and pallor. In all case reports, AEs were reported to have resolved following discontinuation of tizanidine, rofecoxib, both tizanidine and rofecoxib, or following a reduction in tizanidine dose. In one case, when tizanidine alone was re-challenged, no events recurred. In the remaining case reports, no re-challenge was performed with rofecoxib alone, tizanidine alone, or tizanidine and rofecoxib together. In 4 case reports, the use of concomitant medications may have confounded the assessment of a drug interaction between tizanidine and rofecoxib.

Since tizanidine is metabolized by microsomal P450s, whereas rofecoxib is metabolized by reduction by cytosolic enzymes, competitive inhibition is unlikely, but other forms of metabolic interactions are possible. The issue remains unsettled, but seems real given the disproportionate frequency of interaction reports for Vioxx. The sponsor proposes to include this potential interaction in the labeling, and OCPB believes that additional work on this potential AE is not warranted at this time.

Overdosage

During the clinical development of tizanidine, one significant tizanidine overdosage was reported. Attempted suicide by a 46-year old male with MS resulted in coma very shortly after the ingestion of 100 tizanidine 4 mg tablets. The patient had marked respiratory depression with Cheyne-Stokes respiration. Gastric lavage and forced diuresis with furosemide and mannitol were instituted. The patient recovered several hours later without sequelae. Laboratory findings were normal.

The clinical management of tizanidine overdosage, as described in the tizanidine Package Insert, is to ensure the adequacy of an airway and the monitoring of cardiovascular and respiratory systems. The sponsor conducted a review of overdosage experience in the published medical literature post the Zanaflex tablet NDA approval, and a review of cases from the postmarket safety surveillance database.

Published Medical Literature

There were 3 case reports of tizanidine overdosage in the published literature. All 3 cases resulted in CNS effects, ranging from drowsiness to coma; 2 patients suffered additional cardiovascular effects, including bradycardia and hypotension. In general, symptoms resolved within 1-3 days of tizanidine discontinuation.

Luciani et al (1995) reported the occurrence of sino-atrial and atrio-ventricular node dysfunction in a case of tizanidine overdose. An otherwise healthy 27-year-old woman ingested 30 mg lorazepam and 120 mg tizanidine. On arrival to the emergency room, she was in a drowsy state, with hypotension (BP 80/50 mmHg) and sinus bradycardia (34 bpm), first degree atrio-ventricular block (PQ interval 240 mm sec) and Wenckebach type-second degree atrio-ventricular block. In the following hours she regained consciousness and her blood pressure rose gradually.

Inoue et al (1999) reported the case of a 41-year-old woman admitted to hospital because of disturbance of consciousness after taking 23 mg of tizanidine. On admission (about 3 hours after taking of tizanidinel), physical examination revealed bradycardia,

hypotension and hypothermia. Neurological findings were significant for semi comatose state of consciousness with deep tendon reflexes symmetrically hypoactive in all extremities. No pathological reflexes were present. She recovered.

Kurtoglu et al (2000) reported the case of a newborn who was inadvertently administered tizanidine (0.7 mg/kg/day). Apparently, the newborn was also receiving other drugs including diphenoxylate, atropine, and pipenzolate. The newborn survived.

Overdosage Cases from Postmarket Safety Surveillance

A search of the postmarket safety surveillance database identified 18 tizanidine overdosage cases (Table 10). Most cases involved depressed cardiovascular function (bradycardia, hypotension), depressed respiratory function (respiratory depression or failure), and/or depressed consciousness (somnolence, stupor, or coma). A few cases involved excited states of consciousness (delirium and confusion; tremor and hallucinations). There was one case of drug addiction and one case of drug dependence. One of the cases (#656) is also reported in the literature review section above (Kurtoglu et al., 2000). With discontinuation of tizanidine and appropriate therapy, the adverse effects were reversible and no permanent clinical sequelae resulted in most cases. Five patients died because of suicidal overdosage. In some cases, other drugs (i.e. benzodiazepines and other muscle relaxants), as well as antidepressants, and possibly the patient's underlying disease, are likely to have contributed to lethality. In one case, the patient death was related to sepsis and pneumonia.

The post-NDA 20-397 overdosage experience confirms that tizanidine overdosage may cause depressed cardiovascular, respiratory, and/or CNS function. OCPB concluded that the sponsor's proposed labeling _____ was inadequate. OCPB identified that the most common information source used by poison control centers grouped tizanidine with other muscle relaxants and concluded that this was too generic. OCPB suggested that a cross reference to clonidine, pharmacologically similar to tizanidine, should be added. OCPB proposed, in addition to labeling, the publication of a review article of the overdose cases in collaboration with the sponsor, which would allow tertiary sources of drug poisoning information to disseminate more complete information than is possible in the professional labeling. I concur with that proposal.

