PRODUCT MONOGRAPH

[Pr]MYLAN-TIZANIDINE

Tizanidine Hydrochloride Tablets

4 mg

Antispastic Agent

Mylan Pharmaceuticals ULC
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M8Z 2S6

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	tablet 4 mg	Colloidal anhydrous silica, lactose anhydrous, microcrystalline cellulose and stearic acid.

INDICATIONS AND CLINICAL USE

Adults:
MYLAN-TIZANIDINE (Tizanidine Hydrochloride) is a short-acting drug for the management of spasticity.

Geriatrics:
Evidence from clinical studies and experience suggests that use in the geriatric population may be associated with differences in safety or effectiveness and a brief discussion can be found in the appropriate sections **(WARNINGS AND PRECAUTIONS, ACTION AND CLINICAL PHARMACOLOGY).**

Pediatrics (< 18 years of age):
No data are available.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

Co-administration of tizanidine with moderate and potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin is contra-indicated (see WARNINGS AND PRECAUTIONS).

MYLAN-TIZANIDINE is contraindicated in patients for whom spasticity is needed to maintain function, such as maintenance of upright posture and balance in locomotion.

WARNINGS AND PRECAUTIONS

General

Hypotension
Tizanidine Hydrochloride is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. In a single dose study where blood pressure was monitored closely after dosing, two thirds of patients treated with 8 mg of tizanidine had a 20% reduction in either the diastolic or systolic BP. The reduction was seen within 1 hour after dosing, peaked 2 to 3 hours after dosing and was associated, at times, with bradycardia, orthostatic hypotension, lightheadedness/dizziness and rarely syncope. The hypotensive effect is dose related and has been measured following single doses of $\geq$ 2 mg.

The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to a fixed upright position may be at increased risk for hypotensive and orthostatic effects.

Caution is advised when MYLAN-TIZANIDINE is to be used in patients who have a history of orthostatic hypotension or labile blood pressure or who are receiving concurrent antihypertensive therapy. MYLAN-TIZANIDINE should not be used with other α_2-adrenergic agonists.

Risk of Liver Injury
Tizanidine Hydrochloride use occasionally causes drug induced liver injury, most often hepatocellular in type.

In controlled clinical studies, approximately 5% of patients treated with tizanidine had elevations of liver function tests (ALT/SGPT, AST/SGOT) to greater than 3 times the upper limit of normal (or 2 times if baseline levels were elevated). The patients usually remain asymptomatic despite increased aminotransferases. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. The onset of the elevated liver enzymes typically occurred within the first 6 months of treatment with tizanidine and most resolved rapidly upon drug withdrawal with no reported residual problems. In postmarketing experience, three deaths associated with liver failure have been reported in patients treated with tizanidine, including one case of fatal fulminant hepatitis.

Monitoring of aminotransferase levels is recommended during the first 6 months of treatment (e.g., baseline, 1, 3 and 6 months) and periodically thereafter, based on clinical status. Because of the potential toxic hepatic effect of tizanidine, the drug should be used only with extreme caution in patients with impaired hepatic function.

Sedation
In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of tizanidine reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to <1% in the placebo treated patients. Sedation may interfere with every day activity. The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6-hour study. This compares to 76% of the patients on 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of tizanidine.

In the multiple dose studies, the prevalence of patients with sedation peaked following the first week of titration and then remained stable for the duration of the maintenance phase of the study.

Hallucinations
Tizanidine use has been associated with hallucinations. Formed, visual hallucinations or delusions have been reported in 5 of 170 patients (3%) in two North American controlled clinical studies. Most of the patients were aware that the events were unreal. One patient developed psychoses in association with the hallucinations. One patient continued to have problems for at least 2 weeks following discontinuation of tizanidine. Dosage reduction or discontinuation should be considered for patients who experience hallucinations while receiving tizanidine. Particular caution should be observed if tizanidine is administered to patients with a prior history of psychotic illness.

Limited Database for Chronic Use of Single Doses Above 8 mg and Multiple Doses Above 24 mg per day
Clinical experience with long-term use of tizanidine at single doses of 8 to 16 mg or total daily doses of 24 to 36 mg is limited. Approximately 75 patients have been exposed to individual doses of 12 mg or more for at least one year and approximately 80 patients have been exposed to total daily doses of 30 to 36 mg/day for at least one year. There is essentially no long-term experience with single, daytime doses of 16 mg. Because long-term clinical study experience at high doses is limited, only those adverse events with a relatively high incidence are likely to have been identified.

Discontinuation of Treatment with MYLAN-TIZANIDINE
If therapy needs to be discontinued, especially in patients who have been receiving high doses for long periods, the dose should be decreased slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

The following additional precautions are listed alphabetically.

Carcinogenesis and Mutagenesis
Only animal carcinogenesis data and mutagenesis data from *in vitro* and *in vivo* assays are available (see **TOXICOLOGY**).

Cardiovascular

Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m^2 basis. ECG evaluation was not performed in the controlled clinical studies. There have been post-market reports of QT prolongation and a small number of reports of Torsades de Pointes, none of them fatal, during Tizanidine Hydrochloride treatment.

Caution should be exercised when tizanidine is prescribed with drugs known to prolong the QT interval.

Tizanidine Hydrochloride can produce hypotension associated, at times, with bradycardia and orthostatic hypotension, dizziness and rarely syncope (See **WARNINGS AND PRECAUTIONS, General**).

Dependence/Tolerance

Monkeys were shown to self-administer tizanidine in a dose-dependent manner, and abrupt cessation of tizanidine produced transient signs of withdrawal at doses > 35 times the maximum recommended human dose on a mg/m^2 basis. These transient withdrawal signs (increased locomotion, body twitching, and aversive behaviour toward the observer) were not reversed by naloxone administration. Tizanidine is closely related to clonidine, which is often abused in combination with narcotics and is known to cause symptoms of rebound upon abrupt withdrawal. There have been cases of rebound symptoms reported on sudden withdrawal of tizanidine. Some of the case reports suggest that these patients were also misusing opioids. Withdrawal symptoms included but were not limited to: hypertension, tachycardia, hypertonia, convulsions, tremor, and anxiety. As with clonidine, withdrawal is expected to be more likely in cases where high doses are used, especially for prolonged periods. There have been also reports of tizanidine abuse and dependence, most of them with concomitant use of opioids, benzodiazepines, other hypnotics or multiple analgesics. The potential for tizanidine abuse should be monitored, especially in patients simultaneously using opioids or benzodiazepines.

Drug Interaction with CYP1A2 inhibitors

Concomitant use of tizanidine and moderate or potent CYP450 1A2 inhibitors is contraindicated (see **CONTRAINDICATIONS**). Concomitant use of tizanidine with fluvoxamine, a potent CYP450 1A2 inhibitor in man, resulted in a 33-fold increase in the tizanidine AUC by fluvoxamine; concomitant use of tizanidine with ciprofloxacin, another CYP1A2 inhibitor, resulted in a 10-fold increase in tizanidine AUC; in both studies, clinically significant hypotension resulted along with somnolence, dizziness and decreased psychomotor performance (see **DRUG INTERACTIONS**). Co-administration of tizanidine with other inhibitors of CYP1A2 such as antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, other fluoroquinolones (norfloxacin, moxifloxacin), and ticlopidine should be avoided or used with caution.

