CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20639

ADMINISTRATIVE DOCUMENTS

Zeneca Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
Wilmington, DE 19850-5437

SEROQUEL® (quetiapine fumarate) Tablets

ITEM 13: Pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, the attached information is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

1. Active Ingredient(s):

   Bis [2-(2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl) piperazin-1-yl]ethoxy) ethanol], fumarate.

2. Strength(s):

   25 mg, 100 mg, and 200 mg Tablets

3. Trade Name:

   SEROQUEL® (quetiapine fumarate) Tablets

4. Dosage Form, Route of Administration:

   Tablet, Oral

5. Applicant Firm Name/Holder of the New Drug Application:

   Zeneca Limited
   Macclesfield, Cheshire, England

   US Agent:
   Zeneca Pharmaceuticals
   A Business Unit of Zeneca Inc.
   1800 Concord Pike
   Wilmington, DE 19850-5437

6. NDA Number:

   20-639

7. Approval Date:

N/A

8. Applicable Patent(s):

(a) US Patent No. 4,879,288

(i) Expiration date:

March 20, 2007 (subject to change if the patent term is extended pursuant to 35 USC 156).

(ii) Type of Patent:

U.S. Patent No. 4,879,288 claims the active ingredient as a compound per se, a pharmaceutical composition containing the active ingredient, and a method of using the active ingredient.

(iii) Name of Patent Owner:

Zeneca Limited, Macclesfield, Cheshire, England.

(iv) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

Cushman, Darby and Cushman
1100 New York Avenue
Washington, DC 20005-3918

(v) Original Declaration:

The undersigned declares that US Patent No. 4,879,288 covers the formulation, composition, and/or method of use of SEROQUEL® (quetiapine fumarate) Tablets. This product is the subject of this application for which approval is being sought.

Ruth H. Newton

RUTH H. NEWTSON
CHIEF IP COUNSEL
PHARMACEUTICALS

B. EXCLUSIVITY INFORMATION

Applicant claims an exclusivity period of five years from the date of approval of this application pursuant to 21 CFR 314.108(b)(2). To the best of Applicant's knowledge or belief, a drug has not been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act containing any active moiety in SEROQUEL® (quetiapine fumarate) Tablets, the drug for which Applicant is seeking approval.

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DRUG STUDIES IN PEDIATRIC PATIENTS

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

NDA:	**20-639**
Product:	**Seroquel (quetiapine fumarate)**
Sponsor:	**Zeneca**
Project Manager:	**CDR 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:

The potential for the use of this drug in children is unclear at this point. We will explore this issue with the sponsor in future discussions re: the approved action.

Signature of Preparer

6-24-97
Date

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

NDA:	**20-639**
Trade Name:	**Seroquel**
Generic Name:	**quetiapine fumarate**
Applicant Name:	**Zeneca**
Division:	**HFD-120**
Project Manager:	**CDR Steven D. Hardeman, R.Ph.**
Approval Date:	

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

   b. Is it an effectiveness supplement? — 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

   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. — N/A

   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: — N/A

   d. Did the applicant request exclusivity? — Yes

   If the answer "yes," how many years of exclusivity did the applicant request? — 5 yrs

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

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? No

If yes, what is NDA number

If yes, what is Drug Name

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

3. Is this drug product or indication a DESI upgrade? No

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

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PART II

FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product. No

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.

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

2. Combination product. N/A

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.)

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

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

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

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?

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

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?

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.

1) 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?

If yes, explain:

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

      Investigation #2

      Investigation #3

      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

      Investigation #2

      Investigation #3

      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#: Explain:

Investigation #2
IND#: Explain:

Investigation #2
IND#: 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
Explain:

Investigation #2
Explain:

Investigation #3
Explain:

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.)