Table 10: Summary of overdosage cases

Case	Age	Sex	Dose	CV	CNS	Respiratory	General	Metabolic	Outcome
656	1M	?	0.7mg/kg		Hypotonia Somnolence				Recovered
149	46Y	F	240mg	Hypotension	Coma	Resp. failure	Hypothermia	Liver test ↑ WBC↑ RBC Acidosis	Recovering
189	57	F	? + Ambien, Trazodone			Resp. failure			**Death**
263	13	F	40mg	Bradycardia QT ↑					Recovered
341	22	M	?	Arrhythmia	Hypotonia Somnolence	Resp. failure		Liver test ↑	Recovered
377	33	M	360mg + Thorazine		Coma Hypertonia Athetosis				Recovered
391	?	M	16-120mg		Stupor			Renal failure	Continued RF
400	38	M	?						**Death**
420	30	M	160mg (?)						**Death**
442	45	F	360mg	Hypotension Bradycardia	Somnolence				Recovered
443	51	F	284mg	QT ↑	Consciousness↓	Resp. failure	Hypothermia		
545	45	F	?+codeine, diazepam						**Death**
775	30	M	80mg	Bradycardia Hypotension		Resp. failure Pneumonia	Sepsis	Glycemia↑	**Death**
823	49	F	56mg daily X 4 years (addiction)	Hypertension at withdrawal	Dependence Lightheadedness at withdrawal		Fall at withdrawal		Improved
835	44	F	?		Confusion Delirium				?
853	?	F	68mg daily	Hypertension at withdrawal	Dependence				?
627	40	F	Up to 180mg daily X 5 days	Hypertension and tachycardia at withdrawal	Tremor Hallucinations Hallucinations at withdrawal		Vomiting at withdrawal		?
638	?	F	?	Bradycardia					Pacemaker

In several overdose cases, tizanidine was possibly being misused by individuals addicted to opioids. OCPB relates that to a similar used of clonidine, which is commonly misused by addicts to prolong the duration of narcotic effect and minimize opioid withdrawal symptoms. In these post-marketing safety reports, patients appeared to have become addicted to opioids in the context of treatment of chronic pain, and Zanaflex may also have been prescribed off label for chronic pain treatment as a "muscle relaxant" (use distinct of the catapressan use in addition). I concur that labeling changes to mention the occurrence of dependence and withdrawal are warranted. In addition to labeling changes similar to clonidine regarding slow withdrawal, the OCPB reviewer proposes including information in the proposed publication. I encourage this initiative.

D. Adequacy of Safety Testing

In addition to NDA 20-397 safety program, there is extensive clinical experience with tizanidine, with 5 years of post-marketing experience in the United States, and almost 20 years of experience overseas.

The studies part of this NDA added little information on the tizanidine safety profile, except for raising new issues related to the non-bioequivalence of the capsule and tablet in the fed state. This issue can be addressed in the labeling.

An understudied issue is the effect of tizanidine on the QT interval. Animal toxicology studies have suggested QT prolongation at high dosages. The sponsor has not studied QT changes at Cmax. There is no information from the safety database suggesting that tizanidine is inducing QT changes, except for QT prolongation in 2 overdosage cases (Table 10). The sponsor should obtain EKGs at Cmax to evaluate that issue in future PK studies. During the review time of this NDA, the sponsor has submitted IND —— to conduct human studies in the United States.

E. Summary of Critical Safety Findings and Limitations of Data

The safety data from the Elan Pharmaceuticals postmarket safety surveillance database do not change FDA previous assessment of the safety profile of tizanidine established in NDA 20-397, and presented in the Zanaflex Package Insert. Limited new safety information could be expected from these short-term pharmacokinetic studies with relatively low doses of tizanidine.

Study AN021-001 gave additional information of the tizanidine pharmacodynamic effect of blood pressure and cognition, and on the effect of food and formulation on tizanidine PK/PD, which has safety relevance. However, the safety benefit from the capsule formulation appears limited, since the hypotensive effect in the fed state appeared simply

delayed compared to the tablet formulation in the fed or fasted states, but with a similar degree of hypotension.

The most important new safety issue is the risk associated with patients switching from one formulation to the other. This is discussed in "section VIII. Dosing, Regimen, and Administration Issues".

Based upon the findings from reported cases of tizanidine drug interaction in the postmarketing safety surveillance database, the tizanidine tablet and capsule Package Insert information regarding drug interaction must be updated with information regarding possible interaction with rofecoxib (Vioxx- Merck). The sponsor reported 8 case reports of interactions with rofecoxib. Most adverse events were in the CNS or cardiovascular spheres. Some of the AEs fit the expected pharmacology of excessive tizanidine administration, and some of the AEs fit the profile expected with abrupt tizanidine withdrawal. The mechanism and risk from this potential interaction is unclear. The sponsor proposed labeling changes to raise awareness of the possibility of that interaction. I concur that this addition is necessary. I also concur with OCPB that the division of Gastrointestinal and Hematologic drug products should be made aware of this issue.

There is very limited information available in the published medical literature and in the postmarket safety surveillance on the safety of tizanidine in the pediatric population. The types of adverse events reported in children are similar to that seen in adults. However, is unclear if their incidence is similar, and how their incidence relates to tizanidine dosage in different age groups. The impact of somnolence on cognition is particularly problematic in the pediatric population, where there may be a more severe impact on learning and quality of life issue. Even tough side effects appeared to be dose-dependent and generally resolved upon drug discontinuation or lower drug dosage, there is no information on dosing regimen in children where the risk/benefit ratio is favorable. There is clearly a need for a pediatric long term safety study.

The tizanidine overdosage experience described in the published medical literature post NDA 20-397 approval and in the postmarket safety surveillance database confirms that tizanidine may cause depressed cardiovascular, respiratory, and/or CNS function in cases of overdosage. I concur with OCPB that, in addition to labeling, the publication of a review article of the presently known overdose cases in collaboration with the sponsor would allow tertiary sources of drug poisoning information to disseminate more complete information than is possible in the professional labeling

VIII. Dosing, Regimen, and Administration Issues

The proposed dosing is unchanged from the approved tablet formulation and is acceptable. The most important issue is the risk associated with patients switching from one formulation to the other, or with patients taking their usual formulation at various timing relative to their meals, hence modifying their exposure to the drug.