Hepatic/Biliary/Pancreatic
Tizanidine use occasionally causes drug induced liver injury, most often hepatocellular in type (See **WARNINGS AND PRECAUTIONS, General**).

Information to be Provided to the Patients
Patients should be advised of the limited clinical experience with tizanidine both in regard to duration of use and the higher doses required to reduce muscle tone (see **WARNINGS AND PRECAUTIONS, General**).

Because of the possibility of tizanidine lowering blood pressure, patients should be warned about the risk of clinically significant orthostatic hypotension (see **WARNINGS AND PRECAUTIONS, General**).

Because of the possibility of sedation, patients should be warned about performing activities requiring alertness, such as driving a vehicle or operating machinery (See **WARNINGS AND PRECAUTIONS, General**). Patients should also be instructed that the sedation may be additive when tizanidine is taken in conjunction with drugs (baclofen, benzodiazepines) or substances (e.g., alcohol) that act as CNS depressants.

Neurologic

Tizanidine Hydrochloride use has been associated with sedation (See **WARNINGS AND PRECAUTIONS, General**).

Tizanidine Hydrochloride use has been associated with hallucinations (See **WARNINGS AND PRECAUTIONS, General**).

Ophthalmologic
Dose-related retinal degeneration and corneal opacities have been found in animal studies at doses equivalent to approximately the maximum recommended dose on a mg/m^2 basis. There have been no reports of corneal opacities or retinal degeneration in the clinical studies.

Renal
Tizanidine Hydrochloride should be used with caution in patients with renal insufficiency (Clcr <25 mL/min), as clearance is reduced by more than 50%. In these patients, during titration, the individual doses should be reduced. If higher doses are required, individual doses rather than dosing frequency should be increased. These patients should be monitored closely for onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia and dizziness) as indicators of potential overdose.

Special Populations
Use in Women Taking Oral Contraceptives
Tizanidine Hydrochloride should be used with caution in women taking oral contraceptives; as clearance of tizanidine is reduced by approximately 50% in such patients. In these patients, during titration, the individual doses should be reduced.

Pregnant Women: The effect of tizanidine on labor and delivery in humans is unknown.

Reproduction studies performed in rats at a dose of 3 mg/kg, equal to the maximum recommended human dose on a mg/m^2 basis and in rabbits at 30 mg/kg, 16 times the maximum recommended human dose on a mg/m^2 basis did not show evidence of teratogenicity. Tizanidine at doses equal to and up to 8 times the maximum recommended human dose on a mg/m^2 basis increased gestation duration in rats. Prenatal and postnatal pup loss was increased and developmental retardation occurred. Postimplantation loss was increased in rabbits at doses of 1 mg/kg or greater, equal to or greater than 0.5 times the maximum recommended human dose on a mg/m^2 basis. Tizanidine has not been studied in pregnant women. Tizanidine should be given to pregnant women only if the potential benefit clearly outweighs the potential risk to mother and child.

Nursing Women: It is not known whether tizanidine is excreted in human milk, although as a lipid soluble drug, it might be expected to pass into breast milk.

Pediatrics (< 18 years of age): There are no adequate and well-controlled studies to document the safety and efficacy of Tizanidine Hydrochloride in children under 18 years in age.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In multiple dose, placebo-controlled clinical studies, 264 patients were treated with Tizanidine Hydrochloride and 261 with placebo. Adverse events, including severe adverse events, were more frequently reported with Tizanidine Hydrochloride than with placebo.

Common adverse events leading to discontinuation

Forty five of 264 (17%) patients receiving Tizanidine Hydrochloride and 13 of 261 (5%) patients receiving placebo in three multiple dose, placebo-controlled clinical studies discontinued treatment for adverse events. When patients withdrew from the study, they frequently had more than one reason for discontinuing. The adverse events most frequently leading to withdrawal of Tizanidine Hydrochloride treated patients in the controlled clinical studies were asthenia (weakness, fatigue and/or tiredness) (3%), somnolence (3%), dry mouth (3%), increased spasm or tone (2%) and dizziness (2%).

Most Frequent Adverse Clinical Events Seen in Association with the Use of Tizanidine

In multiple-dose, placebo-controlled clinical studies involving 264 patients with spasticity, the most frequent adverse events were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. Three quarters of the patients rated the events as mild to moderate and one quarter of the patients rated the events as being severe. These events appeared to be dose related.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The events cited reflect experience gained under closely monitored conditions of clinical studies in a highly selected patient population. In actual clinical practice or in other clinical studies, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 1 lists treatment emergent signs and symptoms that were reported in greater than 2% of patients in three multiple dose, placebo-controlled studies who received Tizanidine Hydrochloride where the frequency in the Tizanidine Hydrochloride group was at least as common as in the placebo group. These events are not necessarily related to Tizanidine Hydrochloride treatment. For comparison purposes, the corresponding frequency of the event (per 100 patients) among placebo treated patients is also provided.

Table 1 - Multiple Dose, Placebo-Controlled Studies (Frequent (> 2%) Adverse Events Reported for Which Tizanidine Hydrochloride Incidence is Greater Than Placebo)

	Tizanidine Hydrochloride n= 264 (%)	placebo n= 261 (%)
Dry mouth	49	10
Somnolence	48	10
Asthenia*	41	16
Dizziness	16	4
UTI	10	7
Infection	6	5
Constipation	4	1
Liver function tests abnormal	3	<1
Vomiting	3	0
Speech disorder	3	0
Amblyopia (blurred vision)	3	<1
Urinary frequency	3	2
Flu syndrome	3	2
SGPT/ALT increased	3	<1
Dyskinesia	3	0
Nervousness	3	<1
Pharyngitis	3	1
Rhinitis	3	2

* weakness, fatigue and/or tiredness

In the single dose, placebo-controlled study involving 142 patients with spasticity, the patients were specifically asked if they had experienced any of the four most common adverse events dry mouth, somnolence (drowsiness), asthenia (weakness, fatigue and/or tiredness), and dizziness. In addition, hypotension and bradycardia were observed. The occurrence of these adverse events is summarized in Table 2. Other events were, in general, reported at a rate of 2% or less.

Table 2 - Single Dose, Placebo-Controlled Study (Common Adverse Events Reported)

	Tizanidine Hydrochloride 8 mg n= 45 (%)	Tizanidine Hydrochloride l 16 mg n= 49 (%)	placebo n= 48 (%)
Somnolence	78	92	31
Dry Mouth	76	88	35
Asthenia*	67	78	40
Dizziness	22	45	4
Hypotension	16	33	0
Bradycardia	2	10	0

* weakness, fatigue and/or tiredness

Other Adverse Events Observed During the Evaluation of Tizanidine

Tizanidine Hydrochloride was administered to 1187 patients in additional clinical studies where adverse event information was available. The conditions and duration of exposure varied greatly, and included (in overlapping categories) double-blind and open-label studies, uncontrolled and controlled studies, inpatient and outpatient studies, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 1187 patients exposed to Tizanidine Hydrochloride who experienced an event of the type cited on at least one occasion while receiving tizanidine. All reported events are included except those already listed in Table 1. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with Tizanidine Hydrochloride, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients.

