CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Administrative Documents

Groton Laboratories
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

DESK COPY

Pfizer

Global Research & Development

November 28, 2000

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research HFD #120
Woodmont II Building
ATTN: DOCUMENT CONTROL ROOM
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

RE: NDA-20-825 - _____ (ziprasidone) Capsules

UPDATED PATENT AND EXCLUSIVITY INFORMATION

Reference is made to the Patent and Exclusivity information and Patent Certification provided with our original NDA-20-825 and subsequent March 26, 1998 update of Patent and Exclusivity information. This submission further updates Sections 13 and 14 of NDA 20-825 to include applicable patent information covering the commercial oral dosage forms of : pursuant to Patent No. 6,150,366. This Patent was granted on November 21, 2000 and expires on May 27, 2019. Updates to NDA Sections 13 and 14 are found in Enclosures #1 and #2 respectively.

Please include this information in our file for NDA-20-825.

Sincerely yours,

Charles A. Ritrovato, Pharm.D.
Director
Regulatory Affairs Department

CAR/rms
desk copy: Mr. S. Hardeman (cover letter only)
NDA-20-825 Submission No. 116

Section 13. PATENT AND EXCLUSIVITY INFORMATION FOR [redacted] (ZIPRASIDONE)

1.	Active Ingredient:	5 - [2 - [4 - (1,2- benzisothiazol-3-yl) -1- piperazinyl] ethyl] - 6 - chloro-1,3-dihydro-2H-indol-2-one
2.	Strengths:	20, 40, 60, 80 and [redacted] mg
3.	Trade Name:	[redacted]
4.	Dosage Form / Route of Administration:	Capsules / Oral
5.	Application Firm Name:	Pfizer Inc.
6.	NDA Number:	20-825
7.	Exclusivity Period:	
8.	Applicable Patent Numbers and Expiration Dates:	4,831,031 March 2, 2007

Section 14. PATENT CERTIFICATION

Pfizer certifies that the drug, , (ziprasidone), which is the subject of this Application (NDA#20-825) and the formulation of such drug claimed by the listed patent (Patent No. 4,831,031) provided in Section 13 of this NDA is the subject of the approval being sought under Section 505 of the Federal Food, Drug, and Cosmetic Act.

EXCLUSIVITY SUMMARY for NDA # 20-825 **SUPPL #** _____

Trade Name N/A **Generic Name** Ziprasidone HCl

Applicant Name Pfizer **HFD-** 120

Approval Date 1-5-01

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES /✓/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /✓/

   If yes, what type (SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are

there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

Signature of Preparer — Date: 1-5-01

Title: Senior Regulatory Project Manager

/S/

Signature of Office of Division Director — Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

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NDA Number: 020825 **Trade Name:** ((ZIPRASIDONE HCL)20/40/60/80MG CA

Supplement Number: 000 **Generic Name:** ZIPRASIDONE HCL

Supplement Type: N **Dosage Form:**

Regulatory Action: NA **COMIS Indication:** TREATMENT OF PSYCHOSIS

Action Date: 6/17/98

Indication # 1 treatment of schizophrenia

Label Adequacy: Does Not Apply

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any):

	Lower Range	Upper Range	Status	Date
Adult	Adult	Deferred	1/1/01	

Comments: there are some unresolved safety concerns about this drug that render it second line status in adults and should discourage its developemnt in children until further information on its safety becomes available.

This page was last edited on 12/22/00

/S/ 12/22/00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20825	**Trade Name:**	(ZIPRASIDONE HCL) 20/40/60/80MG CA
Supplement Number:		**Generic Name:**	ZIPRASIDONE HCL
Supplement Type:		**Dosage Form:**	CAP
Regulatory Action:	AE	**Proposed Indication:**	treatment of schizophrenia

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

while drugs in this class have some potential for use in children, there are some unresolved safety concerns about htis drug that render it second line status in adults and should discourage its development in children until further information on its safety becomes available

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, STEVE HARDEMANS

/S/ _____ 8/11/00

Signature Date

DRUG STUDIES IN PEDIATRIC PATIENTS

(To be completed for all NME's recommended for approval)

NDA: **20-825**
Product: **(ziprasidone) 20,40,60,80mg Capsules**
Sponsor: **Pfizer**
Project Manager: **Steven D. Hardeman, R.Ph.**
Division: **HFD-120**

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.

____ (2) Protocols have been submitted and approved.

____ (3) Protocols have been submitted and are under review.

____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

✓ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

While drugs in this class have some potential for use in children, there are some unresolved safety concerns about this drug that under it second line status in adults & should discourage it development in children until further information on its safety becomes available.

/S/ 5-12-98

Signature of Preparer Date

cc:
Orig NDA
HFD-120 Division File
NDA Action Package

MEMORANDUM OF MEETING MINUTES

Meeting Date: 1/29/98
Time: 10:00 AM
Location: Conference Room "E"
Application: (ziprasidone) / Pfizer NDA 20-825
Type of Meeting: With Sponsor
Meeting Chair: Paul Leber, M.D.
Meeting Recorder: Steve Hardeman, R.Ph.

FDA Attendees:

HFD-120/Division of Neuropharmacological Drug Products:
Paul Leber, M.D., Thomas Laughren, M.D., Gerry Boehm, M.D., Greg Burkhart, M.D., Andy Mosholder, M.D., Roberta Glass, M.D., Greg Dubitsky, M.D., Lois Freed, Ph.D.