The most problematic potential situation is that of patients switching from the capsule formulation to the tablet formulation in the fed state, where there is a risk of more severe side effects with excessive hypotension and somnolence. In the opposite situation (switching from the tablet to the capsule in the fed state), the risk is mostly decreased efficacy of the drug, which is less problematic and easier to correct.

Another potentially dangerous situation is that of patients taking their usual formulation in various feeding states. The most problematic case scenario is that of patients titrated to take their tablet in the fasted state, but who take a dose in the fed state, hence significantly increasing peek plasma levels and the risks of excessive side effects. This issue is not directly relevant to this NDA which only concerns the capsule formulation, but I recommend correcting it in the dosage and administration section of labeling. Less problematic is the opposite situation of patients used to take their tablet in the fed state but who take it in the fasted state. Finally, similar problems also exist for the capsule formulation: patients titrated to take the capsule in the fed state but who change to the fasted state may increase their peek levels and side effects. Labeling needs to document these issues. The most effective manner is to have a single label for tizanidine tablet and capsule.

IX. Use in Special Populations

No new information about special populations was obtained in this NDA. All information known and summarized here below was obtained in the tizanidine tablet NDA (20-397).

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

No specific pharmacokinetic study was conducted to investigate gender effects. Retrospective analysis in NDA 20-397 showed that gender had no effect on the pharmacokinetics of tizanidine.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

No specific pharmacokinetic study was conducted to investigate age, race or ethnicity effects on safety or efficacy. Cross study comparison of pharmacokinetic data following single dose administration of 6 mg tizanidine in NDA 20-397 (tizanidine tablet) showed that younger subjects cleared the drug four times faster than elderly subjects.

C. Evaluation of Pediatric Program

The Zanaflex tablet is not currently indicated for use in pediatric patients. However, the sponsor recognizes that some physicians may choose to utilize

tizanidine for the treatment of pediatric spasticity. According to the CDC, the 1-year prevalence rate for cerebral palsy (CP) in patients age 17 and under is 2.0 per 1000. Based upon the July 2001 U.S. census data, the total population aged 16 and under is 66,558,000, which translates into approximately 133,116 CP patients under the age of 17. Since about 2/3 CP patients have spasticity, the pediatric CP population with spasticity is about 87,857.

In addition to the CP population, there is a population of pediatric spinal cord injury patients that might be considered candidates for treatment with tizanidine. Of about 200,000 spinal cord injury patients, 5% are thought to be age 15 and under. Of these 5%, 18-25% are thought to have spasticity, which results in a pediatric population (age 15 and under) of 10,000 patients, of whom roughly 2290 are spastic. The sponsor estimated the combined estimated total of pediatric spasticity patients who might be treated with tizanidine at some point at 90,147. There is an additional pediatric population with spasticity resulting from other spinal cord diseases. That category includes spinal tumors, spinal hematomas, spinal infections, inflammatory myelitis, spinal infarcts, degenerative or metabolic diseases, developmental disorder (spina bifida, Chiari malformation, and syringomyelia). This translates in a potential pediatric population probably exceeding 100,000 patients, which can be considered as a substantial number (over 50,000), according to the pediatric rule. The absence of adequate labeling could pose significant risks, since the pharmacokinetics and long term safety of tizanidine in the pediatric population are currently largely unknown.

The sponsor looked at statistical data on the use of Zanaflex tablets for the past 3 years. The sponsor identified that 1 % of all uses of Zanaflex tablets are for pediatric patients. This represents a total of [redacted] prescriptions spread over the past 3 years [redacted] for ages 3-12 and [redacted] for ages 13-17). NDA 20-397 clinical studies were not designed to specifically target the pediatric population, and dealt mainly with an adult MS or SCI population.

The sponsor summarized published data available about the use of tizanidine in the pediatric population and data from postmarket safety surveillance. The sponsor states that the dosage regimens adopted in these studies largely mirror, on a mg/kg basis, those used in adults and that the safety and efficacy profile in this population, is essentially that seen in the adult group. The sponsor believes that these data demonstrate that tizanidine is safe and effective in the pediatric population to treat the symptoms exhibited in CP patients. I do not concur with that assessment, for several reasons, which I developed below. Briefly, these studies were not adequate and/or not well controlled, had an inappropriate design, did not demonstrate efficacy in treating spasticity using validated outcome measures, or were not published in a peer reviewed journal. Many patients in these studies were not even spastic.

Published Medical Literature

A search of the published medical literature revealed 8 studies (Table 11) and 3 case reports.

A total of 269 patients were reported in these studies, with age 0-34 "and older". This means that the actual pediatric population was less than 269, but the sponsor did not give a breakdown of the numbers per age group. The indications included cerebral palsy (CP), Tourette's syndrome, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), and spasticity of origin other than CP. Dosage ranged from 0.5 mg tizanidine /day up to 12 mg tizanidine /day.