Body as a Whole: *Frequent:* fever; *Infrequent:* allergic reaction, moniliasis, malaise, abscess, neck pain, sepsis, cellulitis, death, overdose; Rare: carcinoma, congenital anomaly, suicide attempt.

Cardiovascular System: *Infrequent:* vasodilatation, postural hypotension, syncope, migraine, arrhythmia; Rare: angina pectoris, coronary artery disorder, heart failure, myocardial infarct, phlebitis, pulmonary embolus, ventricular extrasystoles, ventricular tachycardia.

Digestive System: *Frequent:* abdomen pain, diarrhea, dyspepsia; *Infrequent:* dysphagia, cholelithiasis, fecal impaction, flatulence, gastrointestinal hemorrhage, hepatitis, melena; *Rare:* gastroenteritis, hematemesis, hepatoma, intestinal obstruction, liver damage.

Hemic and Lymphatic System: *Infrequent:* ecchymosis, hypercholesteremia, anemia, hyperlipemia, leukopenia, leukocytosis, sepsis; *Rare:* petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional System: *Infrequent:* edema, hypothyroidism, weight loss; Rare: adrenal cortex insufficiency, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, respiratory acidosis.

Musculoskeletal System: *Frequent:* myasthenia, back pain; *Infrequent:* pathological fracture, arthralgia, arthritis, bursitis.

Nervous System: *Frequent:* depression, anxiety, paresthesia; Infrequent: tremor, emotional lability, convulsion, paralysis, thinking abnormal, vertigo, abnormal dreams, agitation, depersonalization, euphoria, migraine, stupor, dysautonomia, neuralgia; *Rare:* dementia, hemiplegia, neuropathy.

Respiratory System: *Infrequent:* sinusitis, pneumonia, bronchitis; *Rare:* asthma.

Skin and Appendages: *Frequent:* rash, sweating, skin ulcer; *Infrequent:* pruritus, dry skin, acne, alopecia, urticaria; *Rare:* exfoliative dermatitis, herpes simplex, herpes zoster, skin carcinoma.

Special Senses: *Infrequent:* ear pain, tinnitus, deafness, glaucoma, conjunctivitis, eye pain, optic neuritis, otitis media, retinal hemorrhage, visual field defect; *Rare:* iritis, keratitis, optic atrophy.

Urogenital System: *Infrequent:* urinary urgency, cystitis, menorrhagia, pyelonephritis, urinary retention, kidney calculus, uterine fibroids enlarged, vaginal moniliasis, vaginitis; *Rare:* albuminuria, glycosuria, hematuria, metrorrhagia.

Post-Market Adverse Drug Reactions

Table 3 includes events determined to be medically significant and/or potentially life threatening and assessed as associated with the use of Tizanidine Hydrochloride or the possible relationship to Tizanidine Hydrochloride cannot be completely excluded.

Table 3 – Tizanidine Hydrochloride l Post-Market Spontaneous Adverse Event Reports				
Adverse Event	**Frequency**			
	≥ 1%	**< 1% and ≥ 0.1%**	**< 0.1% and ≥ 0.01%**	**< 0.01%**
Blood and lymphatic system disorders				
Agranulocytosis				X
Disseminated intravascular coagulation				X
Cardiac disorders				
Tachycardia				X
Pulmonary oedema				X
Cardiac arrest				X
Torsade de pointes				X
Cardio-respiratory arrest				X
Ventricular fibrillation				X
General disorders and administration site conditions				
Pyrexia				X
Hepatobiliary Disorders				
Hepatic function abnormal				X
Hepatitis				X
Hepatic disorder				X
Jaundice				X
Hepatic failure				X
Hepatic necrosis				X
Hepatitis fulminant				X
Hepatic fibrosis				X
Hepatic cirrhosis				X
Immune system disorders				
Anaphylactic shock				X
Investigations				
Electrocardiogram QT prolonged				X
Musculoskeletal and connective tissue disorders				
Rhabdomyolysis				X
Nervous system disorders				
Loss of consciousness				X
Cerebrovascular accident				X
Cerebral infarction				X
Psychiatric disorders				
Confusional state				X
Renal and urinary disorders				
Renal failure acute				X
Renal failure				X
Respiratory, thoracic and mediastinal disorders				
Dyspnea				X
Skin and subcutaneous tissue disorders				
Erythema multiforme				X

Vascular disorders				
Shock				X
Circulatory collapse				X

In post-marketing experience, nausea has also been reported at a frequency of < 0.1% and ≥ 0.01%.

DRUG INTERACTIONS

Serious Drug Interactions

- **Moderate or potent CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin (see CONTRAINDICATIONS).**

Overview

In vitro studies of cytochrome P450 isoenzymes using human liver microsomes indicate that neither tizanidine nor its major metabolites are likely to affect the metabolism of other drugs metabolized by cytochrome P450 isoenzymes. There are reports of drug interaction of tizanidine and CYP1A2 inhibitors, such as oral contraceptives, fluvoxamine, fluoroquinolones, and others.

Acetaminophen:

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

Alcohol:

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

Oral Contraceptives:

No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and Tizanidine Hydrochloride, but retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg Tizanidine Hydrochloride showed that women concurrently taking oral contraceptives had 50% lower clearance of Tizanidine Hydrochloride than women not on oral contraceptives.

Antihypertensives:

In placebo-controlled clinical trials, Tizanidine Hydrochloride has been administered concomitantly with antihypertensive medications in 30 patients. The addition of Tizanidine Hydrochloride to antihypertensive therapy was associated with a 20-30% increase in the incidence of clinically significant decreases in systolic or diastolic blood pressure compared with both placebo plus antihypertensive (N=36) and Tizanidine Hydrochloride alone (N=226).

Concurrent use of antihypertensive and Tizanidine Hydrochloride therapy also resulted in an increase in reports of orthostatic hypotension. Lower initial doses and cautious dose titration should be considered when Hydrochloride is to be administered to patients receiving

antihypertensive therapy or if antihypertensive therapy is to be initiated in a patient receiving Tizanidine Hydrochloride .

Fluvoxamine and other CYP1A2 inhibitors:
Tizanidine Hydrochloride should not be used together with moderate and potent CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin (see **CONTRAINDICATIONS**). Concomitant use of tizanidine with fluvoxamine, a potent CYP450 1A2 inhibitor in man, resulted in a 33-fold increase in the tizanidine AUC by fluvoxamine in 10 healthy male subjects. Concomitant use of tizanidine with ciprofloxacin resulted in a 10-fold increase in tizanidine AUC in 10 healthy male subjects. In both studies, clinically significant hypotension resulted along with somnolence, dizziness and decreased psychomotor performance. Co-administration of tizanidine with other inhibitors of CYP1A2 such as antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, other fluoroquinolones (norfloxacin, moxifloxacin), oral contraceptives, and ticlopidine should be avoided or used in caution (see also **WARNINGS and PRECAUTIONS, Drug Interaction with CYP1A2 inhibitors**).

