) (see 'Do NOT take Tizanidine if you', above)

Please tell your doctor or pharmacist if you are taking

- any medicine to treat an abnormal heart rhythm, such as amiodarone, mexiletine, propafenone
- cimetidine (for indigestion and digestive ulcers)
- some antibiotics known as fluoroquinolones, such as enoxacin, pefloxacin, norfloxacin
- rofecoxib (a painkiller)
- the contraceptive pill. You may respond to a lower dose of Tizanidine if you are taking the contraceptive pill
- ticlopidine (to prevent blood clots)
- any medicines used to treat high blood pressure, including diuretics (water tablets)
- beta blockers e.g. atenolol, propranolol
- digoxin (used to treat congestive heart failure and problems with heart rhythm)
- any sedatives (sleeping pills or medicines for anxiety) e.g. temazepam

- any other medicines which, when taken with Tizanidine, might affect your heart's rhythm, check with your doctor or pharmacist.

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

**Taking Tizanidine with food and drink**

Tizanidine can be taken independently of meals. Alcohol may increase the sedative effect of Tizanidine. It is recommended not to drink alcohol while taking Tizanidine.

**Pregnancy and Breast feeding**

It is not recommended to take Tizanidine during pregnancy or whilst breast feeding. Tell your doctor if you think you may be pregnant, and ask your doctor for advice before taking any medicine.

**Driving and using machines:**

Tizanidine may cause drowsiness (see '4. Possible side effects'). Alcohol and sedatives may increase this effect. If you are affected do not drive or operate machinery.

**Important information about some of the ingredients in your medicine:**

This product 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**

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

The usual dosage instructions are given below:

**Adults:**

Your doctor will usually start you on a single dose of 2 mg which will then be gradually increased. Your dose should not be increased more often than every three to four days. As the dose is increased your doctor will advise you to spread the dose out to three or four times a day.

The usual daily dose is up to 24 mg (4 of the 6 mg tablets). The maximum daily dose is 36 mg.

**Elderly:**

Your doctor will decide if you should take Tizanidine

**Children (under 18 years):**

Tizanidine is not recommended for use in children.

**Patients with kidney problems:**

Treatment should be started with 2 mg once daily. Your doctor will advise you on how to increase your dose.

**If you take more Tizanidine than you should**

If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.

An overdose is likely to cause nausea (feeling sick), vomiting (being sick), low blood pressure, a slow or abnormal heartbeat, dizziness, small pupils, difficulty breathing, coma, restlessness or sleepiness. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

**If you forget to take Tizanidine**

If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Tizanidine**

Do not stop taking Tizanidine unless your doctor tells you to. Treatment with Tizanidine should be stopped gradually, especially if you have been taking a high dose, unless your doctor has told you otherwise. Stopping treatment suddenly may cause effects such as an increase in heart rate and high blood pressure.

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 can cause side effects, although not everybody gets them.

The following side effects have been reported at the approximate frequencies shown:

**Common (affecting fewer than one person in 10 but more than one person in 100):**

- drowsiness, tiredness, dizziness
- reduction in blood pressure
- increase of blood pressure when stopping the treatment suddenly
- dry mouth
- nausea (feeling sick), stomach upsets
- decrease or increase in heart rate.

**Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):**

- hallucinations
- sleep disorders including difficulty in sleeping
- allergic reactions (itching, rash)
- changes in the function of the liver - it may be necessary to have blood tests to monitor this
- muscle weakness.

**Very rare (affecting fewer than one person in 10,000):**

- inflammation of the liver (hepatitis) or liver failure, which may lead to yellowing of the eyes or skin and/or production of dark urine. Consult your doctor immediately if this occurs.

**Other side effects (frequency unknown):**

- abnormal heart rhythms
- headache, abnormal movements
- difficulty focusing the eyes
- loss of appetite
- anxiety

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

**5 HOW TO STORE TIZANIDINE****Keep out of the reach and sight of children.**

Do not use Tizanidine after the expiry date shown on the outer packaging. The expiry date refers to the last day of that month. Do not store above 30°C.

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(s):**

- The active ingredient is tizanidine hydrochloride. Each tablet contains 6 mg of tizanidine (as tizanidine hydrochloride)
- The other ingredients are lactose anhydrous, cellulose microcrystalline, stearic acid and silica colloidal anhydrous.