Table 11: Pediatric studies in the literature

Study	N	Indications	Age (yrs)	Design	Dose
Bonnier	19	Severe chronic spasticity	0.8–16	Double-blind, comparative	0.4 mg/kg/day / Not stated
Foradada	63	Tourette's, motor tic, ADD, ADHD	4–19	Open, non-comparative	Not stated / Not stated
Gaebler-Spira	35	Spasticity (primarily CP)	"Children and young adults"	Open, non-comparative	Not stated / ≥ 6 weeks
Luetschg	26	Spasticity	1–16	Double-blind, comparative	Not stated / ≥ 6 weeks
Mizue	11	Severe multiple dysfunction, psychosomatic dysfunction, mental retardation, etc.	0.3–13	Open, non-comparative	0.5 mg/day up to 6-12 mg/day / ≥ 6 weeks
Tata	45	Spasticity (primarily CP)	3–34	Open, non-comparative	Not stated / ≥ 6 weeks
Tomiwa	37	CP	<1–24	Open, non-comparative	3 mg/day / 12 weeks
Tsuji	33	Moderate to severe pediatric CP	3–15	Open, non-comparative	Up to 6 mg/day / 8 weeks

Does not include case reports of safety issues (Ishida et al, 1989; Johnson and Tobias, 2000; Kurtoglu, 2000)

Bonnier et al. (1987) conducted a double-blind placebo-controlled study in 19 children with severe chronic spasticity in the age range of 0.8-16 year. Tizanidine dosage was 0.4 mg/kg per day. Nine children evidenced a decrease in their spasticity. In five cases, one of which was with placebo, somnolence was so severe that treatment was terminated. This study was published as an abstract and not as a journal article in a peer reviewed journal and is not acceptable in support of an NDA. It however suggests the relevance of the issue of somnolence in the pediatric population.

Foradada (1999) presented a retrospective review of tizanidine in the treatment of 63 children and young adults with Tourette's syndrome, motor tic disorders, ADD, and ADHD. All patients were switched to tizanidine alone or in combination with other drugs. All patients showed greater relief of symptoms when tizanidine was administered alone or added to treatment, than with conventional therapies alone. Side effects (drowsiness, fatigue) were minimal or nonexistent in children over 6 years of age. Younger children (4 to 6 years) were more likely to experience side effects, which were reduced with lowered dose. The authors cautioned tizanidine use in children 4 to 6 years of age. This study was published only in the abstract form and is not acceptable in support of an NDA. In addition, it is unclear how many patients in this study belonged to the pediatric population.

Tomiwa et al. (1991) investigated tizanidine in 37 children with functional impairment unresolved despite other therapies. They administered 3 mg/day of tizanidine for a minimum of 2 weeks. There was no defined primary outcome. 14/30 evaluable subjects (42.2%) showed a slight improvement or better in neurologic findings (spasticity or deep tendon reflex). "Final global improvement" (undefined) was marked in 2 cases (6.1%), moderate (9.1%) in 3 cases, slight in 16 cases (48.5%), none in 10 cases (30.3%) and there was aggravation in 2 cases (6.1%). The population (how many spastic?) and outcome measures were not well defined. The study duration and drug exposure were unclear. Limited information can be retained from that study.

Tsuji et al. (1985) reported on the administration of tizanidine for 8 weeks in 33 cerebral palsy patients, age 3-15 years. The dosing schedule was 1 mg/day for the first 2 weeks, and then increasing at 1 mg/day per week up to a maximum of 6 mg/day at Week 8. Concomitant muscle relaxants and minor tranquilizers were prohibited during the study. In terms of overall response rate which took into account neurological symptoms, ADL assessment, and behavior (not clearly defined), there were no cases of a marked response, five cases (15.2%) of a moderate response, 18 cases (54.5%) of a mild response, 10 cases (30.3%) of no change, and no cases of deterioration. Somnolence was seen in 8 cases.

Ishida et al. (1989) presented a case report of respiratory distress after treatment with tizanidine in a 2-year old male. The patient was administered tizanidine 0.33 mg/day in 3 doses via a NG tube after each meal. Four hours after administration of 5 mL of triclofos as a sedative, the patient choked, vomited, followed by labored breathing 2 hours later. The symptoms resolved with cessation of tizanidine therapy and supportive care. A second challenge with tizanidine, but without triclofos, resulted in respiratory symptoms.

Johnson and Tobias (2000) reported a case of hypotension following the initiation of tizanidine (dose not specified) in a patient treated with an ACE inhibitor, valproic acid and clonazepam. He developed hypotension following the addition of tizanidine.

Kurtoglu et al. (2000) reported on one newborn infant who was inadvertently administered tizanidine (0.7 mg/kg/day), along with other medications including diphenoxylate, atropine, and pipenzolate. The newborn infant survived.

Pediatric Cases from Postmarket Safety Surveillance

The sponsor searched the postmarket safety surveillance database for pediatric cases involving tizanidine. Eight pediatric cases involving the use of tizanidine met the criteria for expedited reporting. There were 13 events (Table 12) reported in 8 patients (Table 13). Two of the pediatric cases in the postmarket safety database are from the literature.

Table 12: Safety events in the pediatric population

	Number of events	Associated with	Associated with
Respiratory distress	2		
Bradycardia	2	QT prolongation	Hypothermia
Hypotension	2	Bradycardia	Hypothermia Seizure
QT prolongation	1	Bradycardia	
Seizures	1	Hypotension	
Rectal prolapse	1		
Hypotonia	1	Somnolence	
Somnolence	1	Hypotonia	
Hyperthermia	1		
Hypothermia	1	Hypotension	Bradycardia

I reclassified circulatory collapse as hypotension and I added adverse events based on the narratives.

