TIZANIDINE 2MG TABLETS
PL 00289/0648
TIZANIDINE 4MG TABLETS
PL 00289/0649

UKPAR

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LAY SUMMARY

On 28th December 2006, the MHRA granted Teva UK Limited Marketing Authorisations (licences) for the medicinal products Tizanidine 2mg and 4mg Tablets (PL 00289/0648-9). These are prescription only medicines (POM) for use in relieving the stiffness and restriction of muscles resulting from multiple sclerosis, injury or diseases of the spinal cord.

Tizanidine 2mg and 4mg Tablets contain the active ingredient tizanidine (as tizanidine hydrochloride). Tizanidine belongs to a group of drugs called skeletal muscle relaxants.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Tizanidine 2mg and 4mg Tablets outweighs the risks, hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Tizanidine 2mg and 4mg Tablets (PL 00289/0648-9) to Teva UK Limited on 28th December 2006. The products are prescription-only medicines for the treatment of spasticity associated with multiple sclerosis or with spinal cord injury or disease.

These applications were submitted as abridged applications under Article 10.1 of Directive 2001/83/EC, as amended, as generic products of the reference products Zanaflex 2mg and 4mg Tablets (PL 14700/0001 and 3), which were originally granted licences in June 1997 to Athena Neurosciences (Europe) Limited.

Tizanidine 2mg and 4mg Tablets contain the active ingredient tizanidine hydrochloride. Tizanidine is an α_2-adrenergic receptor agonist within the central nervous system at supra-spinal and spinal levels. This effect results in inhibition of spinal polysynaptic reflex activity. Tizanidine has no direct effect on skeletal muscle, the neuromuscular junction or on monosynaptic spinal reflexes.

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

PHARMACEUTICAL ASSESSMENT

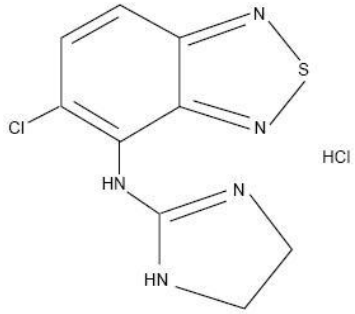
ACTIVE SUBSTANCE

Tizanidine Hydrochloride

INN/Ph.Eur name: Tizanidine hydrochloride

Chemical name: 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiodiazole hydrochloride

Structural formula



Molecular formula: $C_9H_8ClN_5S.HCl$

Molecular weight: 290.2

General Properties

Characteristics: White to slightly yellow crystalline powder with a melting point of 290˚C, none hygroscopic and no polymorphism

Tizanidine hydrochloride is not the subject of a European Pharmacopoeia, British Pharmacopoeia or a US Pharmacopeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. 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.

The active substance is packaged in polyethylene bags, which are then enclosed in polyethylene drums for storage and distribution. Satisfactory specifications and certificates of analysis have been provided for all packaging used. All primary packaging is in compliance with current directives concerning the contact of packaging with food.

Appropriate stability data have been provided for a retest period of 36 months if stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose anhydrous, ProSolv SMCC50, ProSolv SMCC90 and stearic acid. All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of ProSolv SMCC50 and ProSolv SMCC90 (which comply with suitable in-house specifications). The components of ProSolv SMCC50 and ProSolv SMCC90 (microcrystalline cellulose and colloidal anhydrous silica) are stated as complying with the European Pharmacopoeia. Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose anhydrous, none of the excipients used contain materials of animal or human origin. The manufacturer of lactose has confirmed that this is sourced from healthy animals under the same conditions as milk for human consumption and contains no calf rennet or other ruminant materials.

Product development

The applicant has provided a suitable product development section. Comparable impurity and dissolution profiles have been provided by the applicant, comparing the proposed products versus various European products (including the UK reference products).

Manufacture

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength of product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificate of analysis have been provided for all working standards used.

Container Closure System

The finished product is to be packaged in aluminium/polyvinylidene chloride/polyvinylchloride blisters, which are stored in a cardboard container. Pack sizes for all strengths are 15 (2mg only), 20, 30, 50, 100, 120, 200 (4mg only) and 500 tablets. The marketing authorisation holder has stated that not all proposed pack sizes are intended for marketing and has committed to submitting mock-ups before marketing any strengths of finished product.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding the contact of materials with foodstuff.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set for both strengths, with the storage instructions “Do not store above 30 degrees”. These are satisfactory.