HFD-110/Division of Cardio-Renal Drug Products:
Charles Ganley, M.D., John Koerner, Ph.D.

External Constituent Attendees and titles:

Pfizer:
Charles Ritrovato, Pharm.D., Pfizer Regulatory Affairs
(list attached)

Background:

(ziprasidone), submitted for the treatment of psychotic disorders, is currently under review (PFUFA extended to 6/17/98).

Meeting Objectives:

Discussion of ziprasidone safety findings with sponsor.

Discussion Points (bullet format):

1. Ziprasidone, although effective in the treatment of psychotic disorders, exhibits a signal of risk with the association of a dose related QTc interval prolongation.
2. The rate of sudden unexpected death, associated with the use of ziprasidone as compared to other recently reviewed antipsychotics, compounds safety concerns.
3. Possibility exists that signals of risk of these kind may bar approval of ziprasidone unless a benefit over current therapies can be demonstrated.

Decisions (agreements) reached:

None.

Unresolved issues or issues requiring further discussion:

Division/Office to discuss possibility of conducting advisory committee meeting to discuss ziprasidone safety concerns.

Action Items:

Project Manager will:
1. notify sponsor of status of advisory committee meeting
2. provide sponsor with copies of Dr. Boehm's slides
3. provide sponsor with copy of Dr. Ganley's review of report.

Minutes Preparer: /S/ J.R.PL. 1-30-98

Chair Concurrence: /S/ TLS/PDP MD
(designated signatory)

Attachments/Handouts:

cc: Original
Div. Files
HFD-120/Leber/Laughren/Glass/Mosholder
/Dubitsky/Burkhart/Boehm/Freed/Hardeman
HFD-110/Ganley/Koerner

final: 1/29/98

MEETING MINUTES

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 30, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Comments on Proposed Changes to Labeling Recommendation

TO: Robert Temple, M.D., Director, ODE-I, HFD-101
Russell Katz, M.D., Director, DNDP, HFD-120
&
File NDA 20-825
[**Note:** This memo should be filed with the 10-20-00 response to the 9-8-00 approvable letter.]

Based on Dr. Temple's markup of the AP5LABL.DOC, and also comments from DDMAC (see consult), we have modified the labeling (AP6LABL.DOC). We have obtained agreement with Pfizer on this revised document as of 1-30-01.

We have made most of the modifications suggested by Dr. Temple, and some, but not all, of those suggested by DDMAC. I have the following comments on labeling (page numbers refer to page numbers on the new labeling document, and not on Dr. Temple's markup of the AP5LABL.DOC):

Dr. Temple's Proposed Changes:

p.2 (under Absorption): We are recommending dosing with food so that absorption is predictable for individual patients.

p.4 (under Hepatic Insufficiency): Ordinarily we have not recommended dosage adjustments for effects of this size. The different half life for normals is likely a result of the small sample.

p.4 (Drug-Drug Interactions): We've put back in this summary that was removed from an earlier verson of labeling.

p.10 (under Rash): We've added language suggesting time as another possible explanation.

p.14 (under Carcinogenesis): We've not recalculated these multiples, since we do not interpret the D&A section as specifying 160 mg/day as the maximum dose. That is the generally recommended maxiumum dose, however, this section goes on to say that safety has been looked at up to 100 mg bid, so that leaves open the possibility of an individual patient getting up to that dose.

p.14 (under Mutagenesis): We've deleted the interpretive language, and just left the findings.

p.14 (under Impairment of Fertility & Pregnancy): We've not recalculated these multiples, for the reason given under Carcinogenesis.

p.18 (re: demographic interactions): We agree there is not enough information to say anything about age and race, so we've deleted this language.

p.18 (Dose Dependency): We've provided the table this analysis was based on. It did not include placebo.

(table does show. Was plbo omitted from stats? That is totally wrong. Why say I took stat's out

DDMAC Consult:

p.1 (Pharmacodynamics): The language regarding mechanism is the same as for other antipsychotics, and we have not deleted it.

p.3 (Smoking): I have discussed the smoking statement under Population Subgroups with OCPB, and they have indicated that similar findings for other drugs are ordinarily the basis for this statement regarding the absence of a PK interaction. However, we will ask for a consult on the question of a pharmacodynamic interaction with nicotine, regarding QT prolongation, but this will need to be addressed in the future.

p.5 (Indications): Several changes were proposed to this section. It is longer than usual, however, this is a situation that requires some explanation, so we think the length is justified. We have not changed this section.

p.6 (Contraindications/QT Prolongation): We have not made the proposed changes.

p.6 (Warnings): We disagree with the proposed changes and we have not made them. Again, the section is long in order to address a complex set of findings. We do not agree that this section undercuts Contraindications.

p.12 (Information for Patients): We disagree with the suggestion to duplicate here information already contained in Contraindications and Warnings. The information we want physicians to discuss with patients

is entirely included in the PPI, so we do intend for thissection to be a pointer to the PPI. We have used this same approach in multiple other labels.

p.22 (D&A): We disagree that trends cannot be mentioned as a relevant finding. Although the findings are not entirely consistent, there is enough of a suggestion of D/R to justify increasing the dose in a patient not responding at a lower dose. This is important clinical information.

pp.23-26 (PPI): We have adopted some of the proposed changes to this section, but not all.

cc:
Orig NDA 20-825
HFD-120 1-30-01
HFD-120/TLaughren/RKatz/RGlass/SHardeman
HFD-100/RTemple

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 29, 2000

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
(ziprasidone) for the treatment of schizophrenia

TO: File NDA 20-825
[**Note:** This memo should be filed with the 10-20-00 response to the 9-8-00 approvable letter.]