Table 13: Pediatric cases reported in the safety surveillance database

Case # (age)	Adverse event (duration)	Daily dose	Treatment duration	Outcome	Relation
ZANA000128 (16)	Respiratory distress (?) Hypotension (?)	24 mg	7 weeks	Recovered	Not related. Had Chicken pox Treatment continued.
ZANA000263 (13)	Attempted Suicide Bradycardia (?) Prolonged QT (2 weeks)	40 mg	?	Recovered	Possible.
ZANA000331 (5)	Circulatory collapse Hypotension (40 min) Seizures (1 hour)	2.5 mg	3 weeks	?	Possible
ZANA000383 (2)	Respiratory distress (1 day)	0.33 mg	4 days	Recovered	Likely + rechallenge
ZANA000441 (1)	Rectal prolapse (?)	?	?	Improved	Possible - rechallenge
ZANA000656 (?)	Hypotonia (?) Drowsiness (?)	0.7 mg/kg	?	Survived	? Accidental
ZANA000730 (2)	Hyperthermia (1) Tachycardia (1)	3 mg	5 hours	Resolved	On ceftriaxone for tracheitis
ZANA000829 (16)	Bradycardia (?) Hypothermia (?) Hypotension (? Bradycardia (?)	?	?	?	?

The major adverse event in literature pediatric tizanidine studies was somnolence. This is reported in the package insert for the currently marketed product. Some authors found the somnolence to be worse in younger patients, while others found it to be worse in older patients. There were isolated reports of transient increases in liver function tests that disappeared when the dosage was diminished.

From a review of the pediatric events from the countries in which tizanidine has been registered, the sponsor reports that unanticipated adverse events have, for the most part, been found to be related to the following: (1) accidental or purposeful overdoses; (2) concomitant medications; or (3) events of questionable relationship to tizanidine administration.

The sponsor proposes that the data submitted are sufficient to assess the possible use of tizanidine capsules in the pediatric population. I do not concur, since the study reports were not a sufficient quality to provide the necessary information in support of a pediatric use of tizanidine. The sponsor requests to defer assessment of the use of tizanidine capsules in pediatric populations until after the approval of the adult use and the submission of the additional pediatric data if the division does not concur that the NDA supported a pediatric use. I recommend granting deferral of the pediatric assessment.

Since the physiological basis of spasticity, targets for treatment, and the mechanism of action for tizanidine are apparently the same for adults and children, I do not request additional efficacy data.

1 Page(s) Withheld

D. Comments on Data Available or Needed in Other Populations

No new studies were conducted in special populations. The only known information about renal impairment is from NDA 20-397.

Pharmacokinetic differences due to hepatic impairment have not been studied.

Tizanidine clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatine clearance < 25mL/min) compared to healthy elderly subjects.

X. 120-Day update

In a safety update dated April 24, 2000, I did not identify any new important safety data. There was one nonclinical study ongoing during the reporting period Study No. 304-032-01: Pharmacokinetics of tizanidine hydrochloride following intra-intestinal administration to non-naive male beagle dogs. This was a single dose, intra-intestinal instillation via ports to the duodenum, jejunum, ileum, and colon. The purpose of this study was to characterize the absorption parameters following absorption of tizanidine hydrochloride to various sites in the gastrointestinal tract. The highest extent and rate of absorption was following intra-jejunal administration. There were no adverse events associated with this study.

There have been no initiated, ongoing, completed, or terminated clinical studies since the filing of NDA 21-447 on October 31, 2001 (amended January 30, 2002). Therefore, no additional safety information was obtained from clinical studies during this reporting period.

There was one published cases report relevant to safety. Chu et al (2001) evaluated an unintentional overdose with tizanidine which caused hypotension in a middle-aged woman. A 47-year-old woman mistakenly took four 4 mg tablets rather than the usual dosage of one 4 mg tablet. Approximately 3 hours after ingestion, she became hypotensive with a blood pressure of 74/48 mmHg. Her blood pressure normalized with a crystalloid infusion. The authors concluded that although tizanidine may be well-tolerated at therapeutic dosages, this case highlights potentially severe side effects from a small overdosage.

Since the data cut-off date of the fourteenth Zanaflex US Periodic Report (November 30, 2001), there have been no expedited pediatric cases. There have been two drug interaction cases and one overdose case from postmarket safety

surveillance:
1. ZANA000892(1)/4325(3): potential Zanaflex drug interaction with Lipitor (atorvastatin). 46-year-old female patient experienced rhabdomyolysis, loss of consciousness, respiratory failure, hepatic failure, and acute respiratory failure during the use of Zanaflex for the treatment of fibromyalgia. Zanaflex (dose unknown) was started in November 2001. On [redacted], approximately 10 days following initiation of Zanaflex therapy, the patient was found unresponsive in her bed and taken to the Emergency Room. Zanaflex was discontinued upon admission. The patient was diagnosed with rhabdomyolysis and increased liver function tests. The patient also experienced acute renal failure secondary to rhabdomyolysis, respiratory failure, and hepatic failure. She was treated with pressor support, IV sedation, and was intubated and placed on a respirator for 2 weeks. As of December 14, 2001, the patient's renal and hepatic function were returning. Physicians attempted to take the patient off the ventilator, however, as of December 14, 2001,they were unsuccessful. The reporter believed that the events were not related to Zanaflex, and possibly related to the patient's concomitant medication, Lipitor (atorvastatin). No further information was available at the time of this report. Additional information has been requested. [Reviewer's comment: since there was concomitant administration of atorvastatin, and since there is no other reported case of rhabdomyolysis with Zanaflex, I concur that the association between the adverse event and Zanaflex is very unlikely].
2. ZANA000896(0)14436(1): potential Zanaflex drug interaction with Ciproxin (ciprofloxacin). Patient only had two doses of Ciproxin. Probably Ciproxin enhanced effects of Tinazidine (sic)- patient had symptoms of Tinazidine (sic) overaction- bradycardia, hypotension, muscle weakness. [Reviewer's comment: this is the second case of reported enhanced side effects of tizanadine when taken concomitantly with ciprofloxacin. Given that ciprofloxacin is taken very frequently in the patient population receiving Zanaflex, it is very possible that the association of enhanced side effects and co-administration of ciprofloxacin is purely random.]
3. ZANA000908(0)/4580(1): overdose with Zanaflex. A female patient experienced withdrawal symptoms following an overdose of Zanaflex for the treatment of an unspecified indication. No further information was available at this time. Additional information has been requested.