The applicant has provided suitable post approval stability commitments to follow-up the current batches on stability and to add the first three commercial batches as they become available.

Bioequivalence
See Clinical Assessment.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
These are consistent with those for the reference products and are satisfactory.

Labelling
These are satisfactory

Patient Information Leaflet
These are consistent with the SPC and are satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation no later than 1st July 2008 with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups.

MAA Forms
These are satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance used in the proposed and reference products. In addition, similar dissolution and impurity profiles have been provided for the proposed and reference products and bioequivalence to a suitable reference product has been demonstrated.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The applicant commissioned one randomised, single-dose, open-label, crossover, two-period, bioequivalence study comparing Tizanidine 4mg Tablets (test product) and Zanaflex 4mg Tablets (reference product) in fasting healthy subjects.

Pharmacokinetic parameters were measured from blood samples taken pre- and post dose, followed by a suitable washout period.

The main pharmacokinetic results are presented below:

Parameter	Test product	Reference product	Pt estimate (90% CI)
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_{0-inf} (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 limits specified for bioequivalence between products and the test product can be considered a generic medicinal product 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 can be extrapolated to the 2mg strength product.

EFFICACY

No new data have been provided.

SAFETY

No new data have been provided.

EXPERT REPORTS

A clinical expert report has been written by a suitably qualified physician and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

These are consistent with those for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

These are consistent with the SPC and are satisfactory.

LABELLING

These are satisfactory

APPLICATION FORMS (MAA)

These are satisfactory.

DISCUSSION

Bioequivalence has been satisfactorily demonstrated for the 4mg product in accordance with CPMP criteria. As the lower strength, products 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 can be extrapolated to the 2mg strength tablets.

MEDICAL CONCLUSION

The grant of marketing authorisations is recommended for these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Tizanidine 2mg and 4mg 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

A bioequivalence study was carried out and the test and reference products were shown to be bioequivalent.

No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that for the UK reference products.

RISK BENEFIT ASSESSMENT

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 product and the reference product are interchangeable. The proposed products can be considered as generic medicinal products of Zanaflex 2mg and 4mg Tablets. Extensive clinical experience with tizanidine is considered to have demonstrated the therapeutic value of the compound.

The risk-benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 08/12/2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on the 12/02/2004
3	Following assessment of the application the MHRA requested further information on the 10/09/2004, 06/05/2005, 12/04/2006
4	The applicant responded to the MHRA's requests, providing further information on 16/12/2004, 20/07/2005, 25/08/2006, 15/09/2006
5	The application was determined on the 13/12/2006

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

TIZANIDINE 2MG TABLETS
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tizanidine 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of tizanidine (as 2.290 mg tizanidine hydrochloride).

Excipients:

Each tablet contains 57.910 mg of lactose, anhydrous.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, biconvex, round, tablets, debossed “T2” on one side and scoreline on the other.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Patients with renal impairment
In patients with renal insufficiency (creatinine clearance < 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.

Patients with hepatic impairment
Tizanidine is contraindicated in patients with significantly impaired hepatic function.

4.3 Contraindications
Hypersensitivity to tizanidine or to any of the excipients.

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 (serum glutamic-pyruvic transaminase) and/or SGOT (serum glutamic-oxaloacteic transaminase) are persistently above three times the upper limit of normal range.

Tizanidine should be kept out of the reach of children.

This medicinal product contains lactose anhydrous. 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 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 β-adrenoceptor blocking substances or digoxin as the combination may potentiate hypotension or bradycardia.

Caution should be exercised when tizanidine is prescribed with substances 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 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 fetal 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

Tizanidine has minor or moderate influence on the ability to drive and use machines: patients experiencing drowsiness 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 (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to ≤1/100)
Rare (≥1/10,000 to ≤1/1,000)
Very rare, including isolated reports (≤1/10,000)
Not known (cannot be estimated from the available data)

Psychiatric disorders
Rare: hallucinations*

Nervous system disorders
Common: drowsiness**, fatigue**, dizziness**
Rare: insomnia

Cardiovascular disorders
Common: reduction in blood pressure**, bradycardia

Gastrointestinal disorders
Common: dry mouth**
Rare: nausea**, gastrointestinal disturbances**

Hepato-biliary disorders
Rare: Increases in hepatic serum transaminases (reversible on stopping treatment)
Very rare: acute hepatitis

Skin and subcutaneous tissue disorders
Allergic reactions (e.g. pruritus and rash)

Musculoskeletal, connective tissue and bone disorders
Rare: Muscle weakness***

* 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.
*** In controlled clinical trials it was clearly demonstrated that tizanidine does not adversely affect muscle strength.