1.0 BACKGROUND

In our 9-8-00 approvable letter, we requested a regulatory status update, a world literature update, expedited reporting for certain serious adverse events, and a phase 4 commitment to conduct several additional studies. We did not ask for an additional safety update since the 3-10-00 submission contained a sufficiently complete and recent safety update. We reminded Pfizer that the name issue had still not been resolved. We identified our preferred dissolution methodology and specifications. We identified several deficiencies in the genotoxicity testing for ziprasidone. Finally, we also attached our proposal for labeling.

Pfizer responded to our approvable letter with a 10-20-00 submission, including an alternative labeling proposal and responses to the other questions and requests in our letter. Additional materials in response to questions were submitted 12-1-00.

The review team, up to the level of the Team Leader, developed an alternative labeling document that was faxed to Pfizer on 12-4-00. We then met face-to-face with Pfizer on 12-6-00. At that meeting, we reached agreement on some sections of labeling. However, it was left to Pfizer to propose alternative language for other sections of labeling. Importantly, we learned on that day of a possible report of TDP in a Swedish patient who had been receiving ziprasidone. Pfizer promised to provide additional details on the possible case as soon as possible. In the meantime, finalization of labeling was suspended.

In a 12-12-00 submission, Pfizer provided additional information regarding the case of suspected TDP, along with another labeling proposal to address sections where agreement had not yet been reached.

Case of Suspected TDP: In the 12-12-00 submission, Pfizer characterized this as a case of suspected polymorphic ventricular tachycardia (PVT) rather than TDP. This was a 71 y/o female with a history of schizophrenia, possibly dementia, coronary artery disease, asthma, stroke, seizures, and parkinsonism. She had recently been switched from risperidone to ziprasidone (40 mg bid) on 10-19-00. On 12-4-00, she was admitted to a hospital for agitation, nausea, vomiting, and "absence attacks." She apparently experienced several "convulsions" following admission. Then in the afternoon, she experienced ECG changes that were described as VT and TDP, and lasting about 1 hour. During this 1 hour period, she was apparently staring at the ceiling but not responding to questions. The episodes stopped after an hour and did not return. Ziprasidone was stopped, and by 12-7-00 the patient was described as "feeling like she usually does." QTc's were 425 on admission and 414 on 12-5-00.

Pfizer had the case evaluated by two consultant cardiologists (
who both agreed that the ECGs were clear examples of ECG artefact. The strongest evidence for this interpretation was the presence of uninterrupted QRS complexes throughout the apparently widened QRS complexes and the absence of other characteristic features of either PVT or TDP. Shari Targum, M.D., a cardioligist from HFD-110, agreed with this interpretation of artefact, as did her colleagues from the
where she presented the case at rounds. In addition, we sought the advice of Drs. Grebois and Armstrong, two cardiologists from the Cardiorenal AC, who also concurred in this interpretation. Thus, it appears that this does not represent a case of any concern and is not material to our decision regarding the cardiovascular risks associated with this drug.

2.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period from Jan, 1996 through Sept, 2000, and focused on any reports pertinent to the safety of ziprasidone. The results of their search were reviewed by Steven Romano, M.D., the Senior Medical Director at Pfizer. He warranted that there were no new findings that would change current views of the safety profile for ziprasidone, in particular, there were no reports of TDP or QTc assessments that result in a different view than currently held regarding ziprasidone's cardiovascular risks.

3.0 REGULATORY STATUS UPDATE

Pfizer noted in the 10-20-00 submission that ziprasidone is approved in 5 countries (Sweden, the Czech Republic, New Zealand, Brazil, and Venezuela), however, it is marketed only in Sweden, and only since Sept, 2000. It is currently under review in

4.0 EXPEDITED REPORTING FOR CERTAIN SERIOUS ADVERSE EVENTS

In our 9-8-00 approvable letter, we asked Pfizer to report as 15 day reports certain serious events listed in the Other Events table to ensure that any postmarketing signals for these events would not be missed. As an alternative, they have suggested monthly listings for these events, and I consider this an acceptable alternative to 15 day reports.

5.0 PHASE 4 STUDIES

5.1 Dose Response for QTc Effect

Pfizer indicated a willingness to conduct a study to more fully explore the higher end of the dose range for QTc effects, so we should ask, in the approval letter, that they submit a protocol for such a study.

5.2 Additional Drug Interaction Studies

We had asked Pfizer to consider additional drug interaction studies to explore dynamic interactions between ziprasidone and other drugs that prolong the QTc. I think they have made a reasonable argument against such studies, in particular, they plan to contraindicate such combined use regardless of the outcome of such studies.

5.3 A Study of SUD with Ziprasidone and other Atypical Antipsychotics

We had asked Pfizer to consider a large, head-to-head comparison of ziprasidone with other atypicals to explore relative risks for SUD. In their 10-20-00 response, they have indicated that they have just reached agreement with the regulatory agency on a final design for a trial comparing ziprasidone with olanzapine on a number of serious outcomes: all non-suicide mortality; cardiovascular mortality; suicide; all cause hospitalization; hospitalization for arrhythmia, MI, and syncope. There will be 9000 patients per group. The study will be randomized, but open label. I would have preferred SUD as a key outcome, nevertheless, I think this is a good effort.