**What Tizanidine tablets look like and contents of the pack:**

- Tizanidine 6 mg tablets are white to off-white, biplane, round tablets, 9 mm in diameter, debossed "T6" on one side and plain on the other.
- Available in pack sizes of: 10, 20, 30, 50 100 and 120 tablets

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer.**

TEVA UK Limited, Eastbourne BN22 9AG

This leaflet was revised in October 2007

PL 00289/0704

## Tizanidine 6mg Tablets – PL 00289/0705

**TIZANIDINE 6 mg TABLETS**  
tizanidine hydrochloride**PACKAGE LEAFLET: INFORMATION FOR THE USER**

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 any further questions, ask your doctor or 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.
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**IN THIS LEAFLET:**

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2. Before you take Tizanidine
3. How to take Tizanidine
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- Have liver problems
- Are taking medicines such as fluvoxamine (for depression) or ciprofloxacin (an antibiotic) (see also 'Taking other medicines', below)

**Take special care with Tizanidine**

Tell your doctor before taking Tizanidine if you:

- have kidney problems
- have heart problems
- have liver problems

**Taking other medicines**

Tizanidine must not be taken at the same time as fluvoxamine (to treat depression) ciprofloxacin (an antibiotic) (see 'Do NOT take Tizanidine if you', above)

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**Marketing Authorisation Holder and Manufacturer.**

TEVA UK Limited, Eastbourne BN22 9AG

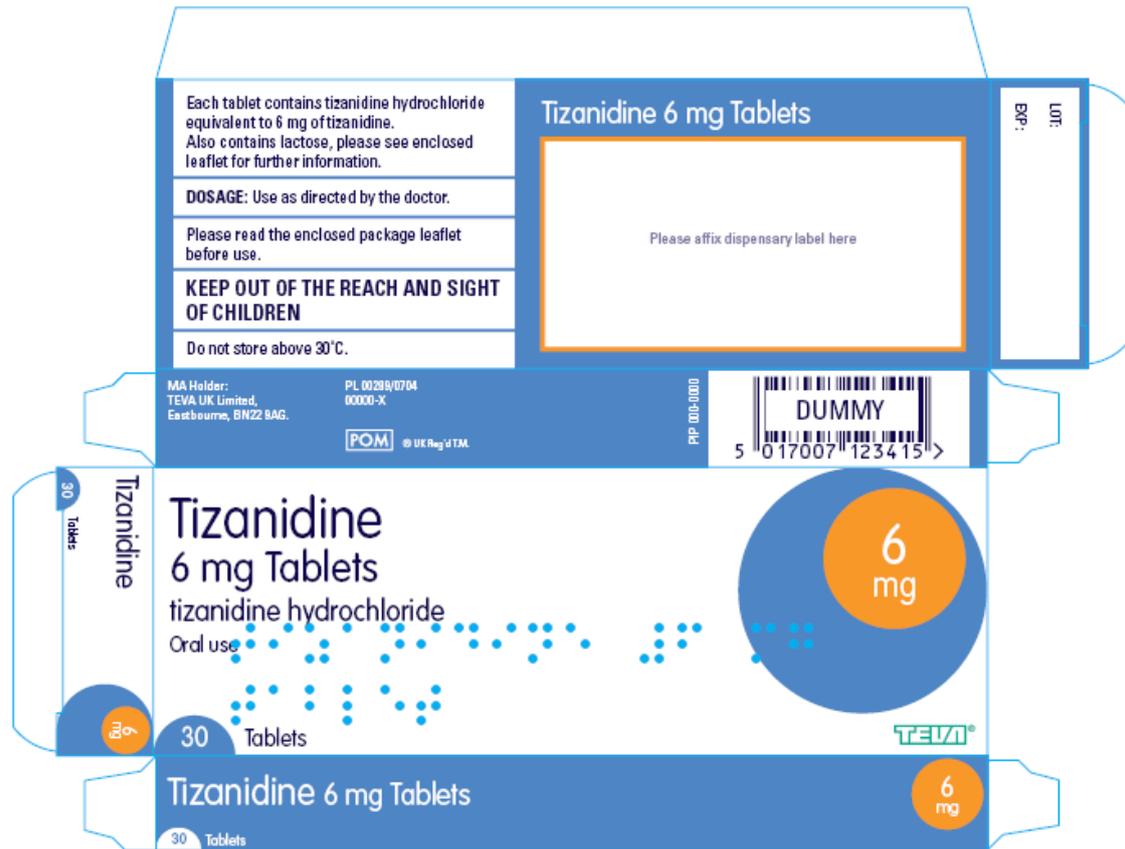
**This leaflet was revised in October 2007**