If yes, explain:

Steven D. Hardeman, R.Ph.
Project Manager
DNDP, HFD-120

6/25/97
Paul Leber, M.D.
Director
DNDP, HFD-120

c:\docs\nda\seroquel\exclusiv.sum
Final: June 6, 1997

cc:
Original NDA
Division File
HFD-120/Hardeman
HFD-85/Holovac

ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.

1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437
Telephone (302) 886-2132
Fax (302) 886-2822

William J. Kennedy, Ph.D.
Vice President
Drug Regulatory Affairs Department

JUL 2 9 1996

Re: SEROQUEL® (quetiapine fumarate)
NDA 20-639

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of Zeneca Pharmaceuticals, a Business Unit of Zeneca Inc., that we did not and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

William J. Kennedy, Ph.D.

WJK/car/23963/120

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: **September 24, 1997**

FROM: **Paul Leber, M.D.**
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: **Seroquel (quetiapine fumarate)**
Approval Action Recommendation

TO: **File NDA 20-639**
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my formal recommendation that Zeneca Pharmaceuticals' NDA 20-639 for Seroquel which allows for quetiapine's use as an antipsychotic be approved. The application was declared approvable on 7/28/97.

My views of the evidence bearing on quetiapine's safety for use and effectiveness in use at the time of the issuance of the approvable action letter are provided in my memorandum of 7/2/97.

The Division's review team has now completed its assessment of 1) safety updates providing reports of adverse events arising from additional clinical experience with quetiapine, 2) an updated summary of the world archival literature and 3) a summary of the product's current regulatory status elsewhere in the world.

The primary medical review officer, Dr. Mosholder (memorandum of 8/19/97), and the team leader, Dr. Laughren, concur that these reports and summaries do not contain any finding of sufficient importance to cause the agency to revise its conclusion that the NDA shows quetiapine to be both safe and effective as an antipsychotic under the version of labeling

jointly agreed upon by the Division review team and the sponsor.

Negotiations concerning final product labeling were conducted under the direction of Dr. Laughren and involved not only iterative interactions between the firm and the Division's review team, but a face to face meeting attended by representatives of the firm, their ophthalmological expert consultant, Dr. Leo Chylack, the agency's ophthalmological expert, Dr. Wiley Chambers, and the ODE I Office Director. Dr. Temple. A brief overview of all these activities is provided in Dr. Laughren's memorandum to the file of 8/21/97.

Conclusions:

If marketed under the conditions of use described in the labeling attached to the approval action letter being forwarded to the Office for issuance, Seroquel will be safe for use and effective in use within the meaning of the FD&C Act as currently interpreted. Accordingly, the NDA may be approved.

Recommendations:

Issue the approval action letter.

Paul Leber, M.D.
9/24/97

APPEARS THIS WAY
ON ORIGINAL

CC:
NDA 20-639
HFD-120
Katz
Laughren
Mosholder
Fitzgerald
Hardeman

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MEMORANDUM

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

DATE: August 21, 1997

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

SUBJECT: Recommendation for Approval Action for
Seroquel (quetiapine) for the treatment of psychotic disorders

TO: File NDA 20-639
[**Note:** This overview should be filed with the 7-31-97 submission.]

1.0 BACKGROUND

In our 7-28-97 approvable letter, we requested a safety update, a foreign regulatory update, a world literature update, and a commitment to conduct several phase 4 studies, including a relapse prevention study, a cataract study, a thyroxine study, and a 3A4 inhibitor interaction study. In the biopharmaceutics area, we identified our preferred dissolution methodology and specifications. We also attached our proposal for labeling. In anticipation of our approvable action, Zeneca submitted a second safety update on 6-30-97, and then responded formally to the approvable letter with the 7-31-97 submission, including a very brief third safety update.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several days to arrive at the version of labeling [LABSRQPS.AP2] that is included with the approval letter. We initially faxed a labeling document [LABSRQPS.AP1] on 8-20-97 in response to the sponsor's labeling response to our approvable letter. We held a teleconference with the sponsor on 8-21-97 and were able to agree on all aspects of labeling except for language pertinent to monitoring for cataracts. We acknowledged this as the one area of disagreement that needed resolution at a higher level. In the meantime, I have included [LABSRQPS.AP2] as labeling that I consider appropriate for the approval of this product.