Drugs known to prolong the QT interval:
Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m2 basis. ECG evaluation was not performed in the controlled clinical studies. There have been post-market reports of QT prolongation and a small number of reports of Torsades de Pointes, none of them fatal, during Tizanidine Hydrochloride treatment.
Tizanidine Hydrochloride should be used with caution in patients taking drugs known to prolong the QT interval.

Drug-Food Interactions
Administering tizanidine with food increases the Cmax, the time to peak concentration, and the extent of absorption of tizanidine (see ACTION and CLINICAL PHARMACOLOGY). These pharmacokinetic differences may result in clinically significant differences when switching between fed or fasted states, such as changed incidence of adverse events or delayed/more rapid onset of activity, depending on the nature of the switch (see DOSAGE and AMINISTRATION).

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Administering tizanidine with food increases the Cmax, the time to peak concentration, and the extent of absorption of tizanidine. These pharmacokinetic differences may result in clinically significant differences when switching between fed or fasted states, such as changed incidence of adverse events or delayed/more rapid onset of activity, depending on the nature of the switch. For this reason, the prescriber should recommend patients to always take tizanidine the same way with regard to fed and fasted state (see ACTION and CLINICAL PHARMACOLOGY).
- If therapy needs to be discontinued, especially in patients who have been receiving high doses for long periods, the dose should be decreased slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

Recommended Dose and Dosage Adjustment

A single oral dose of 8 mg of Mylan-Tizanidine (tizanidine hydrochloride) reduces muscle tone in patients with spasticity for a period of several hours. The effect peaks at approximately 1 to 2 hours and dissipates between 3 to 6 hours. Tizanidine Hydrochloride dosing should be scheduled such that the peak effect coincides with activities for which relief of spasticity is most desirable. Effects are dose-related.

Although single doses of less than 8 mg have not been demonstrated to be effective in controlled clinical studies, the dose-related nature of Tizanidine Hydrochloride's common adverse events, particularly blood pressure reduction, make it prudent to begin treatment with single oral doses of 2 mg by cutting the 4 mg scored tablet in half. Increase the dose gradually (2 to 4 mg steps) to optimum effect (satisfactory reduction of muscle tone at a tolerated dose).

The dose can be repeated at 6 to 8 hour intervals, as needed, to a maximum of three doses in 24 hours. The total daily dose should not exceed 36 mg.

Experience with single doses exceeding 8 mg and daily doses exceeding 24 mg is limited. There is essentially no experience with repeated, single, daytime doses greater than 12 mg or total daily doses greater than 36 mg (see **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE

There have been cases of tizanidine overdose reported in post-marketing experience. Most of these were intentional overdoses, about a quarter have resulted in fatality, and in at least half of these cases, other CNS depressants were involved. The majority of cases involved depressed consciousness (somnolence, stupor, or coma), depressed cardiovascular function (bradycardia, hypotension), and depressed respiratory function (respiratory depression or failure).

Should overdosage occur, basic steps to ensure the adequacy of an airway and the monitoring of cardiovascular and respiratory systems should be undertaken. For the most recent information concerning the management of overdose, contact a poison control centre.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct

effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

The imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure.

Pharmacokinetics

Absorption:

Following oral administration, tizanidine is essentially completely absorbed and has a half-life of approximately 2 hours. Following administration of tizanidine peak plasma concentrations occurred at approximately 1 hour after dosing. Food increases the mean Cmax by approximately 30% and increases the median time to peak concentration by approximately 25 minutes, from 1 hour to 1 hour and 25 minutes. Food increases the extent of absorption of tizanidine by approximately 30%. Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg.

Metabolism:

The absolute oral bioavailability of tizanidine is approximately 40%, due to extensive first-pass metabolism in the liver; approximately 95% of an administered dose is metabolized. Tizanidine metabolites are not known to be active; their half-lives range from 20 to 40 hours.

Distribution:

Tizanidine is widely distributed throughout the body; mean steady state volume of distribution is 2.4 L/kg following intravenous administration in healthy adult volunteers. Tizanidine is approximately 30% bound to plasma proteins, independent of concentration over the therapeutic range.

Excretion:

Following single and multiple oral dosing of ^{14}C-tizanidine, an average of 60% and 20% of total radioactivity was recovered in the urine and feces, respectively.

Special Populations and Conditions

Age Effects: No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data, following single dose administration of 6 mg Tizanidine Hydrochloride showed that younger subjects cleared the drug four times faster than the elderly subjects. Tizanidine Hydrochloride has not been evaluated in children (see **WARNINGS AND PRECAUTIONS**).

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

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

Hepatic Insufficiency: Pharmacokinetic differences due to hepatic impairment have not been studied (see **WARNINGS AND PRECAUTIONS**).

Renal Insufficiency: Tizanidine Hydrochloride clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatinine clearance < 25 mL/min) compared to healthy elderly subjects; this would be expected to lead to a longer duration of clinical effect. Tizanidine Hydrochloride should be used with caution in renally impaired patients (see **WARNINGS AND PRECAUTIONS**).

STORAGE AND STABILITY

The product should be stored between 15 ^{o}C and 30^{o}C. Dispense in containers with child resistant closure.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MYLAN-TIZANIDINE contains 4 mg tizanidine as tizanidine hydrochloride for oral administration.

MYLAN-TIZANIDINE (tizanidine hydrochloride) is supplied as 4 mg tablets for oral administration. The 4 mg tablets are flat bevel edged uncoated white to off-white tablets debossed 'TI' and '4' on one side and a quadrisecting score on the other side.

MYLAN-TIZANIDINE (tizanidine hydrochloride) is available in white high density polyethylene (HDPE) bottles of 150 tablets for the 4 mg strength.

MYLAN-TIZANIDINE (tizanidine hydrochloride) is available in tablets containing 4 mg tizanidine as tizanidine hydrochloride. Non-medicinal ingredients include silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

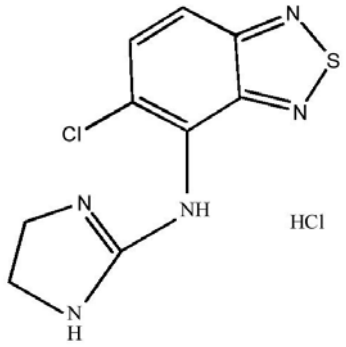
Drug Substance

Proper name: Tizanidine Hydrochloride (USAN)

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

Molecular formula: $C_9H_9Cl_2N_5S$

Structural formula:



Molecular weight: 290.2 g/mol

Appearance: pale yellow, fine crystalline powder, odorless or faint characteristic odor

Solubility: approximately 5% soluble in water and methanol; solubility in water decreases as the pH increases

pK_a value: 7.35 determined potentiometrically

pH: 4.3 - 5.3

Partition coefficient: 3.6:1

Melting point: 285°C - 290°C

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDY

A randomized, 2-way crossover comparative bioequivalence study of Mylan-Tizanidine 4 mg (Mylan Pharmaceuticals ULC) and Zanaflex® (tizanidine hydrochloride) 4 mg (Novartis Pharma AG) was performed in healthy volunteers (n=31). The study was performed under fasting conditions.