5.4 Studies to Demonstrate Possible Advantages for Ziprasidone

They have offered to discuss trial designs for studies to look at advantages in treatment resistant patients. There remain problems in defining what is meant by treatment resistant and in designing such studies, nevertheless, we can discuss this issue further with Pfizer.

6.0 NAME ISSUE

We reminded Pfizer in our 9-8-00 approvable letter that the name . is not acceptable to the agency, and that we had consulted their alternative name, "Geodon," to OPDRA. In their 10-20-00 response, Pfizer still argues that the name can be used safely, and they proposed an educational program they are prepared to implement in order to reduce risks of medication errors. Following our 12-6-00 meeting with Pfizer, we provided them with a copy of the most recent OPDRA consult. They have not yet responded to this, but in the meantime, we are in agreement with Pfizer to simply refer to the new product in labeling as "Ziprasidone."

7.0 DISSOLUTION SPECIFICATION

We have reached agreement with the sponsor on a dissolution method and specifications, and these details are included in the approval letter.

8.0 DEFICIENCIES IN THE GENOTOXICITY TESTING

We reached agreement with Pfizer on what additional studies would be needed to effect further changes in the Mutagenesis section of labeling.

9.0 REQUIREMENT FOR PEDIATRIC STUDIES

We have included in the approval letter a deferment of the requirement for pediatric studies in schizophrenia until we can determine whether or not there would be health benefits from such studies and, if so, what study designs would be appropriate for such studies.

10.0 LABELING/PPI

Following the 12-6-00 meeting with Pfizer, they proposed alternative language for labeling in a 12-12-00 document. Through subsequent negotiations, we reached final agreement on labeling with Pfizer on 12-29-00 (E-Mail from Charlie Ritrovato of Pfizer on this day). The final labeling document is as follows:

The major issues for labeling involved how best to characterize the risks associated with QTc prolongation and how to advise prescribers on how best to select patients and monitor for this potential problem. In the final agreed upon labeling forwarded with the package, ziprasidone is not characterized explicitly as a second line drug, however, it is pointed out that, given its status as an outlier regarding QTc prolongation,

it would not be unusual for other antipsychotics to be tried first. The Warnings statement regarding QTc prolongation provides comparative QTc prolongation data for ziprasidone and the five other antipsychotics examined in study 54. While I agree with the sponsor regarding the lack of justification for routine screening of electrolytes and ECGs, the language proposed recommends electrolyte monitoring for patients at risk for significant electrolyte disturbances. It also lists the various cardiac conditions in which ziprasidone should be avoided due to their possible association with QTc prolongation.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Pfizer has submitted sufficient data to support the conclusion that ziprasidone is effective and acceptably safe in the treatment of schizophrenia. I recommend that we issue the attached approval letter with the version of labeling for which we were able to reach mutual agreement with the sponsor.

cc:
Orig NDA 20-825
HFD-120 12/29/00
HFD-120/TLaughren/RKatz/RGlass/SHardeman
HFD-100/RTemple

MEMORANDUM

DATE: January 3, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-825

&

Director
Office of Drug Evaluation I

SUBJECT: Recommendation for Action on NDA 20-825, for the use of Ziprasidone in patients with schizophrenia

NDA 20-825, submitted by Pfizer Central Research for the use of ziprasidone in patients with schizophrenia, was the subject of an Approvable letter on 9/8/00. That letter included a number of relatively routine requests (world literature update, dissolution specifications, etc.) as well as several requests related to ziprasidone's known capacity to prolong the QTc interval. Those requests included requests for the sponsor to perform several Phase 4 studies (to evaluate further the dose response for QTc prolongation, interaction studies with other drugs known to prolong the QTc interval, a comparative study with other anti-psychotic drugs to evaluate the risk of sudden unexplained death, and studies to further examine any possible advantages of ziprasidone in comparison to other anti-psychotic drugs). In addition, the letter was accompanied by labeling which contained language in several sections related to the QTc prolongation.

The sponsor responded to the letter in a submission dated 10/20/00. However, in early December, 2000, we were informed by the sponsor of a case of potential torsades in a patient who had received ziprasidone in Sweden, where the drug had recently been approved. Because of this information, and subsequent submissions by the sponsor to further clarify this possible case, the response to the Approvable letter, which had initially been classified as a Type 1 response, with an associated 2 month review clock, was re-classified as a Type 2 response, re-setting the PDUFA due date to 4/23/01.

While further information about this case was being gathered by the sponsor, labeling negotiations were proceeding. Ultimately, and given our subsequent view that the reported event in Sweden was not a case of torsades (see below), the Division and the sponsor agreed to the labeling accompanying the package. There were a number of sections in the draft labeling accompanying our Approvable letter with which the sponsor argued, including the following:

1) Requirement for Pre-Treatment EKG in the Warnings Section-the sponsor has convinced us that a single routine EKG is unlikely to be a useful screening measure for detecting patients who might be at risk for a prolonged QTc interval and/or serious arrhythmias when treated with ziprasidone. The labeling accompanying this package instead warns that patients with a history of cardiovascular disease, including, among other things, QT prolongation, should not receive ziprasidone, and that patients being treated with ziprasidone who develop persistent QTc intervals >500 msec should be discontinued. In addition, it states that patients at risk for hypokalemia (especially patients receiving diuretics) should have electrolytes measured before treatment, and that these electrolytes should be corrected if abnormal prior to initiation of treatment with ziprasidone.
2) Second Line Status-We originally proposed that ziprasidone be used only in those patients who failed or could not tolerate other anti-schizophrenia drugs. After discussions with the sponsor, we are now prepared to state in labeling that the prescriber should consider ziprasidone's capacity to prolong the QTc interval before prescribing the drug, and that ordinarily, this would result in other drugs being tried first.
3) Dose Regimen-We had proposed that a dose of 20 mg BID be recommended as an effective dose; the sponsor wished to propose 40 mg BID as the lowest effective dose. After discussions, the sponsor has agreed to recommend 20 mg BID as the starting (and an effective) dose. In addition, we have included in the Dosage and Administration section language stating that ordinarily, patients should be observed for several weeks at a given dose before consideration is given to increasing the dose (to a maximum of 80 mg BID), to insure that the lowest effective dose is administered.
4) Warning Section-The sponsor objected to our description of the study that evaluated QTc prolongation among various anti-psychotic drugs, as well as several other statements in this section. The labeling to which we have agreed contains a description of this study very similar to that which we originally suggested. In addition, several other more minor changes have been made.
5) Mutagenesis and Pregnancy-The sponsor had objected to our original language; the language to which we have agreed is, again, similar to that which we had proposed.

Dr. Laughren, in his memo of 12/29/00, describes the sponsor's responses to other of our requests made in the Approvable letter (request for expedited reporting of certain ADRs and Phase 4 study commitments), and our final disposition of these issues. In addition, the Agency has objections to the use of ... as the tradename for this product. The sponsor responded to our initial objections, but the Nomenclature Committee continued to have objections to the use of this name. The sponsor has apparently performed a study which suggests to them that there will be little confusion with other drugs, but has not yet submitted the results of this study, or other arguments to rebut the

Committee's most recent stated objections. For this reason, the labeling in this package refers to the product only as Ziprasidone HCl.

As noted above, we recently became aware of a potential case of torsades in a patient in Sweden. As Dr. Laughren notes, the sponsor's 2 experts have concluded that this was an artifact, and our 2 independent experts (Dr. Thomas Grayboys, Director of the Lown Cardiovascular Center in Boston, and Dr. Paul Armstrong, Professor in the Department of Medicine at the University of Alberta in Canada, and both members of the CardioRenal Drug Products Advisory Committee) have both, independently, reviewed the available data and have concluded unequivocally that this is an artifact (see my memo of 12/22/00). Therefore, I agree with Dr. Laughren that it is reasonable for us to conclude that this is not a case of torsades or other life-threatening arrhythmia.

In addition, the sponsor has agreed to adopt dissolution specifications proposed by the Office of Clinical Pharmacology and Biopharmaceutics.

For these reasons, we are recommending that the attached Approval letter, with accompanying labeling, be issued.

/S/

Russell Katz, M.D.

Cc:
NDA 20-825
HFD-120
HFD-120/Katz/Laughren/Glass/Freed/Rosloff/Seevers/Hardeman
HFD-860/Al-Habet/Baweja

MEMORANDUM

DATE: August 30, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-825

SUBJECT: Division's Recommendation for Action on NDA 20-825, for the use of . (ziprasidone) in patients with schizophrenia

NDA 20-825, for the use of . (ziprasidone) in patients with schizophrenia, was submitted by Pfizer Central Research on 3/18/97. A Not Approvable letter was sent on 6/17/98, citing as the primary reason for this action ziprasidone's capacity to increase the QTc interval in a dose related fashion. This finding emerged out of an analysis of EKGs obtained during clinical trials, EKGs performed not necessarily at peak plasma concentrations of drug (indeed, there was some evidence that they had been performed at close to trough levels; see Dr. Laughren's memo of 5/14/98, page 12).

In the Not Approvable letter, the Agency noted:

As a general matter, we would find QTc prolongation at maximum blood levels in the 5-10 msec range, with adequate assurances that there are very few outliers and that there are no factors that lead to substantially greater values in individuals (such as drug-drug interactions) sufficiently reassuring, in the absence of contrary evidence, to support approval of a new antipsychotic such as ziprasidone.

In response to the Not Approvable letter, the sponsor performed Study 54, which was specifically designed to address most of the concerns expressed in the above paragraph (it was not expected to be able to detect if there were "very few outliers", given its small size). This study compared the QTc prolonging effects of ziprasidone, at maximal plasma levels, with and without maximum metabolic inhibition, with several other atypical antipsychotic medications and thioridazine and haloperidol, all given under similar appropriate conditions. The full report of this study was first submitted on 1/3/00, and then again with the sponsor's resubmission (dated 3/10/00), along with updated safety information including mortality and sudden death data.

This resubmission has been reviewed by Dr. Roberta Glass, medical officer (review dated 7/28/00), Dr. Maryann Gordon, cardiology consultant from HFD-110 (review dated 6/14/00), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 8/9/00). Dr. Greg Burkhart, formerly Team Leader of the Division's safety group, reviewed Study 54 in a memo dated 1/11/00. The re-

submission was also reviewed by Dr. Lois Freed, pharmacologist (review dated 8/21/00). In this memo, I will offer the Division's recommendation for action on this NDA.