XI. Conclusions and Recommendations

A. Conclusions

The data submitted with this application demonstrate that the bioequivalence of the capsule to the corresponding approved tablet dosage in the fasted state. The sponsor has not modified the indication, so that new efficacy data are not necessary if bioequivalence is established. There are no new safety signals significantly modifying tizanidine risk/benefit ratio.

There is a switchability issue when a patient takes the medication with food or changes formulations between the tablet and the capsule. The rate of absorption and Cmax is decreased when the capsule is administered with food relative to fasting conditions. This is opposite to what occurs with the tablet. Consequently, the capsule and tablet are bioinequivalent under fed conditions. Description in the labeling with warning regarding switchability should be adequate to manage the risk.

There is very limited information available in the published medical literature and in the postmarket safety surveillance on the safety of tizanidine in the pediatric population. There is no information on dosing regimen in children with an acceptable risk/benefit ratio. A development plan for the pediatric population is needed.

B. Recommendations

I recommend approval of NDA.

There is a switchability issue when a patient takes the medication with food or changes formulations between the tablet and the capsule. The capsule and tablet are bioinequivalent under fed conditions. Description in the labeling with warning regarding switchability should be adequate to manage the risk. I recommend to combine the tablet and capsule labeling, in order to better address the issue of switchability.

The tizanidine tablet and capsule Package Insert information must be updated regarding a possible drug interaction with rofecoxib (Vioxx).

The tizanidine overdosage post-marketing experience confirms that tizanidine may cause depressed cardiovascular, respiratory, and/or CNS function. The issue of rebound hypertension in case of abrupt withdrawal should be discussed in labeling. Several other labeling recommendations are discussed in "section B. Comments to OCPB labeling review".

XII. Labeling

The draft tizanidine hydrochloride (HCl) patient instructions contain three primary changes from the enclosed approved Zanaflex patient instructions. These changes are included under pharmacokinetics, drug interactions, and adverse events; primarily, as a result of the studies being submitted in this application.

A. Sponsor's proposed changes from approved package insert

Description

The sponsor describes the capsule composition. New active ingredients are titanium oxide, gelatin and colorants.

Clinical pharmacology

Mechanism of action: Unchanged

Pharmacokinetics: This section was updated to reflect the new formulation (capsule)

Special populations

Age effects: Unchanged

Hepatic impairment: Unchanged

Renal impairment: Unchanged

Gender effects: Unchanged

Race effects: Unchanged

Drug interactions – oral contraceptives: Unchanged

Clinical studies

Unchanged.

Indication and usages

Unchanged.

Contraindications

Unchanged

Warnings

Limited data for chronic single use of single doses above 8 mg and multiple doses above 24mg per day

"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 36mg/day for at least one year or more" has been replaced by [redacted]

Hypotension

Unchanged.

Risk of liver injury

Unchanged.

Sedation

Unchanged.

Precautions

Cardiovascular

Unchanged.

Ophthalmic

Unchanged.

Use in renally impaired patients

Unchanged.

Use in women taking oral contraceptives

Unchanged.

Information for patients

Unchanged.

Drug Interactions

Rofecoxib section was added.

Carcinogenesis, mutagenesis, impairment of fertility

Unchanged.

Pregnancy

Unchanged.

Labor and delivery

Unchanged.

Nursing mothers

Unchanged.

Geriatric use

Unchanged.

Pediatric use

Unchanged.

Adverse reactions

Common adverse events leading to discontinuation

Unchanged

Most frequent adverse clinical events seen in association with the use of tizanidine

Unchanged

Adverse events reported in controlled studies

Table number changes since table 1 was added in the PK section.

Table 1 becomes table 2 and table 2 becomes table 3.

Other adverse events observed during the evaluation of tizanidine

Patient number was updated to 1385 (from 1187).

Drug abuse and dependence

Unchanged.

Overdosage

This section was updated to include two additional cases of overdosage.

The section reads as:"

A search of a safety surveillance database revealed a total of 18 tizanidine overdosage cases. The majority of cases involved depressed cardiovascular function (bradycardia, hypotension), depressed respiratory function (respiratory depression or failure), and/or depressed consciousness (somnolence, stupor, or coma).

Dosage and administration

Unchanged

How supplied

Changed to:

2mg

Tizanidine hydrochloride is available as a 2 mg two-piece hard gelatin capsule consisting of a standard blue opaque body with a standard blue opaque cap. The capsules are printed with 2 mg in white.

They are supplied in:

Bottles of 150.

4 mg

Tizanidine hydrochloride is available as a 4 mg two-piece hard gelatin capsule consisting of a light blue opaque body with a light blue opaque cap. The capsules are printed with 4 mg in white.

They are supplied in:

Bottles of 150.

6 mg

Tizanidine hydrochloride is available as a 6 mg two-piece hard gelatin capsule consisting of a light blue opaque body with a standard blue opaque cap.

The capsules are printed with 6 mg in white.

They are supplied in:

Bottles of 150.

Store at 2500 (770F); excursions permitted to 15-30CC (59-860F) [see USP Controlled Room Temperature]. Dispense in containers with child-resistant closure.