A summary of the results is presented in the following table.

Table 4: Summary Table of the Comparative Bioavailability Data under Fasted Conditions

Tizanidine
(1 x 4 mg tablet)
From measured data
Geometric Mean
Arithmetic Mean (CV %)

PARAMETER	TEST[a]	REFERENCE[b]	% RATIO OF GEOMETRIC MEANS	**90 % CONFIDENCE INTERVALS**
AUC_{0-t} (pg·h/mL)	5079.97 7349.78 (72.72)	4998.35 6943.88 (69.55)	101.63	93.99% - 109.90%
AUC_{0-inf} (pg·h/mL)	5571.32 7723.01 (70.14)	5482.10 7340.00 (67.06)	101.63	94.13% - 109.73%
C_{max} (pg/mL)	2278.72 3013.19 (68.69)	2154.33 2903.06 (72.80)	105.77	96.01% - 116. 53%
T_{max}* (h)	0.914 (31.15)	1.00 (30.67)	-	-
$T_{1/2\ el}$* (h)	1.54 (19.54)	1.54 (17.42)	-	-

[a]Mylan-Tizanidine 4 mg tablets
[b]Zanaflex® 4 mg tablets manufactured by Novartis Pharma AG, Basel, Switzerland for Elan Pharmaceuticals, Inc., South San Francisco, California U.S.A.
* expressed as arithmetic mean (CV%) only.

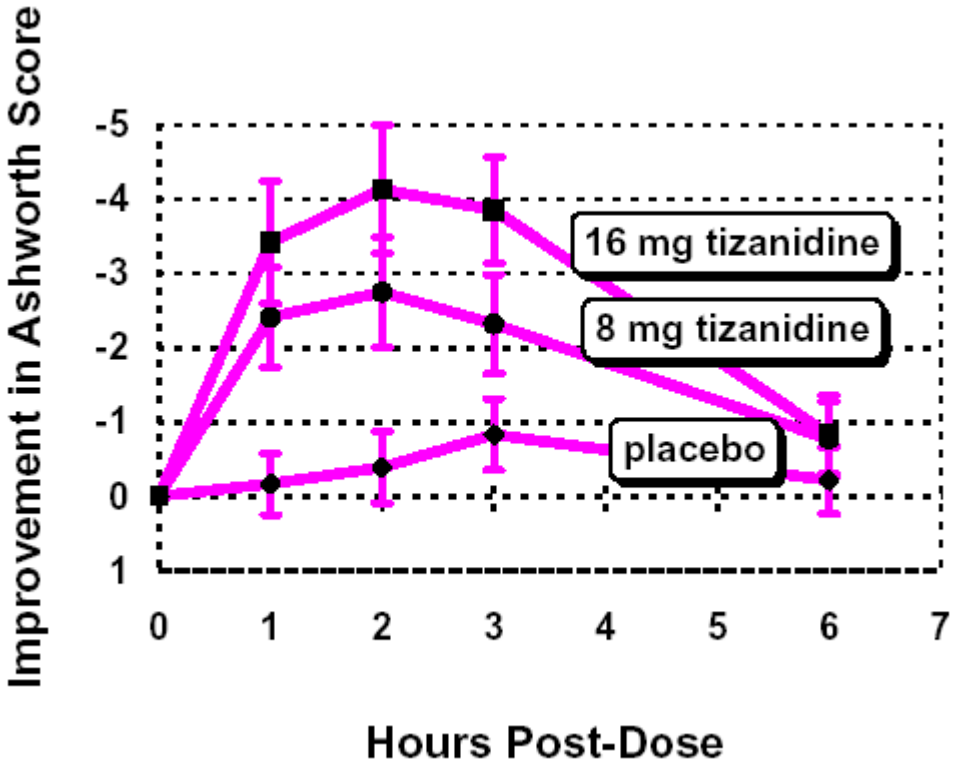
The capacity of Tizanidine Hydrochloride to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal injury.

In one study, patients with multiple sclerosis were randomized to receive single oral doses of drug or placebo.4 Patients and assessors were blind to treatment assignment and efforts were made to reduce the likelihood that assessors would become aware indirectly of treatment assignment (e.g., they did not provide direct care to patients and were prohibited from asking questions about side effects). In all, 140 patients received either placebo, 8 mg or 16 mg of Tizanidine Hydrochloride.

Response was assessed by physical examination; muscle tone was rated on a 5 point scale (Ashworth score), with a score of 0 used to describe normal muscle tone. A score of 1 indicated a slight spastic catch while a score of 2 indicated more marked muscle resistance. A score of 3 was used to describe considerable increase in tone, making passive movement difficult. A muscle immobilized by spasticity was given a score of 4. Spasm counts were also collected.

Assessments were made at 1, 2, 3 and 6 hours after treatment. A statistically significant reduction of the Ashworth score for Tizanidine Hydrochloride compared to placebo was detected at 1, 2 and 3 hours after treatment. Figure 1 below shows a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale. The greatest reduction in muscle tone was 1 to 2 hours after treatment. By 6 hours after treatment, muscle tone in the 8 and 16 mg tizanidine groups was indistinguishable from muscle tone in placebo treated patients. Within a given patient, improvement in muscle tone was correlated with plasma concentration. Plasma concentrations were variable from patient to patient at a given dose. Although 16 mg produced a larger effect, adverse events including hypotension were more common and more severe than in the 8 mg group. There were no differences in the number of spasms occurring in each group.

FIGURE 1: Single Dose Study - Mean Change in Muscle Tone from Baseline as Measured by the Ashworth Scale ± 95% Confidence Interval
(A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)



In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or Tizanidine Hydrochloride.[5] Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three unequal doses (e.g., 10 mg given in the morning and afternoon and 16 mg given at night). Patients were then maintained on their maximally tolerated dose for 4 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale within a period of 2.5 hours following either the morning or afternoon dose and counts of spasms were collected by patient diary.

At endpoint (the protocol specified time of outcome assessment), there were statistically significant reductions in muscle tone and spasms in the Tizanidine Hydrochloride treated group compared to placebo. The reduction in muscle tone was not associated with a reduction in muscle strength (a desirable outcome) but also did not lead to any consistent advantage of Tizanidine Hydrochloride treated patients on measures of activities of daily living. Figures 2 and 3 below show a comparison of the mean change in muscle tone from baseline as measured by the Ashworth scale and a comparison of the mean change in daytime spasms as recorded in patient diaries, respectively.