BACKGROUND

As noted by Drs. Glass and Laughren, the total exposure to ziprasidone, as of the cut-off date of 2/5/00, was about 5300 people, with 4571 in Phase 2/3 trials, resulting in about 1700 patient-years of exposure in Phase 2/3.

Examination of the overall mortality in the Phase 2/3 experience (counting only those deaths that occurred within 30 days of exposure to drug) and the rate of sudden unexplained deaths (defined as patients found dead or who died within 24 hours of the onset of symptoms) reveals the following (taken from Dr. Glass' tables on page 3 and 4 of her review):

Drug	Exposure (pt-yrs)	Deaths/100 pt-yrs	Sudden deaths/1000 py
Ziprasidone	1732.6	1.62	6.3
Placebo	91.8	5.45	0
Haloperidol	298.6	1.00	0
Risperidone	196.4	0.51	5.1

QTc Effects of Ziprasidone

As noted, the sponsor performed Study 54 to address the areas of concern outlined in the Not Approvable letter. This study has been described in detail by Drs. Glass and Gordon. Briefly, patients were randomized to receive the following target doses (mg/day), achieved by titration, of either ziprasidone (160), risperidone (16), olanzapine (20), quetiapine (750), thioridazine (300), or haloperidol (15). EKGs were obtained at the appropriate Tmax ~~for~~ each drug at steady-state, both with and without maximal metabolic inhibition. The following results were obtained for mean change from baseline in QTc (taken from Dr. Burkhart's review of 1/11/00, in which he utilized a more appropriate correction for heart rate than Bazett's):

Drug	QTc without inhibition	QTc with inhibition
Ziprasidone	16.5	17.0
Risperidone	4.3	2.7
Olanzapine	2.3	3.3
Quetiapine	6.9	9.5
Thioridazine	30.8	29.3
Haloperidol	6.8	12.8

As Dr. Gordon notes in her review (page 5), although the numbers were small, the percentage of patients treated with ziprasidone (with and without metabolic inhibition) who had QTc increases of 30, 60, and 75 msec was greater than with the other drugs, except for thioridazine, which was greater in all cases than ziprasidone. As the sponsor has noted, however, in general, patients with the longest baseline QTc intervals tended to experience a decrease in QTc over time, compared to the reverse phenomenon in the patients with shorter baseline QTc intervals (e.g., regression to the mean).

In the NDA database, there were no unambiguous reports of patients achieving a QTc interval of >500 msec, and there were no cases detected of torsades de pointe or polymorphic ventricular arrhythmias.

Finally, as noted by Drs. Glass and Laughren, there were no other safety issues identified in the sponsor's resubmission that would preclude approval or that were unexpeeted.

The application was presented to the Psychiatric Drugs Advisory Committee (augmented by 3 expert cardiology consultants) on July 19, 2000. As has been reported by Drs. Laughren and Glass, the committee voted 11-0 that ziprasidone has been shown to be an effective anti-psychotic drug, and 9-1 that the drug could be used safely with appropriate labeling (the committee's statistician abstained, and one of the invited cardiology experts voted no on this question because of a lack of sufficient information about interactions with other drugs known to prolong the QTc interval). However, the Committee in general voiced a strong preference that the labeling of the drug make clear that ziprasidone has the capacity to increase the QTc interval, that it was different in this regard than other atypical antipsychotics, and that the prescriber should be clearly warned of this effect. They, in general, (there was no formal vote) explicitly rejected the proposal that labeling should include a Boxed Warning, and also generally felt that the drug should not be relegated to second line status (again, no formal vote was taken on this question).

COMMENTS

Ziprasidone has been shown to be an effective anti-psychotic drug, and were it not for its capacity to prolong the QTc interval, its safety in use with routine labeling would be non-controversial. However, it is clear that ziprasidone does prolong the QTc interval, an effect widely regarded to be a surrogate for the occurrence of potential fatal ventricular arrhythmias, especially torsades de pointes.

What is the degree of QTc prolongation, and how does this affect the risk of such life-threatening events?

Unfortunately, the answers to these questions are not clear. If one chooses to assess the degree of prolongation by comparing the average increase on treatment to baseline, Study 54 provides the best estimate, both for ziprasidone, as well as comparatively for other relevant drugs in the class. Unfortunately, as noted by the review team, the absence of a placebo group in this study prevents a reliable estimate of the treatment effect in this trial. As Dr. Laughren notes, though, there is considerable evidence from several sources that suggests that oral haloperidol in the usual doses does not produce any QTc prolongation compared to placebo. If we accept that haloperidol is a substitute for placebo in Study 54, we see that the average increase from baseline in QTc attributable to ziprasidone is about 10 msec. This is also about the difference between ziprasidone and quetiapine, with the difference being somewhat greater compared with olanzapine (about 14 msec) and risperidone (about 12 msec). This difference is essentially consistent with the dictates of the Not Approvable letter, although it is at the upper end of what the letter suggested was an acceptable range. Clearly, the changes seen with thioridazine are considerably larger.

If we choose to look at specific degrees of increase of the QTc interval, we see that, again, ziprasidone shifts the distribution of patients with 30, 60, and 75 msec increases from baseline, although, as I previously mentioned, the data suggest that the phenomenon of regression to the mean is occurring.

What risk do these degrees of QTc increase confer?

