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*APPLICATION NUMBER:*

**21-483**

**MEDICAL REVIEW**

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 21483  
SPONSOR: Pfizer  
DRUG: Ziprasidone  
MATERIAL SUBMITTED: Application for Oral Suspension Formulation  
DATE SUBMITTED: September 2, 2002  
REVIEWER: Roberta L. Glass, M.D.  
REVIEW COMPLETION DATE: June 24, 2003

Background

Ziprasidone is an "atypical" antipsychotic with serotonin (5-HT<sub>2A</sub>) and dopamine (D<sub>2</sub>) antagonist properties. It was first marketed in the oral dosage form on February, 5, 2001 with a bolded warning describing ziprasidone's ability to prolong the QTc and the associated risks of sudden death. Ziprasidone is currently also marketed as an intramuscular formulation. The current submission proposes labeling to include an oral suspension formulation and includes four open label Phase 1 bioequivalence trials to support this claim.

This review will discuss only the safety information included in this submission in support of the oral suspension formulation. There were 54 healthy adult subjects exposed to the suspension formulation in the four open-label Phase 1 bioequivalence trials. In one study (A1281037), subjects received multiple doses (ziprasidone 20 mg bid x 11 days plus one dose on Day 12), and the other three studies (128-056, 128-055, and 128-034) were single dose (ziprasidone 20 or 40 mg); all studies were conducted in the fed state. On occasion, reference will be made to events occurring during an oral suspension study which has previously been reported (NDA 20825).

~~\_\_\_\_\_~~ the sponsor included a study report for Study 128-044, a nonrandomized Phase 1 single dose study using an oral suspension of ziprasidone in 24 children/adolescent patients diagnosed with Tourette's syndrome and/or chronic motor or vocal tic disorder. A cursory review did not show any unexpected events. Of note, at least one patient had a QTc change > 30 msec (using Bazett's formula). Also, prolactin elevation was observed in all patients, which seemed to resolve 24 after this single dose administration. ~~\_\_\_\_\_~~

Demographics

Of the 54 healthy adult subjects in this data base, 30 were male and 24 female. The mean age was 27.4 years for males (range: 19-44) and 24.7 years for females (range 18-42). The majority of patients were Caucasian.

## Withdrawals

There were three subjects who had early withdrawals; two subjects were exposed to the oral suspension and one subject was giving the capsule formulation of ziprasidone. These early withdrawals are summarized below:

1. An 18 year old healthy Afro-American female (Subject # 056-50010011) experienced nausea, headache, back pain, stomach ache and vomiting after receiving a single dose of 20 mg of ziprasidone suspension;
2. A 33 year old Asian female (Subject 034-05010014) discontinued due to an inability to take blood samples.
3. After taking a 20 mg capsule of ziprasidone bid, a 19 year old healthy Hispanic female (Subject A1281037 3) discontinued on Day 2 after experiencing tongue numbness, severe throat tightness, and shortness of breath 9-10 hours after receiving a morning dose of 20 mg ziprasidone capsule. The event resolved after administration of diphenhydramine and methylprednisolone, suggesting perhaps an anaphylactic reaction.

Of note, in a previously submitted data base (NDA 20825), a 36 year old Afro-American male (002-05010012) discontinued on Day 9 of 20 mg bid ziprasidone powder in suspension due to hypertension; his blood pressure elevated up to 165/109 mm Hg after the morning dose on days 8 and 9, and resolved within 1 hour.

## Adverse Events

The database in this submission is quite small, and it is difficult to make any conclusions regarding adverse events. The sponsor presented the adverse events by comparing subjects exposed to the oral suspension of ziprasidone to subjects exposed to ziprasidone capsules in the selected bioequivalence studies. The following table selects out the treatment emergent events which were more prevalent in subjects exposed to the oral suspension:

Select treatment emergent adverse events in ziprasidone bioequivalence studies (based on the sponsor's Table 3.1)

	SUSPENSION N=53	CAPSULE N=52
Syncope	4 (7.5)	1 (1.9)
Nausea	8 (15.1)	3 (5.8)
Vomiting	6 (11.3)	0
Dizziness	7 (13.2)	4 (7.7)
Asthenia	6 (11.3%)	4 (7.7)
Headache	5 (9.4)	4 (7.7)
Back pain	2 (3.8)	1 (1.9)
Diarrhea	2 (3.8)	1 (1.9)
Dyspepsia	2 (3.8)	1 (1.9)
Hot flashes	1 (1.9)	0
Hemorrhage	1 (1.9)□	0

As can be seen from the table above, syncope, nausea, vomiting and dizziness were more commonly observed in subjects exposed to oral suspension compared to subjects taking the capsule formulation. Somnolence was the most common adverse event observed in both groups (suspension: 24.5%; capsule: 26.9%). No details regarding the case of hemorrhage were located in this submission; it is noted that rectal, gum, uterine, and vagina hemorrhage have been previously described in labeling.

Although it is not uncommon for healthy subjects to experience syncope when exposed to an antipsychotic medication, it is noted that 3 of 4 subjects (034 05010002, 034 05010014, 056 50010010) had a syncopal event at or near Tmax ((5 hours). The fourth subject experienced syncope about 8 hours after dose administration.

#### ECGs

Study A1281037 was the only bioequivalence study which obtained post-baseline ECGs. Study A1281037 included post-dose ECGs conducted at 6 hours post dosing of Day 7 (tmax is at approximately 5 hours). However, because of the cross-over design, some subjects in Study A1281037 may have been taking the capsule form of ziprasidone on Day 7; therefore, not all subjects obtained a repeat ECG while taking the oral suspension.

Patients with heart rates > 90-100 bpm on screening ECG and QTc at baseline  $\geq$  450 msec were excluded from the study. ECGs were collected prior to dosing on Day 1 and 6 hours after the morning dose on Day 7. It is noted that since the tmax is approximately 5 hours; therefore, ECGs were not collected at the optimal time. No subjects were reported to have a QTc interval >450 msec, and no subject had a mean change in QTc >30 sec. Individual subject data was not located in this submission; therefore, outliers were not able to be identified. The following sponsor table summarized the mean change from baseline:

#### Labeling

The proposed labeling does not include any clinical changes. There did not appear to be any unexpected adverse events observed in this study. The adverse events reported in this submission have been previously described in the labeling for ziprasidone capsules and IM formulation. The only questionable event is the case involving hemorrhage, as it was not described further in this submission. It is noted that rectal, gum, uterine, and vagina hemorrhage have been previously described in labeling.

#### Conclusion

There are no clinical changes proposed for this labeling. Please see the section for labeling above for any proposed changes. Reviews from Office of New Drug Chemistry (ONDC) and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) to determine adequacy of the data to support labeling changes are pending.

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/s/

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6/25/03 03:04:08 PM  
MEDICAL OFFICER

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7/7/03 12:06:52 PM  
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There are no clinical changes in labeling. I agree  
with Dr Glass that there were no events  
in the submitted studies that required additional safety  
information in labeling.