TIZANIDINE HYDROCHLORIDE- tizanidine hydrochloride tablet
Lake Erie Medical DBA Quality Care Products LLC

Tizanidine Hydrochloride 4 mg

DESCRIPTION

Tizanidine hydrochloride USP, is a centrally acting α_2-adrenergic agonist. Tizanidine HCl USP (tizanidine) is a white to off-white, fine crystalline powder, which is odorless or with a faint characteristic odor. Tizanidine is slightly soluble in water and methanol; solubility in water decreases as the pH increases. Its chemical name is 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiodiazole hydrochloride. Tizanidine's molecular formula is $C_9H_8ClN_5S.HCl$, its molecular weight is 290.2 and its structural formula is

Tizanidine tablets USP, is supplied as 2 mg and 4 mg tablets for oral administration. Tizanidine tablets USP, are composed of the active ingredient, tizanidine hydrochloride USP (2.29 mg equivalent to 2 mg tizanidine base and 4.58 mg equivalent to 4 mg tizanidine base), and the inactive ingredients, anhydrous lactose, microcrystalline cellulose, colloidal silicon dioxide and stearic acid.

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.

INDICATIONS AND USAGE

Tizanidine tablets are a short-acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Concomitant use of tizanidine with fluvoxamine or with ciprofloxacin, potent inhibitors of CYP1A2, is contraindicated. Significant alterations of pharmacokinetic parameters of tizanidine including increased AUC, $t_{1/2,}$ Cmax, increased oral bioavailability and decreased plasma clearance have been observed with concomitant administration of either fluvoxamine or ciprofloxacin. This pharmacokinetic interaction can result in potentially serious adverse events (See **WARNINGS** and **CLINICAL PHARMACOLOGY: Drug Interactions**). Tizanidine tablets are contraindicated in patients with known hypersensitivity to tizanidine or its ingredients.

WARNINGS

Limited Data Base 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 doses of 8 to 16 mg single doses or total daily doses of 24 to 36 mg (see **DOSAGE AND ADMINISTRATION**) is limited. In safety studies, approximately 75 patients have been exposed to individual doses of 12 mg or more for at least one year or more and approximately 80 patients have been exposed to total daily doses of 30 to 36 mg/day for at least one year or more. 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 (see **WARNINGS**, **PRECAUTIONS AND ADVERSE REACTIONS**).

Hypotension

Tizanidine 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 ^{3} 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 hypotension and orthostatic effects. Caution is advised when tizanidine is to be used in patients receiving concurrent antihypertensive therapy and should not be used with other a_2-adrenergic agonists. Clinically significant hypotension (decreases in both systolic and diastolic pressure) has been reported with concomitant administration of either fluvoxamine or ciprofloxacin and single doses of 4 mg of tizanidine. Therefore, concomitant use of tizanidine with fluvoxamine or with ciprofloxacin, potent inhibitors of CYP1A2, is contraindicated (see **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interactions**).

Risk Of Liver Injury

Tizanidine occasionally causes 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) compared to 0.4% in the control patients. Most cases resolved rapidly upon drug withdrawal with no reported residual problems. In occasional symptomatic cases, nausea, vomiting, anorexia and jaundice have been reported. Based upon postmarketing experience, death associated with liver failure has been a rare occurrence reported in patients treated with tizanidine.

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.

SedationIn 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 greater than 1% in the placebo treated patients. Sedation may interfere with everyday activity. The effect appears to be dose related. In a single dose study, 92% of the patients receiving16 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.

Hallucinosis/Psychotic-Like Symptoms

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. These 5 cases occurred within the first 6 weeks. Most of the patients were aware that the events were unreal. One patient developed psychoses in association with the hallucinations. One patient among these 5 continued to have problems for at least 2 weeks following discontinuation of tizanidine.