There has been, of course, extensive consideration of this question throughout the review of this NDA. Our cardiology consultants have consistently advised that any degree of QTc prolongation presages an increased risk of potentially life-threatening ventricular arrhythmias. The cardiologists at the PDAC meeting on July 19, 2000 suggested that what is of most importance clinically is reaching a threshold of QTc, and that any drug that has the capacity to induce a mean increase in QTc (compared to placebo) can be considered to effectively increase the proportion of patients who will reach that threshold, and thereby increase the likelihood of potentially fatal arrhythmias. However, in response to direct questioning, all the experts (those on the panel as well as those brought by the sponsor) acknowledged that these views were not supported by adequate evidence. For example, the precise level of the threshold that is considered to be associated with an increased risk is unknown (there was general agreement that it was somewhere around 500 msec), and there was acknowledged to be no evidence to support any statement about the degree of mean QTc prolongation and its relationship to the number of patients who would reach any given worrisome threshold (although, again, there was general agreement that the greater the mean increase in QTc, the greater the proportion of patients in any given population that would reach such a threshold).

Study 54 addressed another of the important dictates of the Not Approvable letter as well. Specifically, the sponsor was able to document that even with maximal inhibition of ziprasidone metabolism, the QTc interval was not prolonged beyond that seen when ziprasidone was administered without metabolic inhibition (despite an increase in ziprasidone plasma concentrations of about 30% when it was given with the metabolic inhibitor).

Of course, Study 54 was not expected to be able to address the issue of outliers (those whose QTc reached a meaningful threshold, which we can take to be about 500 msec), given the very small numbers studied. However, an examination of the NDA database revealed that there were no clear cases of any patient (of the 4500 patients in Phase 2/3 studies, representing about 1700 patient-years of exposure) reaching such a threshold, nor were there any recorded cases of potentially life-threatening ventricular arrhythmias.

The interpretation of the mortality data (including the sudden unexplained death data) is not obvious. While, in the Phase 2/3 studies, ziprasidone had a lower mortality than the placebo patients (1.6/100 pt-yrs vs 5.5/100 pt-yrs, respectively), ziprasidone's mortality was about 1.5 times that of haloperidol, and about 3 times that of risperidone. Further, although ziprasidone and risperidone had similar rates of SUD, the rates for haloperidol and placebo were 0. However, the exposure to ziprasidone was so much greater than any of these comparators (1700 patient-years compared to 300 patient-years for the next closest drug, haloperidol), that, in my view, relative risk calculations are bound to be unreliable.

As Dr. Glass notes (page 4), ziprasidone has the highest rate of SUD of all recently approved anti-psychotic drugs (olanzapine, risperidone, and quetiapine),

As Dr. Glass also notes, however, comparing rates of SUD across studies is particularly unreliable.

In summary, ziprasidone use is associated with prolongation of the QTc interval. While the exact degree of this increase is unknown, it seems to be, on average, about 10 msec greater than several other anti-psychotic drugs (except, of course, thioridazine), and including haloperidol, for which we have some evidence, from other sources, that it is not associated with any QTc prolongation. There seems to be some consistency to this estimate; this was about the degree of increase seen in the controlled trials, and was the size of the difference seen in Study 54. Given that the EKGs in the controlled trials were performed at close to Cmin, and given the fact that in Study 54, in which EKGs were performed at Cmax, there was no further increase in QTc despite an increase in plasma levels of about 30% after metabolic inhibition, it is possible that this represents the maximum average increase, at least up to 160 mg/day (I note Dr. Laughren's comment-

page 11 of his 5/14/98 memo-that the data at 200 mg/day suggest that the QTc prolongation is slightly less than at 160 mg/day, but this remains unexplained, although the number of patients exposed to this higher dose is relatively small).

The degree of increased risk associated with this finding is entirely unknown. Several other drugs which are associated with a degree of prolongation of the QTc similar to that seen with ziprasidone are also associated with the occurrence of torsades de pointes and other potentially life-threatening ventricular arrhythmias, and experts seem to generally agree that the greater the mean prolongation, the greater the proportion of patients who are likely to reach a meaningful threshold, which, in turn, is believed to carry with it an increased risk of these arrhythmias. There are not even vague guesses offered by experts about the actual, absolute risk either of the proportion of patients in a given population who might reach such a threshold (given a specific mean QTc increase in this population) or of the risk of suffering a ventricular event of concern given a QTc interval at or above this threshold. Indeed, the sponsor notes that terfenadine, in the absence of an inhibitor of its metabolism, was associated with a mean increase in QTc of about 18 msec, but was not associated with any reports of torsades de pointes in the absence of metabolic inhibition. The matter is, of course, extremely complicated, and QTc can be considered, at best, an imperfect surrogate for clinical events of concern, but it is currently considered, by experts, important in the assessment of a drug's potential to cause harm; I believe my summary of the view generally expressed by experts is fairly described above, as I understand it.

