ZANAFLEX- tizanidine 4mg capsule
Advanced Rx Pharmacy of Tennessee, LLC

Tizanidine 4mg capsules #90

Adverse Reactions Section

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in other sections of the prescribing information:

Hypotension [see Warnings and Precautions (5.1)].
Liver Injury [see Warnings and Precautions (5.2)].
Sedation [see Warnings and Precautions (5.3)].
Hallucinosis/Psychotic-Like Symptoms [see Warnings and Precautions (5.4)].
Hypersensitivity Reactions [see Warnings and Precautions (5.6)].

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.
Three double-blind, randomized, placebo controlled -clinical studies were conducted to evaluate the effect of tizanidine on spasticity control. Two studies were conducted in patients with multiple sclerosis and one in patients with spinal cord injury. Each study had a 13-week active treatment period which included a 3-week titration phase to the maximum tolerated dose up to 36 mg/day in three divided doses, a 9-week plateau phase where the dose of tizanidine was held constant and a 1-week dose tapering. In all, 264 patients received tizanidine and 261 patients received placebo. Across the three studies patient ages ranged from 15 to 69 years and 51.4 percent were women. The median dose during the plateau phase ranged from 20 to 28 mg/day.
The most frequent adverse reactions reported in multiple dose, placebo-controlled clinical studies involving 264 patients with spasticity 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.
Table 1 lists 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 greater than the placebo group. 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 Reactions Reported for Which Tizanidine Tablets Incidence is Greater than Placebo
Event
Placebo

N = 261%
Tizanidine Tablets
N = 264%
Dry mouth
10
49
Somnolence
10
48
Asthenia*
16
41
Dizziness
4
16
UTI
7
10
Infection
5
6
Constipation
1
4
Liver test abnormality
2
6
Vomiting
0
3
Speech disorder
0
3
Amblyopia (blurred vision)
<1
3
Urinary frequency
2
3
Flu syndrome
2
3
Dyskinesia
0
3
Nervousness
<1
3
Pharyngitis
1

3
Rhinitis
2
3
*(weakness, fatigue, and/or tiredness)

In the single dose, placebo-controlled study involving 142 patients with spasticity due to multiple sclerosis (Study 1) [see Clinical Studies (14)], the patients were specifically asked if they had experienced any of the four most common adverse reactions: dry mouth, somnolence (drowsiness), asthenia (weakness, fatigue and/or tiredness) and dizziness. In addition, hypotension and bradycardia were observed. The occurrence of these reactions 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 Reactions Reported
Event
Placebo
N = 48
%
Tizanidine Tablet,
8 mg, N = 45
%
Tizanidine Tablet,
16 mg, N = 49
%
Somnolence
31
78
92
Dry mouth
35
76
88
Asthenia*
40
67
78
Dizziness
4
22
45
Hypotension
0
16
33
Bradycardia
0
2
10

*(weakness, fatigue, and/or tiredness)

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of tizanidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Certain events, such as somnolence, dry mouth, hypotension, decreased blood pressure, bradycardia, dizziness, weakness or asthenia, muscle spasms, hallucinations, fatigue, liver function test abnormality and hepatotoxicity, have been observed in post marketing and clinical trials and are discussed in previous sections of this document.

The following adverse reactions have been identified as occurring in the post marketing experience of tizanidine. Based on the information provided regarding these reactions, a causal relationship with tizanidine cannot be entirely excluded. The events are listed in order of decreasing clinical significance; severity in the post marketing setting is not reported.

Stevens Johnson Syndrome
Anaphylactic Reaction
Exfoliative Dermatitis
Ventricular Tachycardia
Hepatitis
Convulsion
Depression
Arthralgia
Paresthesia
Rash
Tremor

Dosage and Administration Section

2 DOSAGE & ADMINISTRATION

2.1 Dosing Information

Tizanidine hydrochloride capsules may be prescribed with or without food. Once the formulation has been selected and the decision to take with or without food has been made, this regimen should not be altered.
Food has complex effects on tizanidine pharmacokinetics, which differ with the different formulations. Tizanidine hydrochloride capsules and tizanidine tablets are bioequivalent to each other under fasting conditions (more than 3 hours after a meal), but not under fed conditions (within 30 minutes of a meal). These pharmacokinetic differences may result in clinically significant differences when switching administration of tablet and capsules and when switching administration between the fed or fasted state. These changes may result in increased adverse events, or delayed or 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 (12.3)].
The recommended starting dose is 2 mg. Because the effect of tizanidine hydrochloride capsule peaks at approximately 1 to 2 hours post-dose and dissipates between 3 to 6

hours post-dose, treatment can be repeated at 6 to 8 hour intervals, as needed, to a maximum of three doses in 24 hours.
Dosage can be gradually increased by 2 mg to 4 mg at each dose, with 1 to 4 days between dosage increases, until a satisfactory reduction of muscle tone is achieved. The total daily dose should not exceed 36 mg. Single doses greater than 16 mg have not been studied.

2.2 Dosing in Patients with Renal Impairment

Tizanidine hydrochloride capsules should be used with caution in patients with renal insufficiency (creatinine clearance < 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 [see Warnings and Precautions (5.7)].

2.3 Dosing in Patients with Hepatic Impairment

Tizanidine hydrochloride capsules should be used with caution in patients with any hepatic impairment. 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. Monitoring of aminotransferase levels is recommended for baseline and 1 month after maximum dose is achieved, or if hepatic injury is suspected. [see Use in Specific Populations (8.7)]

2.4 Drug Discontinuation

If therapy needs to be discontinued, particularly in patients who have been receiving high doses (20 mg to 36 mg daily) for long periods (9 weeks or more) or who maybe on concomitant treatment with narcotics, the dose should be decreased slowly (2 mg to 4 mg per day) to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia [see Drug Abuse and Dependence (9.3)].

Indications and Usage Section

1 INDICATIONS & USAGE

Tizanidine hydrochloride is a central alpha-2-adrenergic agonist indicated for the management of spasticity. Because of the short duration of therapeutic effect, treatment with tizanidine hydrochloride should be reserved for those daily activities and times when relief of spasticity is most important [see Dosage and Administration (2.1)].

Principal Display Panel

ZANAFLEX

tizanidine 4mg capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:80425-0144(NDC:67877-611)
Route of Administration	ORAL		

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

Product Characteristics			
Color	white, blue	**Score**	no score
Shape	CAPSULE	**Size**	15mm
Flavor		**Imprint Code**	4MG;Tiza
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:80425-	90 in 1 BOTTLE; Type 0: Not a Combination	03/29/2019	

1	0144-3	Product	03/29/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA212196	03/29/2019	

Labeler - Advanced Rx Pharmacy of Tennessee, LLC (117023142)

Establishment

Name	Address	ID/FEI	Business Operations
Advanced Rx Pharmacy of Tennessee, LLC		117023142	repack(80425-0144)