FIGURE 2: Multiple Dose Study - Mean Change in Muscle Tone 0.5-2.5 Hours after Dosing as Measured by the Ashworth Scale ± 95% Confidence Interval (A Negative Ashworth Score Signifies an Improvement in Muscle Tone from Baseline)

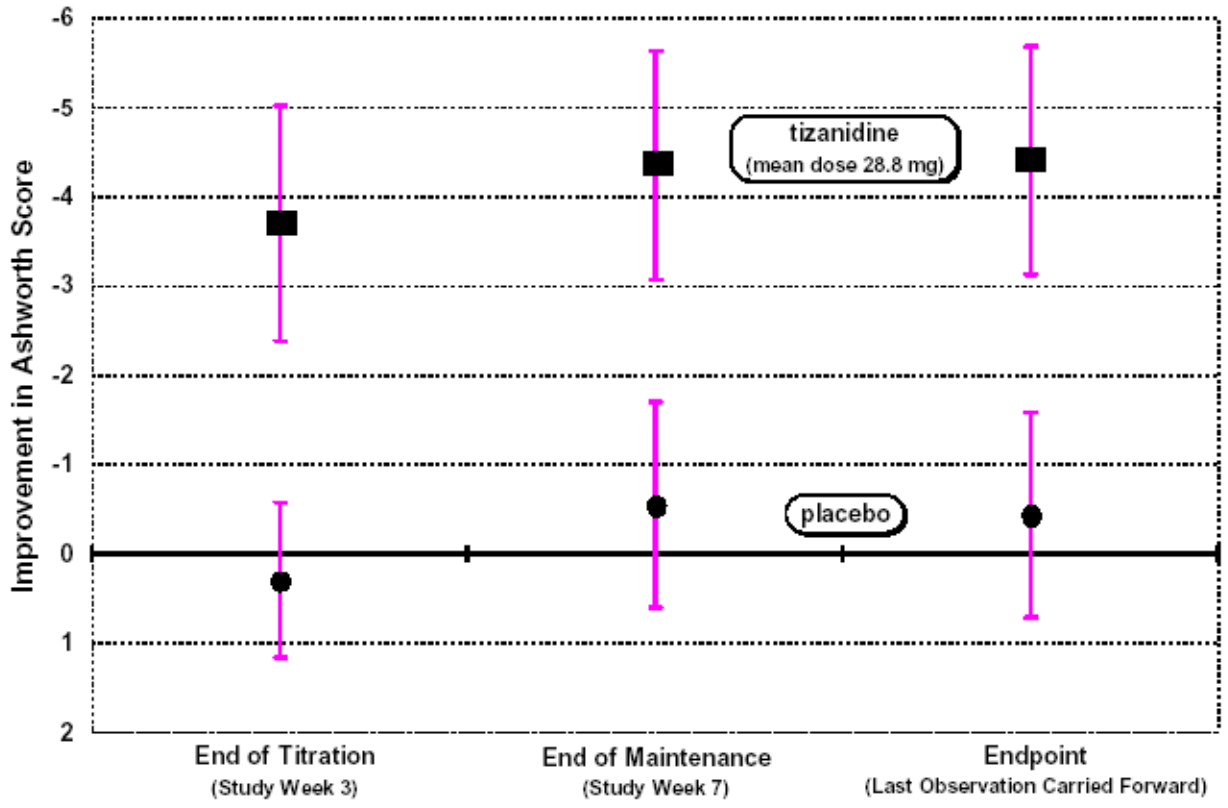
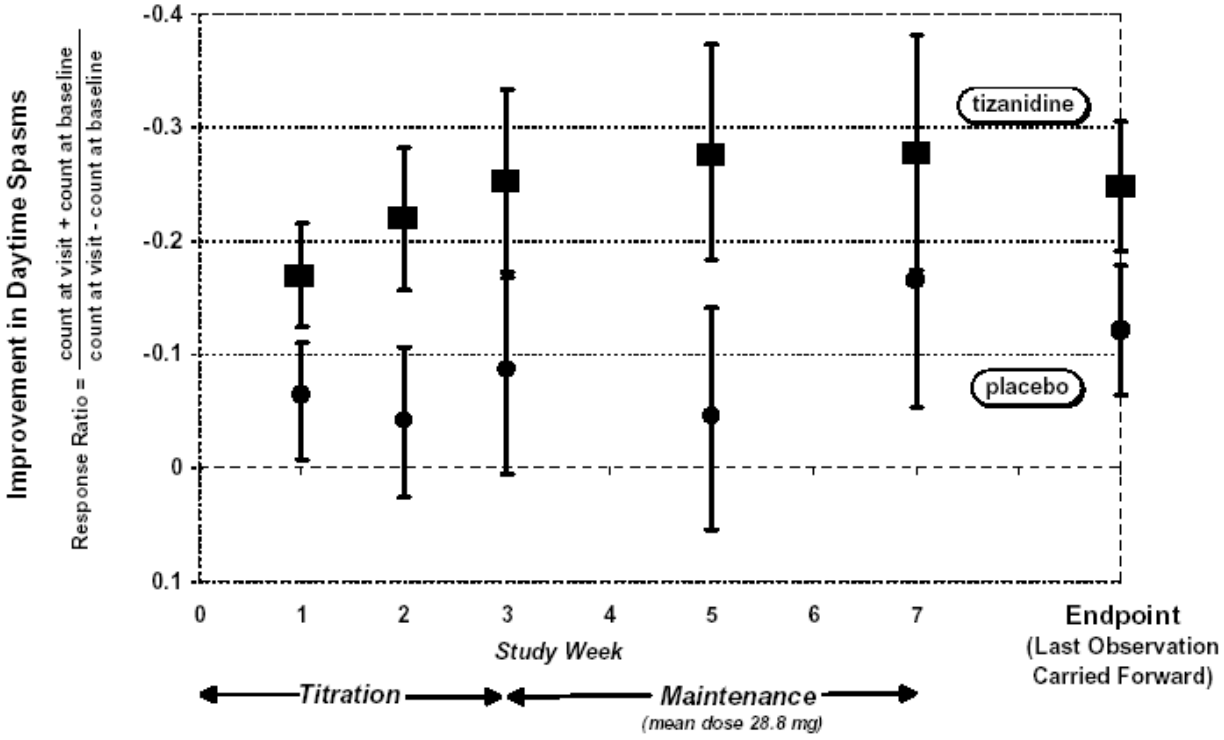


FIGURE 3: Multiple Dose Study - Mean Change in Response Ratio of Daytime Spasms ± 95% Confidence Interval

(A Negative Response Ratio Signifies an Improvement in Spasms from Baseline)



In a second multiple dose study, 187 patients with spasticity secondary to multiple sclerosis were randomized to either placebo or Tizanidine Hydrochloride.[6] Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three equal doses. Patients were then maintained on their maximally tolerated dose for 9 additional weeks (i.e., maintenance phase).

Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale and global efficacy was assessed by both patient and investigator.

There was a statistically significant reduction in muscle tone in the Tizanidine Hydrochloride treated group as compared to placebo at the last maintenance phase measurement of muscle tone (the protocol specified time of outcome assessment) and throughout the maintenance phase. The reduction in muscle tone was not associated with a reduction in muscle strength.