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, 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 or activated charcoal. The patient should be well hydrated.

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 an α2-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 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 α2-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.

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 fetal 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 fetal 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 15, 20, 30, 50, 100, 120 and clinical pack 500 (10x50) 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 00289/0648

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/12/2006

10 DATE OF REVISION OF THE TEXT

28/12/2006

TIZANIDINE 4MG TABLETS
PL 00289/0649

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tizanidine 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg of tizanidine (as 4.58 mg tizanidine hydrochloride).

Excipients:
Each tablet contains 115.82 mg of lactose, anhydrous.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White to off-white, biconvex, round, tablets, debossed “T4” on one side and quadrisected by scorelines on the other.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Patients with Renal impairment
In patients with renal insufficiency (creatinine clearance < 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.

Patients with Hepatic Impairment
Tizanidine is contraindicated in patients with significantly impaired hepatic function.

4.3 Contraindications
Hypersensitivity to tizanidine or to any of the excipients.

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 (serum glutamic-pyruvic transaminase) and/or SGOT (serum glutamic-oxaloacteic transaminase) are persistently above three times the upper limit of normal range.

Tizanidine should be kept out of the reach of children.

This medicinal product contains lactose anhydrous. 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 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 β-adrenoceptor blocking substances or digoxin as the combination may potentiate hypotension or bradycardia.

Caution should be exercised when tizanidine is prescribed with substances 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 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 fetal 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

Tizanidine has minor or moderate influence on the ability to drive and use machines: patients experiencing drowsiness 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 (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to ≤1/100)
Rare (≥1/10,000 to ≤1/1,000)
Very rare, including isolated reports (≤1/10,000)
Not known (cannot be estimated from the available data)

Psychiatric disorders
Rare: hallucinations*

Nervous system disorders
Common: drowsiness**, fatigue**, dizziness**
Rare: insomnia

Cardiovascular disorders
Common: reduction in blood pressure**, bradycardia

Gastrointestinal disorders
Common: dry mouth**
Rare: nausea**, gastrointestinal disturbances**

Hepato-biliary disorders
Rare: Increases in hepatic serum transaminases (reversible on stopping treatment)
Very rare: acute hepatitis

Skin and subcutaneous tissue disorders
Allergic reactions (e.g. pruritus and rash)

Musculoskeletal, connective tissue and bone disorders
Rare: Muscle weakness***

* 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.
*** In controlled clinical trials it was clearly demonstrated that tizanidine does not adversely affect muscle strength.

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, 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 or activated charcoal. The patient should be well hydrated.

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 an α2-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 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 α2-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.

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 fetal 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 fetal 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 15, 20, 30, 50, 100, 120 and clinical pack 500 (10x50) 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 00289/0649

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/12/2006

10 DATE OF REVISION OF THE TEXT

28/12/2006

TIZANIDINE 2 and 4 mg TABLETS

PATIENT INFORMATION LEAFLET

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, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

IN THIS LEAFLET:

The name of your medicine is **Tizanidine 2 mg or 4 mg Tablets.**

- The active ingredient is tizanidine hydrochloride.
- Other ingredients are lactose anhydrous, cellulose microcrystalline, stearic acid and silica colloidal anhydrous.
- Each tablet contains 2 or 4 mg of tizanidine (as tizanidine hydrochloride).
- The 2 mg tablets are available in pack sizes of 15, 20, 30, 50, 100, 120 & 500.
- The 4 mg tablets are available in pack sizes of 20, 30, 50, 100, 120, 200 & 500.

Not all pack sizes may be marketed.

The Marketing Authorisation holder and company responsible for manufacture: TEVA UK Limited, Eastbourne, BN22 9AG.

1 TIZANIDINE; WHAT IT IS AND WHAT IT'S USED FOR

- Tizanidine belongs to a group of drugs 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 sensitive to any of the ingredients in your medicine
- Have liver problems.

Check with your doctor before taking Tizanidine if you:
- Have kidney problems
- Are taking any medicine that may affect the heart's normal rhythm
- Are taking any medicine to treat high blood pressure
- Are taking beta blockers, e.g. atenolol, propranolol
- Are taking digoxin (used to treat congestive heart failure and problems with heart rhythm)
- Are taking any sedatives, e.g. temazepam
- Are on the contraceptive pill
- Are pregnant or breast-feeding.