PL 00289/0705

### LABELLING

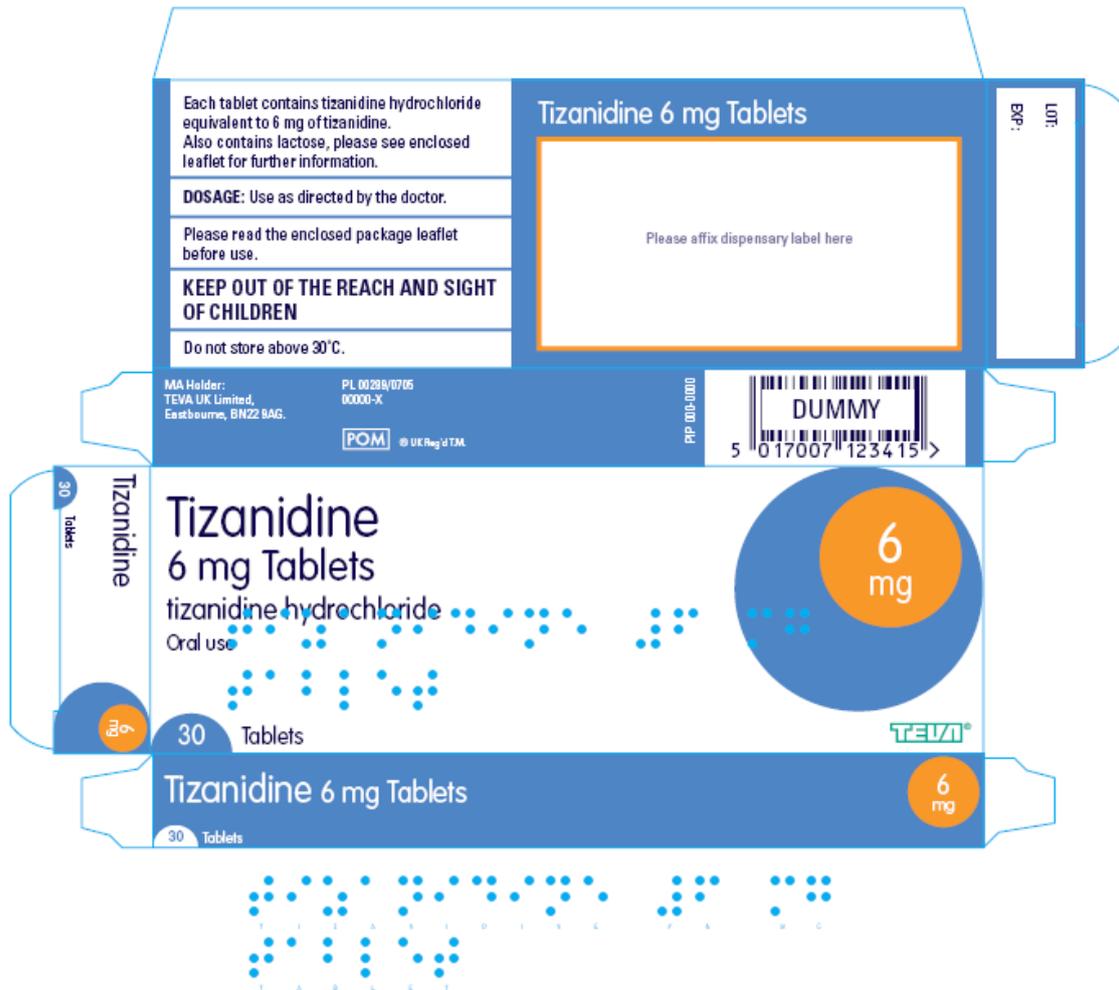
#### Tizanidine 6mg Tablets – PL 00289/0704

Carton for blisters, with braille



Braille reads: Tizanidine (numeral sign) 6 mg tablet

**Tizanidine 6mg Tablets – PL 00289/0705**  
Carton for blisters, with braille



Braille reads: Tizanidine (numeral sign) 6 mg tablet

Blister foil

Each blister will be embossed with the batch number and expiry date

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