DETAILED PHARMACOLOGY

In calf cerebral cortex, tizanidine exhibited a selective affinity for α_2-adrenergic receptors (IC_{50}= 2.1 nM) over α_1 receptors (IC_{50}= 4,687 nM). In rat kidney membrane, tizanidine exhibited a higher affinity for imidazoline receptors (K_i= 4 nM) than for α_2-adrenergic receptors (K_i= 91 nM).

The α_2-adrenoreceptor sub-type specificity of tizanidine was investigated using tissues and cell lines which express only one of the three receptor sub-types, α_2A-, α_2B-, and α_2C. The Ki values for tizanidine were 65, 167, and 107 nM at the α_2A-, α_2B-, and α_2C-receptors, respectively.

Tizanidine at concentration of 3 nM to 1 FM exhibited α_2-agonist activity in two *in vitro* peripheral smooth muscle tissues, rat vas deferens and guinea pig ileum. Tizanidine was demonstrated to inhibit the contractile response to electrical stimulation, an effect which was antagonized by the α_2-antagonist, yohimbine, but not by the α_1-antagonist, prazosin.

Unlike dantrolene, tizanidine showed little or no activity in two models for demonstration of direct effects on muscle (direct stimulation of the peroneal nerve in chloralose-anaesthetized cats and of an *in vitro* rat diaphragm-phrenic nerve preparation).

Tizanidine was, however, found to be active in whole animal models for effects on reflex activity. In conscious rabbits, tizanidine inhibited hind limb tonic stretch reflex activity with a potency which was 12 times greater than that of diazepam and 16 times greater than that of baclofen. The inhibitory effect of tizanidine on the extensor reflex was maximal at 5 minutes and exhibited a duration of activity with a half-life of 21 minutes. Tolerance to this effect did not develop over a 14-day course of treatment.

The flexor reflex in rats was used as a model for polysynaptic reflex. In intact, anaesthetized rats and unanaesthetized decerebrate rats, tizanidine ablated the electromyelogram response to flexor reflex stimulation, an effect which could be prevented by pretreatment with the α_2-antagonist, yohimbine. However, in acutely spinalized rats, tizanidine was observed to facilitate reflex activity, an effect which was reversible in the presence of the α_1-antagonist, prazosin, but not the α_2-antagonist, yohimbine.

Tizanidine exhibited activity in a model of droperidol/fentanyl-induced rigidity in rats. Tizanidine was more potent in this regard than either baclofen or diazepam (ED50 values for tizanidine, diazepam, and baclofen were 0.5, 4, and 5.2 mg/kg p.o., respectively).

Tizanidine, baclofen, and diazepam were likewise efficacious in abolishing the rigidity observed in a decerebrate model of gamma-rigidity in rats (ED50 values of 0.5 mg/kg, 1.3 mg/kg, and 3.8 mg/kg i.v.). The two major metabolites of tizanidine identified in human blood and urine, metabolites 3 and 4, were without pharmacological activity in this model.

Reduced motor activity, disturbed gait, and ataxia were observed in mice after 10 mg/kg oral doses of tizanidine and in rats after 2.5 mg/kg oral doses of tizanidine. These doses were 5 to 20

fold higher than the oral ED50 for inhibition of droperidol/fentanyl-induced muscle rigidity in rats (0.5 mg/kg).

Sedative effects were observed in rhesus monkeys at oral doses of 6 to 10 mg/kg and in baboons after oral doses of 8 to 16 mg/kg and an intravenous dose of 1 mg/kg.

In normotensive rats, 0.3 and 1.0 mg/kg oral doses of tizanidine were associated with an initial small decrease in blood pressure (maximum 12%), followed by an increase in blood pressure at 1.5 to 7 hours (maximum 12%). At an oral dose of 3.0 mg/kg, statistically significant decreases in both systemic blood pressure and heart rate were observed (approximately 13% decrease) which were sustained for 5 and 2 hours, respectively. In a hypertensive rat model, an oral dose of 5 mg/kg tizanidine was associated with a maximum 25% reduction in mean arterial blood pressure.

In both anaesthetized rats and dogs, intravenously administered tizanidine at doses of 0.03 and 0.1 mg/kg produced an initial, transient pressor response, followed by sustained hypotension and bradycardia. The α_1- and α_2-adrenergic antagonist, phenoxybenzamine, inhibited the initial pressor response to tizanidine in anaesthetized rats. In anaesthetized cats, tizanidine at a cumulative intravenous dose of 0.7 mg/kg, decreased blood pressure by a maximum of 35%.

Tizanidine appears to influence blood pressure through α-adrenoreceptor-mediated vasoconstriction in the peripheral vasculature and by activities on the centrally located α-adrenoreceptors regulating peripheral sympathetic activity.

TOXICOLOGY

Slight, reversible increases in SGPT/ALT were observed after the oral administration of tizanidine in subchronic (13 week) studies in rats and dogs and a chronic (52 week) study in dogs. Mild, reversible histopathological changes in the liver were also reported in the subchronic studies in rats and dogs at doses representing about 55 and 6 times the maximum recommended human dose, respectively. For this and all subsequent comparisons the reference weight for a small human is 50 kg.

In the 13-week subchronic toxicity studies, the maximum dose at which no toxic effect was observed was 1.7 mg/kg in rats and 0.3 mg/kg in dogs.

In dogs receiving doses of 1.5 mg/kg during the 52-week chronic toxicity study, the heart rate was reduced by 40% and the QT interval was prolonged. Slight sedation or unstable equilibrium, emesis, and salivation were also observed at this dose. The maximum dose at which no toxic effects were observed in this study was 0.45 mg/kg.

Teratology Studies
Reproduction studies in rats performed at oral doses of tizanidine up to approximately 4 times the maximum recommended human dose did not provide evidence of embryotoxic or teratogenic effects. However, at dose levels producing exaggerated pharmacodynamic effects in rats (from 5 to over 130 times the maximum recommended human dose), the duration of pregnancy was prolonged, prenatal and perinatal mortality was increased, and development retardation (reduced fetal weight, increased incidence of skeletal retardation) was observed.

Tizanidine has been found to pass into the milk of nursing rats with a milk to blood concentration ratio of 1.8:1. In young nursing rats, abnormal results were obtained in tests indicative of central nervous system function. Several changes were noted in the development of the pups that may have been attributable either to the toxicity of the drug on the dams or else to direct drug effects on the offspring, following ingestion through milk.

Reproduction studies in rabbits with tizanidine doses over 40 times the maximum recommended human dose showed no evidence of embryotoxicity or teratogenicity.

Mutagenesis
Tizanidine was not mutagenic or clastogenic in the following in vitro assays: the bacterial Ames test and the mammalian gene mutation test and chromosomal aberration test in Chinese hamster cells.

It was also negative in the following in vivo assays: the bone marrow micronucleus test in mice, the bone marrow micronucleus and cytogenicity test in Chinese hamsters, the dominant lethal mutagenicity test in mice, and the unscheduled DNA synthesis (UDS) test in mice.