Use in Patients With Hepatic Impairment

The influence of hepatic impairment on the pharmacokinetics of tizanidine has not been evaluated. Because tizanidine is extensively metabolized in the liver, hepatic impairment would be expected to have significant effects on the pharmacokinetics of tizanidine. Tizanidine should ordinarily be avoided or used with extreme caution in patients with hepatic impairment (See also **Risk Of Liver Injury**).**Potential Interaction With Fluvoxamine Or Ciprofloxacin** In a pharmacokinetic study, tizanidine serum concentration was significantly increased (Cmax 12-fold, AUC 33-fold) when the drug was given concomitantly with fluvoxamine. Potentiated hypotensive and sedative effects were observed. Fluvoxamine and tizanidine should not be used together. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interactions**).

In a pharmacokinetic study, tizanidine serum concentration was significantly increased (Cmax 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin. Potentiated hypotensive and sedative effects were observed. Ciprofloxacin and tizanidine should not be used together (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interactions**).

Possible Interaction With Other Cyp1A2 Inhibitors

Because of potential drug interactions, concomitant use of tizanidine with other CYP1A2 inhibitors, such as zileuton, other fluoroquinolones, antiarrythmics (amiodarone, mexiletine, propafenone, and verapamil), cimetidine, famotidine, oral contraceptives, acyclovir and ticlopidine (see **CLINICAL PHARMACOLOGY: Drug Interactions**) should ordinarily be avoided. If their use is clinically necessary, they should be used with caution.

PRECAUTIONS

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. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose controlled study (see **WARNINGS**).

Ophthalmic

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.

Use in Renally Impaired Patients

Tizanidine should be used with caution in patients with renal insufficiency (creatinine clearance greater than 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 the onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia and dizziness) as indicators of potential overdose.

Use in Women Taking Oral Contraceptives

Because drug interaction studies of tizanidine with oral contraceptives have shown that concomitant use may reduce the clearance of tizanidine by as much as 50%, concomitant use of tizanidine with oral contraceptives should ordinarily be avoided (see **CLINICAL PHARMACOLOGY: Drug Interactions**). However, if concomitant use is clinically necessary, the starting dose and subsequent titration rate of tizanidine should be reduced.

Discontinuing Therapy

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

ADVERSE REACTIONS

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

Common Adverse Events Leading To Discontinuation

Forty-five of 264 (17%) patients receiving tizanidine 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 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 effects were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. Three-quarters of the patients rated the events as mild to moderate and one-quarter of the patients rated the events as being severe. These events appeared to be dose related.

Adverse Events Reported In Controlled Studies

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 where the frequency in the tizanidine group was at least as common as in the placebo group. These events are not necessarily related to tizanidine 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 (less than 2%) Adverse Events Reports for which Tizanidine Tablets Incidence is Greater than Placebo

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 effects are 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

Other Adverse Events Observed During The Evaluation Of Tizanidine Tizanidine was administered to 1385 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 1385 patients exposed to tizanidine 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, 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, rare adverse events are those occurring in fewer than 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

OVERDOSAGE

A review of the safety surveillance database revealed cases of intentional and accidental tizanidine overdose. Some of the cases resulted in fatality and many of the intentional overdoses were with multiple drugs including CNS depressants. The clinical manifestations of tizanidine overdose were consistent with its known pharmacology. In the majority of cases a decrease in sensorium was observed

including lethargy, somnolence, confusion and coma. Depressed cardiac function are also observed including most often bradycardia and hypotension. Respiratory depression is another common feature of tizanidine overdose.

Should overdose occur, basic steps to ensure the adequacy of an airway and the monitoring of cardiovascular and respiratory systems should be undertaken. In general, symptoms resolve within one to three days following discontinuation of tizanidine and administration of appropriate therapy. Due to the similar mechanism of action, symptoms and management of tizanidine overdose are similar to those following clonidine overdose. For the most recent information concerning the management of overdose, contact a poison control center.

DOSAGE AND ADMINISTRATION

A single dose of 8 mg of tizanidine 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. 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's common adverse events make it prudent to begin treatment with single oral doses of 4 mg. 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.