Taking into account all of the above data and arguments, I believe that it is reasonable to conclude that ziprasidone can be approved. First, it is clear that ziprasidone is an effective anti-psychotic drug. I note that there are various reviews in the file which suggest that the NDA should be approved only if some advantage for ziprasidone has been shown. As Drs. Glass and Gordon note, the sponsor suggests that ziprasidone causes less weight gain than other recently approved anti-psychotics (an adverse event that is responsible for treatment discontinuation of other drugs according to the sponsor), and also lowers triglycerides and cholesterol levels. While I believe that there is some evidence for these claims (although the comparative results are not uniform with all drugs, and there is no evidence that patients discontinue treatment with ziprasidone any less frequently than with other anti-psychotics), there is certainly no evidence that ziprasidone offers any advantage with regard to effectiveness (indeed, as Dr. Leber noted in his memo of 6/1/98, the results of Study 115 suggest that ziprasidone was less efficacious than haloperidol). Further, I would agree with Dr. Gordon that these putative changes in weight gain and serum lipids do not mitigate the risk of acute, unpredictable, unrecognized (and therefore untreatable) life-threatening arrhythmias. Indeed, even if these claimed advantages were adequately demonstrated, it would still not be clear that they would confer a survival benefit for ziprasidone (as noted by Dr. Califf at the

PDAC meeting, we do not know if a ziprasidone-induced decrease in serum cholesterol, for example, is associated with any clinical benefit).

These reservations notwithstanding, I believe that there are good reasons to make ziprasidone available, assuming it could be done safely. Specifically, schizophrenia is a devastating disease, and despite the availability of a number of effective agents (including a number of newly approved atypical drugs), the armamentarium is not complete. While, as noted, there is no evidence that ziprasidone offers an advantage over currently available drugs, it is at least possible that some patients who have failed on, or cannot tolerate, other drugs may benefit from ziprasidone. This possibility alone is sufficient, in my view, to make ziprasidone available (given the uncertainties about the risk), with appropriate labeling.

Given this view, it follows that I agree with Dr. Laughren that the drug should be indicated for second line use. Additional language in the labeling we are proposing is intended to transmit to the prescriber the very real concerns raised by the effect of ziprasidone on the QTc interval.

On one point I disagree with Dr. Laughren. He recommends that the 20 mg dosage form not be approved. He argues that it is not needed, given the dosage schedule he recommends (initial treatment of 40 mg BID, with a maximum recommended dose of 80 mg BID). However, I believe the 20 mg capsule should be made available for the following reasons.

1) In one controlled trial, 20, 60, and 100 mg BID were all shown to be effective on the BPRS total score, BPRS psychosis cluster, and CGI severity (although only the 100 mg group-a dose Dr. Laughren proposes not be generally used-was different from placebo for the PANSS negative subscale. According to proposed labeling, there was no clear evidence for dose response in this dose range.
2) A relapse prevention study evaluated 20, 40, and 80 mg BID, and found all doses to be superior to placebo; with no apparent difference between the dose groups.
3) Another short term controlled trial yielded no differences between 5, 20, and 40 mg BID (a dose recommended by Dr. Laughren) and placebo.
4) In another short term controlled trial comparing 20 and 60 mg BID to placebo, only the 60 mg BID dose was superior to placebo on various outcomes.

In summary, a dose of 20 mg BID was evaluated in 3 short term trials and one relapse prevention trial. This dose was superior to placebo in one short term trial and in the relapse prevention trial. In one of the short term trials in which this dose was not distinguished from placebo, neither was 40 mg BID, a dose we clearly believe is effective, and in the other study, 60 mg BID was superior to placebo on some outcomes, but not all, suggesting that that study also failed to fully distinguish a clearly effective dose from placebo. Indeed, there is only a

single short term controlled trial that demonstrates the effectiveness of 40 mg BID in addition to the relapse prevention trial. Further, in the 2 trials in which 20 mg BID was significantly different from placebo, there was no clear evidence of a dose response. Given this array of results, I believe it is reasonable to conclude that 20 mg BID has anti-schizophrenia activity. Further, given the relatively weak evidence for dose response for effectiveness, and given the dose relatedness of the QTc prolongation (at least within the dose range of 20-80 mg BID), it makes sense to me to describe 20 mg BID as an effective dose in labeling.

Given the experts' view of the capacity of drugs that can increase the QTc to cause potential fatal ventricular arrhythmias, it would not be surprising to expect ziprasidone's use to be associated, once it is widely available, with occurrences of such arrhythmias, and also with deaths due to them. We would expect these events to be relatively rare, given our experience in the development cohort, although the occurrence of these events can not be completely ruled out in the development cohort (given that patients were not monitored for serious ventricular arrhythmias continuously throughout exposure, and given the possibility that some of the deaths could have been related to such an event). Nonetheless, if current understanding is correct, we should expect reports of these events over time. For this reason, labeling should be clear about the potential risks associated with ziprasidone's use, and should attempt to mitigate these risks as much as is feasible. We believe that the draft labeling included with this package achieves that goal.

Therefore, for the reasons stated above, and with the attached draft labeling, we recommend that the attached Approvable letter be sent to the sponsor.

In particular, the letter will ask the sponsor to perform several studies to further explore various aspects of the QTc issue. We will ask them to evaluate the effects of doses greater than 160 mg/day on the QTc interval, as well as to evaluate the effects on QTc when ziprasidone is administered with other drugs known to prolong the QTc (both of these studies were recommended by the PDAC). Finally, we will ask the sponsor to undertake to study the comparative risk of sudden unexplained death with ziprasidone and several recently approved atypical anti-psychotics.

The letter also will contain a number of comments about the pre-clinical data; as Dr. Freed notes in her review, some of her earlier comments were inadvertently omitted from the Not Approvable letter, and therefore these requests are included in this letter.

/S/

Russell Katz, M.D.

Cc:
NDA _ 20-825
HFD-120
HFD-120/Katz/Laughren/Glass/Hardeman/Freed/Fitzgerald/Seevers
HFD-860/Al-Habet
HFD-710/Jin/Chi