Carcinogenesis
No evidence for carcinogenicity was seen in two dietary studies in rodents. Tizanidine was administered to mice for 78 weeks at doses up to 16 mg/kg, which is equivalent to 2 times the maximum recommended human dose on a mg/ m^2 basis. Tizanidine was also administered to rats for 104 weeks at doses up to 9 mg/kg which is equivalent to 2.5 times the maximum recommended human dose on a mg/m^2 basis. There was no statistically significant increase in tumors in either species.

Impairment of Fertility
Tizanidine did not affect fertility in male rats at doses of 10 mg/kg, approximately 2.7 times the maximum recommended human dose on a mg/m2 basis and in females at doses of 3 mg/kg, approximately equal to the maximum recommended human dose on a mg/ m^2 basis; fertility was reduced in males receiving 30 mg/kg (8 times the maximum recommended human dose on a mg/ m^2 basis) and in females receiving 10 mg/kg (2.7 times the maximum recommended human dose on a mg/m2 basis). At these doses, maternal behavioral effects and clinical signs were observed including marked sedation, weight loss, and ataxia.

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7. Product Monograph for ^{Pr}ZANAFLEX®, Date of Preparation October 15, 2012 Control # 154316. Paladin Labs Inc.

PART III: CONSUMER INFORMATION

PrMYLAN-TIZANIDINE

Tizanidine Hydrochloride Tablets

4 mg

This leaflet is part III of a three-part "Product Monograph" published when MYLAN-TIZANIDINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYLAN-TIZANIDINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MYLAN-TIZANIDINE (tizanidine hydrochloride) is a drug used to reduce the spasticity which may be caused by medical conditions such as spinal cord injury or multiple sclerosis.

What it does:
Tizanidine presumably reduces spasticity by decreasing the activity of nerves that cause muscle spasticity. The overall effect is muscle relaxation.

When it should not be used:
Do not use MYLAN-TIZANIDINE if you:

- are allergic to it or to any of the nonmedicinal ingredients (see below). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effects.
- are currently taking fluvoxamine or ciprofloxacin.
- need spasticity to maintain upright posture and balance for your movements.

What the medicinal ingredient is:
Tizanidine hydrochloride

What the important nonmedicinal ingredients are:
Anhydrous lactose.
Other non-medicinal ingredients include: microcrystalline cellulose, silicon dioxide colloidal, and stearic acid.

What dosage forms it comes in:
4 mg tablets

WARNINGS AND PRECAUTIONS

BEFORE you use MYLAN-TIZANIDINE, talk to your doctor or pharmacist if any of the following conditions apply to you:

- history of an unusual or allergic reaction to MYLAN-TIZANIDINE or to any other substances, such as foods, preservatives or dyes
- pregnancy or breast-feeding
- liver disease
- kidney disease
- low blood pressure
- presently receiving treatment with antihypertensives (high blood pressure medicine), oral contraceptives (birth control pills), fluvoxamine, ciprofloxacin, or phenytoin.

Do not drive or operate hazardous machinery if you are unsure how this medication will affect you or if you experience drowsiness, coordination problems, or blurred vision.

It is important to tell your doctor or pharmacist about all medicines that you are taking including other medicines that a doctor has prescribed, medicines that you buy yourself without a prescription, and any herbal remedies that you are taking. While on MYLAN-TIZANIDINE, do not start taking a new medicine or herbal remedy before checking with your doctor.

INTERACTIONS WITH THIS MEDICATION

Do not use MYLAN-TIZANIDINE if you are taking fluvoxamine or ciprofloxacin.

Alcohol and other central nervous system depressants (medicines causing drowsiness or decreased alertness such as antihistamines, sedatives, tranquilizers, sleeping medicines, prescription pain medicines, narcotics, anti-epileptics, other muscle relaxants, and anaesthetics) may increase the drowsiness experienced with MYLAN-TIZANIDINE.

Other drugs that may interact with MYLAN-TIZANIDINE include: acetaminophen, oral contraceptives, blood pressure lowering drugs, antiarrythmic heart medications (e.g. amiodarone, mexiletine, propafenone), cimetidine (to reduce stomach acid), fluoroquinolone-type antibiotics (e.g. norfloxacin, moxifloxacin), and ticlopidine (to prevent blood clotting).

PROPER USE OF THIS MEDICATION

Usual dose:
Take MYLAN-TIZANIDINE as directed by your doctor. Do not take larger or more frequent doses

than your doctor has prescribed. During the first weeks of treatment, your doctor may want to adjust your dose to meet your individual needs.

If you need to stop taking MYLAN-TIZANIDINE, follow your doctor's instruction on how to gradually reduce your dose.

Food can affect the absorption of MYLAN-TIZANIDINE in your body - so it is important to take it in the same way all the time. For example, if you normally take MYLAN-TIZANIDINE with a meal, you should take it with food each time. If you normally take MYLAN-TIZANIDINE on an empty stomach, then you should always take it before you eat.

Overdose:
The majority of the cases of tizanidine overdose reported in post-marketing experience involved sleepiness, very long or deep sleeplike state from which a person can be awakened only briefly by vigorous stimulation (stupor) or cannot be at all (coma), heart beat at an unusually slow rate, fall in blood pressure, and difficulty breathing.

In case of drug overdose, contact a health care practitioner , hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

MYLAN-TIZANIDINE may cause dry mouth, drowsiness, weakness, fatigue, hallucinations, or dizziness in some patients.

MYLAN-TIZANIDINE may cause a decrease in your blood pressure. In some cases, decreased blood pressure may result in dizziness, lightheadedness, or fainting when a person rises suddenly from a sitting or lying position. Rising slowly may decrease the risk of these problems.

Rare cases of liver damage have been reported in patients receiving Tizanidine Hydrochloride. Monitoring of liver function tests (ALT/SGPT and AST/SGOT) during treatment with MYLAN-TIZANIDINE may be required by your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	Hallucination		√	
	Hypotension (feeling dizzy, lightheaded, or faint)		√	
Uncommon	Liver disorder [symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine]		√*	
	Allergic reactions (red and lumpy skin, rash, hives, swelling, trouble breathing)			√*
	Breakdown of muscle fibers [symptoms include abnormal urine color (dark, red, or cola colored), muscle tenderness, weakness of the affected muscle(s), generalized weakness or muscle stiffness or aching]		√	

*If you think you have these side effects, it is important that you seek medical advice from your doctor straight away.

This is not a complete list of side effects. For any unexpected effects while taking MYLAN-TIZANIDINE, contact your doctor or pharmacist.

HOW TO STORE IT

MYLAN-TIZANIDINE should be stored between 15 °C and 30°C out of the reach of children and away from heat and direct light.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  -Fax toll-free to 1-866-678-6789, or
  -Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379

This leaflet was prepared by Mylan Pharmaceuticals ULC Etobicoke, Ontario M8Z 2S6

Prepared on/Revised on: April 19, 2013

Mylan

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