B. Comments to OCPB labeling review

The OCPB reviewer noted that in addition to labeling for the capsules that the sponsor has proposed in this NDA (21-447), the sponsor has also submitted a labeling supplement to the tablet NDA, (20-397 SLR-014), that proposes changes to the tablet labeling regarding food effects. The labeling change for the tablet is based upon food effect study AN021-101 that is included in both the capsule NDA and the tablet labeling supplement. Consequently, the OCPB reviewer identified 2 options with regards to labeling: a) separate labeling for the tablet and capsule formulations b) combined labeling for both formulations. In order to assess the two approaches, OCPB reviewed concurrently the proposed tablet labeling and the proposed capsule labeling. I refer the reader to OCPB's review for full details. OCPB proposed a combined label for the tablets and capsules, which I copied here below. I highlighted the changes from current tizanidine tablet labeling. I added my comments to the text as [reviewer's comment:].

(tizanidine hydrochloride)

Tablets 2 and 4 mg

Capsules 2mg, 4mg and 6mg

DESCRIPTION

ZANAFLEX* (tizanidine hydrochloride) is a centrally acting α 2-adrenergic agonist. Tizanidine HCl (tizanidine) is a white to off-white, fine crystalline powder, 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 molecular formula is C9H8CIN5S-HCl, its molecular weight is 290.2 and its structural formula is:

Zanaflex is supplied as 2 and 4 mg tablets and 2 mg, 4 mg and 6 mg capsules for oral administration.

Zanaflex tablets are composed of the active ingredient, tizanidine hydrochloride (2.— mg equivalent to 2 mg tizanidine base and 4 —mg equivalent to 4 mg tizanidine base), and the inactive ingredients, silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

Zanaflex capsules are composed of the active ingredient, tizanidine hydrochloride (2.29 mg equivalent to 2 mg tizanidine base, 4.58 mg equivalent to 4 mg tizanidine base, and 6.87 mg equivalent to 6 mg tizanidine base), and the inactive ingredients, hydroxypropyl methyl cellulose, silicon dioxide, —— titanium dioxide, gelatin, and colorants. * Registered trademark of Elan Pharmaceuticals, Inc.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

A single dose of either two 4 mg tablets or two 4 mg capsules was administered under fed and fasting conditions in an open label, four period, randomized crossover study in 96 human volunteers, of which 81 were eligible for the statistical analysis.

Zanaflex® tablets and capsules are bioequivalent to each other under fasted conditions, but not under fed conditions.

Following oral administration of either the tablet or capsule (in the fasted state), tizanidine has peak plasma concentrations occurring 1.0 hours after dosing with a half-life of approximately —. hours.

When two 4 mg tablets are administered with food: the mean maximal plasma concentration is increased by approximately 30%, and the median time to peak plasma concentration is increased by 25 minutes, to 1 hour and 25 minutes.

In contrast, when two 4 mg capsules are administered with food: the mean maximal plasma concentration is decreased by 20%, the median time to peak plasma concentration is increased by 2 hours to 3 hours. Consequently, the mean Cmax for the capsule when administered with food is approximately 2/3's the Cmax for the tablet when administered with food.

Food also increases the extent of absorption for both the tablets and capsules. The increase with the tablet (~30%) is significantly greater than with the capsule (~10%). Consequently when each is administered with food, the amount absorbed from the capsule is about 80% of the amount absorbed from the tablet (See Figures 1 and 2).

Administration of the capsule contents sprinkled on applesauce is not bioequivalent to administration of an intact capsule under fasting conditions. Administration of the capsule contents on applesauce results in a 15% - <20% increase in Cmax and AUC of tizanidine compared to administration of an intact capsule while fasting, and a 15 minute decrease in the median lag time and time to peak concentration.

Figure 1 Mean Tizanidine Concentration vs. Time Profiles for Zanaflex® Tablets and Capsules (2 x 4 mg) under Fasted and Fed Conditions

[Reviewer's comment: this study had several limitations, as described in OCPB's review.

SPECIAL POPULATIONS

Drug Interactions—Oral Contraceptives

CLINICAL STUDIES

INDICATIONS AND USAGE

CONTRAINDICATIONS

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 more than 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).

[Reviewer's comment: I concur with OCPB. The sponsor proposed to replace "approximately 75 patients" by " After the tizanidine tablet NDA (20-397), the sponsor has conducted 2 long term studies (AN021-002 and AN021-004) exceeding 12 months of total duration. However, the sponsor did not submit exposure datasets supporting that some patients indeed were exposed to individual doses of 12 mg or more for that time period, so that the statement "approximately" should be maintained.]

HYPOTENSION

RISK OF LIVER INJURY

...In one case, a 49-year-old male developed jaundice and liver enlargement following 2 months of tizanidine treatment, primarily at 6 mg t.i.d...

[Reviewer's comment: replacement of " by "t.i.d." is acceptable].

SEDATION

HALLUCINOSIS/PSYCHOTIC-LIKE SYMPTOMS

PRECAUTIONS

CARDIOVASCULAR

OPHTHALMIC

USE IN RENALLY IMPAIRED PATIENTS

USE IN WOMEN TAKING ORAL CONTRACEPTIVES

DISCONTINUING THERAPY

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.

[Reviewer's comment: this addition is acceptable].

INFORMATION FOR 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).

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

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). 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.

Patients should be advised of the change in the absorption profile of Zanaflex® if taken with food and the potential changes in efficacy and adverse effect profiles (see PHARMACOKINETICS).