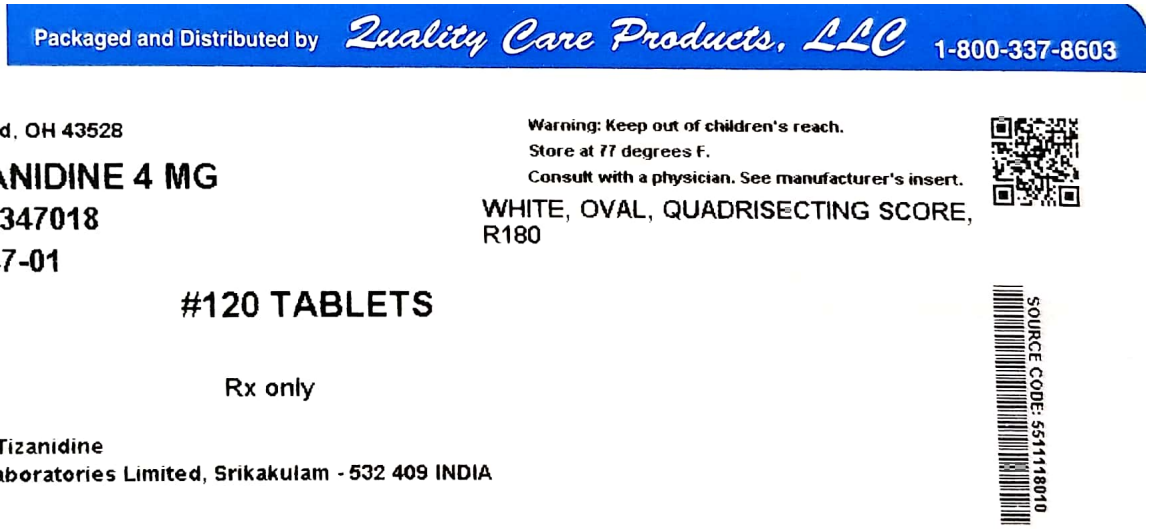
Experience with single doses exceeding 8 mg and daily doses exceeding 24 mg is limited. There is essentially no experience with repeated, single, daytime doses greater than 12 mg or total daily doses greater than 36 mg (see **WARNINGS**).

Food has complex effects on tizanidine pharmacokinetics, which differ with the different formulations. These pharmacokinetic differences may result in clinically significant differences when switching administration of the tablet between the fed or fasted state. These changes may result in increased adverse events or delayed/more rapid onset of activity, depending upon the nature of the switch. For this reason, the prescriber should be thoroughly familiar with the changes in kinetics associated with these different conditions (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

HOW SUPPLIED

Tizanidine Tablets USP, 2 mgare white to off white, oval, flat, beveled edged tablets embossed with "R179" on one side and "bisecting score" on other side. The tablets are available in bottles of 30, 150, 300 and 1000.

Tizanidine Tablets USP, 4 mg are white to off white, oval, flat, beveled edged tablets embossed with "R180" on one side and "quadrisecting score" on other side. The tablets are available in bottles of 30, 150, 300 and 1000.



TIZANIDINE HYDROCHLORIDE

tizanidine hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49999-347(NDC:55111-180)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TIZANIDINE HYDROCHLORIDE (UNII: B53E3NMY5C) (TIZANIDINE - UNII:6AI06C00GW)	TIZANIDINE	4 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

Product Characteristics			
Color	white (white to off-white)	**Score**	4 pieces
Shape	OVAL	**Size**	11mm
Flavor		**Imprint Code**	R;180
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:49999-347-01	120 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/23/2010	

2	NDC:49999-347-15	15 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/19/2019	
3	NDC:49999-347-30	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/23/2010	
4	NDC:49999-347-60	60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/23/2010	
5	NDC:49999-347-90	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/23/2010	
6	NDC:49999-347-28	28 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	11/23/2010	01/01/2012

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076286	11/23/2010	

Labeler - Lake Erie Medical DBA Quality Care Products LLC (831276758)

Establishment

Name	Address	ID/FEI	Business Operations
Lake Erie Medical DBA Quality Care Products LLC		831276758	repack(49999-347)

Revised: 1/2020 Lake Erie Medical DBA Quality Care Products LLC