Dr. Andrew Mosholder reviewed the clinical sections of the 7-31-97 response to the approvable letter, including the second and third safety updates, the literature update, and the regulatory status update.

2.0 SAFETY UPDATE

The safety updates included reports of deaths, serious adverse events, adverse dropouts, and other adverse events. The second update covered a period from 3-1-96 through 11-7-96 for the primary integrated database. This safety update comprised data for 504 quetiapine patients, including data for 136 new patients and additional exposure data for 368 patients for whom some safety data had already been reviewed in earlier submissions. All of this new data came from uncontrolled experience with quetiapine. Additional deaths and serious events were reported for a period from 11-8-96 through 5-30-97. Finally, the third safety update included deaths and serious adverse events covering a period from 5-30-97 through 7-15-97.

-There were 16 additional deaths, many in elderly individuals in dementia trials. Dr. Mosholder concluded that none of these deaths could be reasonably attributed to quetiapine treatment, and I agree.
-There were 16 additional overdoses with quetiapine, revealing a similar profile of adverse events as seen with overdoses in the original database.
-Dr. Mosholder reviewed and organized the deaths, other serious adverse events, and the adverse dropouts using a body systems approach as was done in his original review. He concluded that these additional data did not alter his view about the approvability of quetiapine and did not reveal any important new information that would impact on the labeling of quetiapine. I agree.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period from the cutoff date for the original NDA submission to 7-14-97, including both clinical and preclinical references. Lisa Arvanitis, M.D., from Zeneca, reviewed this literature and warranted that "No findings were discovered during my review of this literature that would adversely affect conclusions about the safety of Seroquel." Dr. Mosholder reviewed abstracts for these same references, concluding likewise that they contained no findings that would adversely affect conclusions about quetiapines's safety.

4.0 FOREIGN REGULATORY UPDATE

The sponsor warranted in the 7-31-97 submission that Seroquel is not approved in any countries at the present time.

5.0 REQUEST FOR PHASE 4 CLINICAL TRIALS

The sponsor has committed to conducting the four phase 4 studies requested in our approvable letter. No details have been provided.

6.0 BIOPHARMACEUTICS

The sponsor accepted our proposed dissolution method and specifications.

7.0 LABELING

Zeneca proposed several changes to the labeling for Zyprexa, some of which we found acceptable, while others were the subject of negotiations with the review team. As noted, we were able to reach agreement at a Team Leader level on labeling, with the exception of language in the "Cataracts" subsection under Precautions, General. I continue to feel, based on the information available and advice from our ophthalmological consultant, Dr. Chambers, that it is essential to advise clinicians to obtain slit lamp exams at 6-month intervals in patients undergoing chronic therapy with Seroquel. It is my view that the more general advice proposed by the sponsor, i.e., for "careful ocular examination during chronic treatment," would not ensure that patients receive sufficient monitoring for the detection of this potential adverse event. The need for this level of monitoring would, of course, be subject to change, once the sponsor has completed a more definitive study of this concern, should the study provide evidence favorable to Seroquel. The other issues, for which we were able to reach agreement, were minor, in my view.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Zeneca has submitted sufficient data to support the conclusion that Seroquel is effective and acceptably safe in the treatment of psychosis. I recommend that we issue the attached approval letter with a version of labeling for which we were able to reach mutual agreement with the sponsor, except for the requirement for cataract monotoring, as noted above. We have tentatively scheduled a meeting to discuss the cataract monitoring issue, including ophthalmological consultants representing both FDA and the sponsor.

cc:
Orig NDA 20-639
HFD-120
HFD-120/TLaughren/PLeber/AMosholder/SHardeman
HFD-100/RTemple

DOC: MEMSRQPS.AP1