Patients should be advised not to stop tizanidine suddenly as rebound hypertension and tachycardia may occur (see

Tizanidine should be used with caution where spasticity is utilized to sustain posture and balance in locomotion or whenever spasticity is utilized to obtain increased function.

[Reviewer's comment: I concur with the proposed changes].

DRUG INTERACTIONS

Rofecoxib

Rofecoxib may potentiate the effects of tizanidine. Eight case reports of a potential rofecoxib-tizanidine drug interaction have been identified in postmarketing safety reports. In all cases adverse events resolved following discontinuation of tizanidine, rofecoxib, or both. Rechallenges with both drugs were not performed. The possible mechanism and the potential for a drug interaction between tizanidine and rofecoxib remain unclear.

[Reviewer's comment: I concur with proposed changes.]

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

PREGNANCY

LABOR AND DELIVERY

NURSING MOTHERS

GERIATRIC USE

Tizanidine should be used with caution in elderly patients because clearance is decreased [redacted]

PEDIATRIC USE

There are no adequate and well-controlled studies to document the safety and efficacy of tizanidine in children. [redacted]

[Reviewer's comment: the statement " [redacted] is probably too speculative, and I recommend not adding it.]

ADVERSE REACTIONS

Table 1: Multiple Dose, Placebo-Controlled Studies—Frequent (2%) Adverse Events Reported for Which Tizanidine Incidence is Greater than Placebo

	Placebo N=261	[redacted] N=264
Event	%	%
Dry Mouth	10	49
Somnolence	10	48
Asthenia*	16	41
Dizziness	4	16
UTI	7	10
Infection	5	6
Constipation	1	4
Liver function tests abnormal	<1	3
Vomiting	0	3
Speech disorder	0	3
Amblyopia (blurred vision)	<1	3
Urinary frequency	2	3
Flu symptom	2	3
SGPT/ALT increased	<1	3
Dyskinesia	0	3
Nervousness	<1	3
Pharyngitis	1	3

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 (> 2%) Adverse Events Reported for Which Zanaflex Tablets Incidence is Greater than Placebo

Event	Placebo N = 261 %	Zanaflex Tablet 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 function tests abnormal	<1	3
Vomiting	0	3
Speech disorder	0	3
Amblyopia (blurred vision)	<1	3
Urinary frequency	2	3
Flu symptom	2	3
SGPT/ALT increased	<1	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, 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.

	Placebo	[redacted]
Rhinitis	2	3
* (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 effects 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 Event

	Placebo N=48	[redacted] 8mg N=45	[redacted] 16mg N=49
Event	%	%	%
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)

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

If the COSTART term for an event was so general as to be uninformative, it was replaced by 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.

[Reviewer's comment: the update of patient exposure is acceptable].

DRUG ABUSE AND DEPENDENCE

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. Three cases of rebound symptoms on sudden withdrawal of tizanidine have been reported. The case reports suggest that these patients were also misusing narcotics. Withdrawal symptoms included hypertension, tachycardia, hypertonia, tremor, and anxiety. As with clonidine, withdrawal is expected to be more likely in cases where high doses are used, especially for prolonged periods.

[Reviewer's comment: I concur with the addition of the above paragraph.]

OVERDOSAGE

A search of a safety surveillance database revealed a total of 18 cases of tizanidine overdose. Of the fourteen intentional overdoses, five have resulted in fatality, and in at least 3 of these cases other CNS depressants were involved. One fatality was secondary to pneumonia and sepsis, which were sequelae of the ingestion. The majority of cases involve depressed consciousness (somnolence, stupor, or coma), depressed cardiovascular function (bradycardia, hypotension), and depressed respiratory function (respiratory depression or failure). 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, [redacted]. symptoms resolve within one to three days. Due to the similar mechanism of action, symptoms and management of tizanidine overdose is similar to [redacted] For the most recent information concerning the management of overdose, contact a poison control center.

[Reviewer's comment: I agree with OCPB proposed changes.]

DOSAGE AND ADMINISTRATION

[redacted]

[Reviewer's comment:

HOW SUPPLIED

2 MG Tablets

Zanaflex® (tizanidine hydrochloride) is available as 2 mg white tablets, with a bisecting score on one side and debossed with "A592" on the other. bottles of 150 (NDC 59075- 592-15).

4 MG Tablets

Zanaflex® (tizanidine hydrochloride) is available as 4 mg white tablets, with a quadrisecting score on one side and debossed with "A594" on the other. in bottles of 150 (NDC 59075-594-15).

2 MG Capsules

ZANAFLEX® (tizanidine hydrochloride) is available as a 2 mg two-piece hard gelatin capsule consisting of a standard blue opaque body with a standard blue opaque cap. The capsules are printed with 2 mg in white.

They are supplied in:

Bottles of 150.

4 MG Capsules

Zanaflex® (tizanidine hydrochloride) is available as a 4 mg two-piece hard gelatin capsule consisting of a light blue opaque body with a light blue opaque cap. The capsules are printed with 4 mg in white.

They are supplied in: Bottles of 150.

6 MG Capsules

Zanaflex® (tizanidine hydrochloride) is available as a 6 mg two-piece hard gelatin capsule consisting of a light blue opaque body with a standard blue opaque cap. The capsules are printed with 6 mg in white.

They are supplied in: Bottles of 150.

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Dispense in containers with child resistant closure. Rx Only

Distributed by: Elan Pharmaceuticals, Inc. San Diego, California

XIII. Appendices

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Bastings
8/7/02 04:51:42 PM
MEDICAL OFFICER

Armando Oliva
8/12/02 08:20:38 AM
MEDICAL OFFICER