Driving and using machines:
Tizanidine may cause drowsiness. 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:
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

Your doctor has decided the dose which is suited to you. Always follow your doctor's instructions and those which are on the pharmacy label. If you do not understand these instructions, or you are in any doubt, ask your doctor or pharmacist.

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. After one or two months, your doctor may give you 4 mg tablets to reduce the number of tablets you have to take.

The usual daily dose is up to 24 mg (12 of the 2 mg tablets or 6 of the 4 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.

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. Take the remaining doses at the correct time.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Tizanidine can have side effects.

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
- Dry mouth
- Decrease in heart rate.

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):
- Hallucinations
- Difficulty in sleeping
- Nausea, stomach upsets
- 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):
- Yellowing of the eyes or skin and/or production of dark urine. Consult your doctor immediately if this occurs.

Other side effects:
- Allergic reactions such as rashes or itching.

If you notice these or any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5 STORING TIZANIDINE

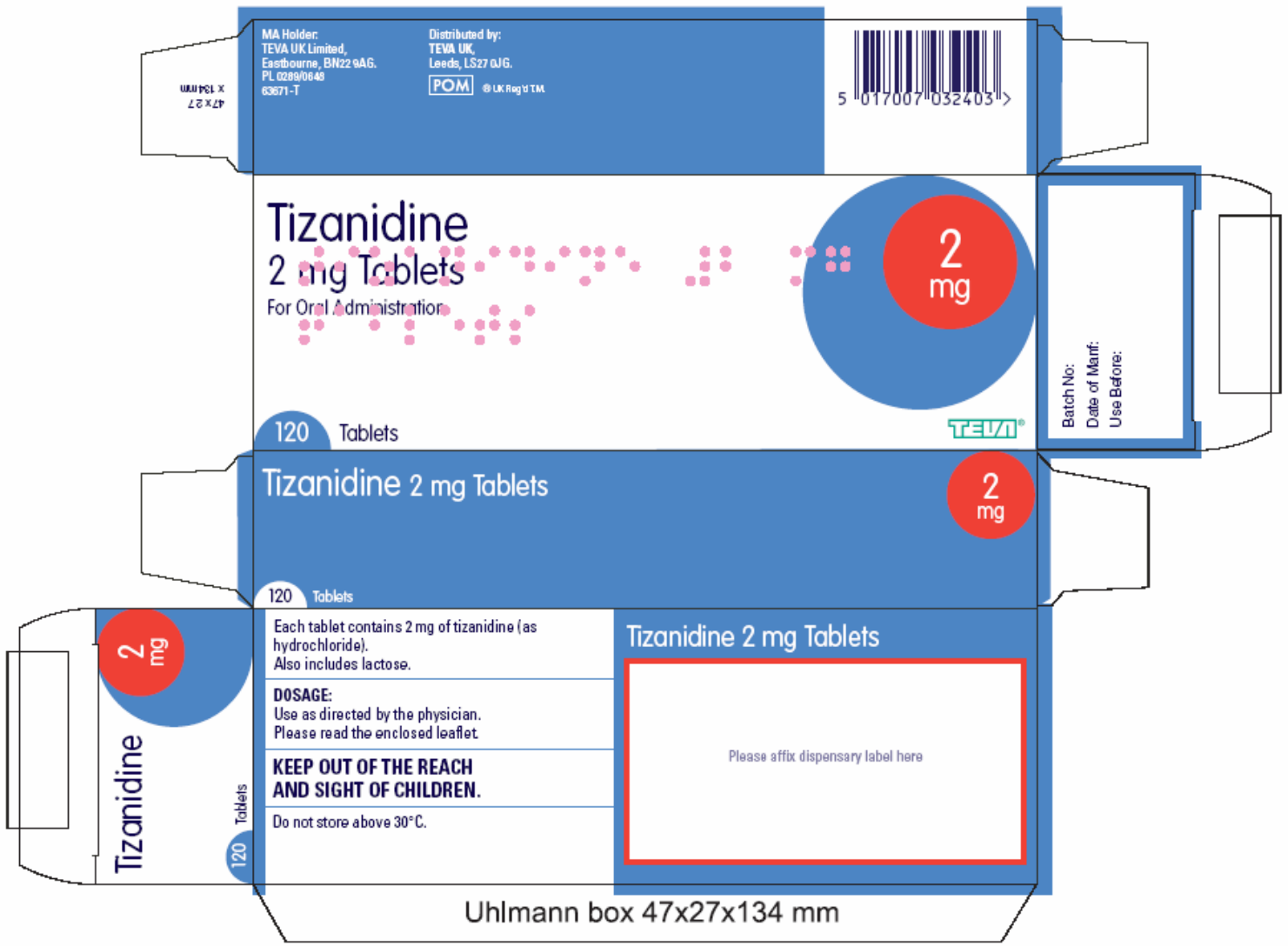
Keep Tizanidine out of the reach and sight of children. Do not transfer to another container. Do not use Tizanidine after the expiry date shown on the outer packaging. Do not store above 30°C. Return all unused medicines to your pharmacist for safe disposal.

Revised: December 2006.

Distributed by TEVA UK, Leeds, LS27 0JG.

TEVA UK Limited 63675-U

TIZANIDINE 2MG TABLETS
PL 00289/0648



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Tizanidine 2 mg Tablets
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Tizanidine 2 mg Tablets
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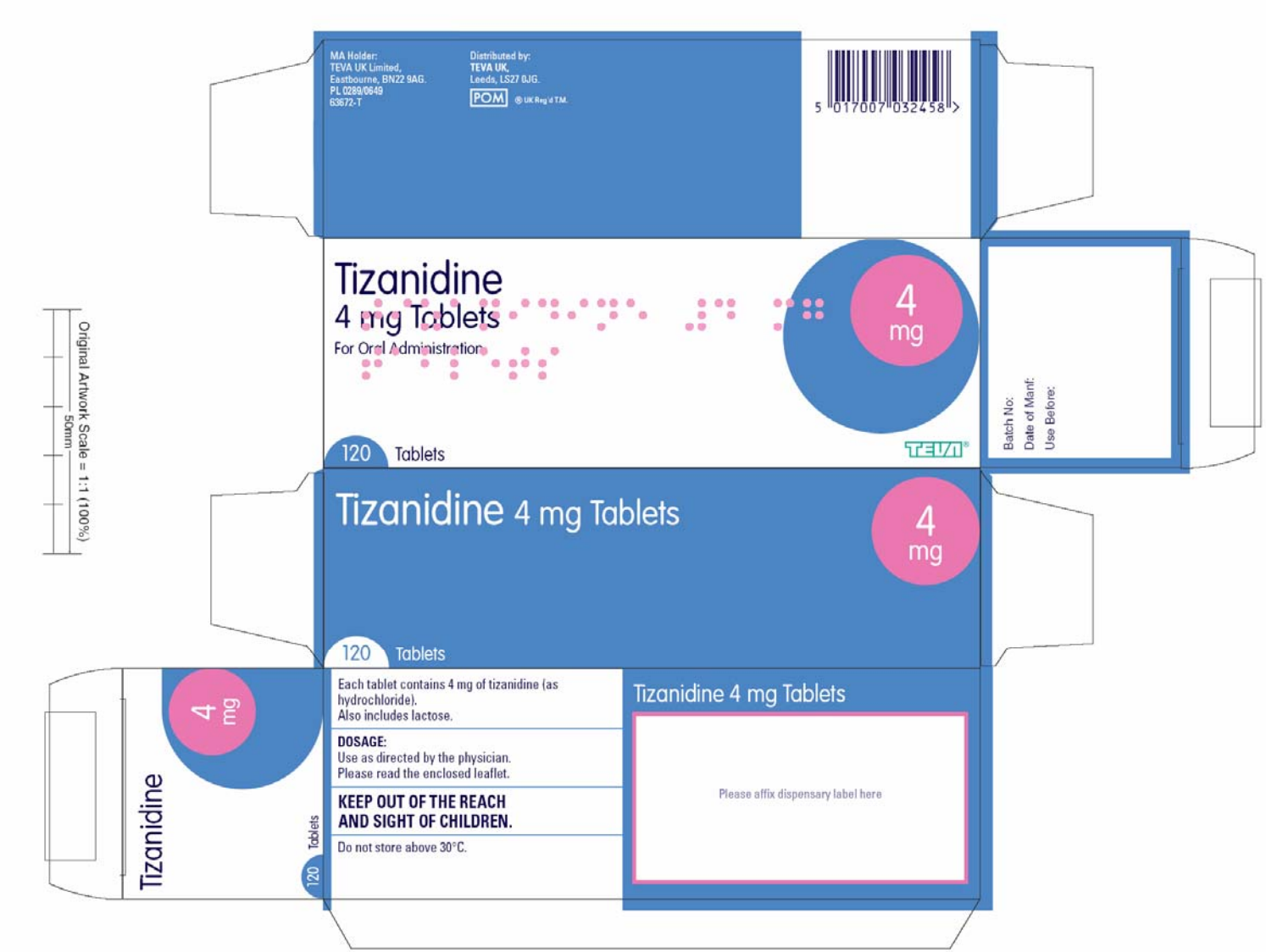
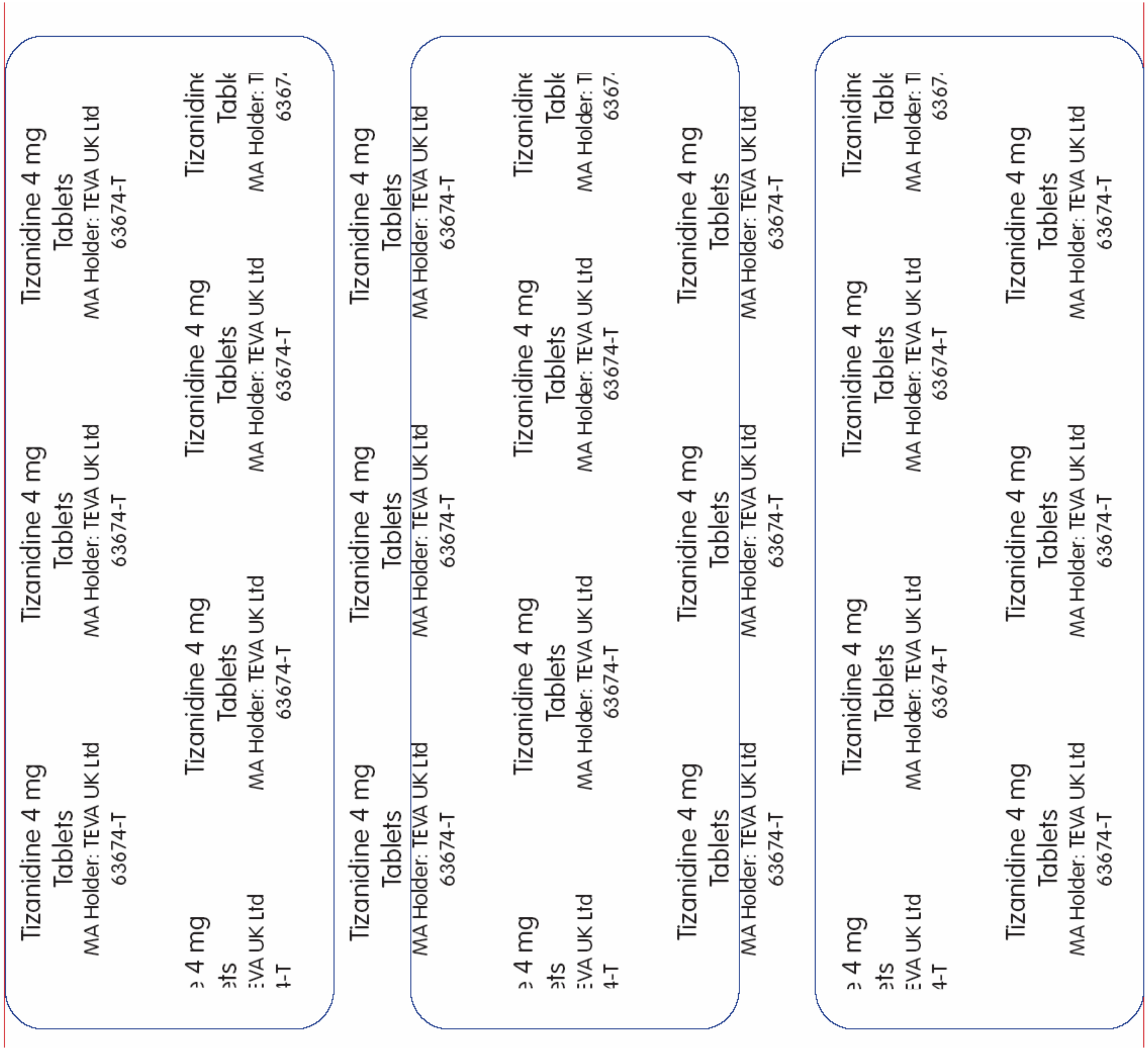
63673-T

TIZANIDINE 4MG TABLETS
PL 00289/0649




Tizanidine 4 mg
Tablets
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