CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022047Orig1s000

<u>OTHER REVIEW(S)</u>

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-047 Supplement # 000 Efficacy Supplement Type SE-

Proprietary Name: Seroquel SR
Established Name: Quetiapine sustained release tablets
Strengths: 50, 200, 300, 400 mg

Applicant: AstraZeneca
Agent for Applicant (if applicable): Gerald Limp

Date of Application: 7/17/06
Date of Receipt: 7/17/06
Date clock started after UN:
Date of Filing Meeting: 08/31/06
Filing Date: 60 days
Action Goal Date (optional): User Fee Goal Date: 5/17/07

Indication(s) requested: Once daily dosing for the treatment of schizophrenia in adults

Type of Original NDA: (b)(1) X (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO X
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES X NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats X

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES X NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES X
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO ☐

- Exclusivity requested? YES, _____ Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☐ NO X

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO X

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES X NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers:

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 5/13/05 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 6/20/02 ; 10/11/05(Cancelled per Sponsor request) NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☐ NO
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☐ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO X

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO X

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 09/09/06

NDA #: 22-047

DRUG NAMES: Quetiapine sustained-release tablets

APPLICANT: AstraZeneca

BACKGROUND: Immediate-release tablets are currently approved for treatment of schizophrenia in adult patients. This IND is for the sustained-release tablets.

ATTENDEES: Laughren, Khin, Oliver, Rosloff, Hardeman, Updegraff, Chuen, Baewja

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Chuen
Secondary Medical:	Dubitsky
Statistical:	Dinh
Pharmacology:	Rosloff
Statistical Pharmacology:	
Chemistry:	Shiromani
Environmental Assessment (if needed):	Bloom
Biopharmaceutical:	Kumi
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Samuels
OPS:	
Regulatory Project Management:	Updegraff
Other Consults: DMETS	Kellie Taylor

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site audit(s) needed? With comments YES X NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE X REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☐

PHARMACOLOGY/TOX N/A ☐ FILE X REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Kimberly Updegraff
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(*b*) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?
YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Kimberly Updegraff
5/17/2007 10:45:57 AM
CSO

MEMORANDUM	Division of Medication Errors and Technical Support (DMETS) Office of Surveillance and Epidemiology WO22, Mail Stop 4447 Center for Drug Evaluation and Research

TO: Thomas Laughren, MD
Director, Division of Psychiatry Products, HFD-130

THROUGH: Denise Toyer, PharmD, Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Kellie Taylor, PharmD, MPH
Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

DATE: March 20, 2007

SUBJECT: DMETS Label and Labeling Review
Seroquel XR
(Quetiapine Fumarate) Extended- Release Tablets
50 mg, 200 mg, 300 mg, and 400 mg
NDA# 22-047
Sponsor: AstraZeneca

This memorandum is in response to a request from your Division for feedback on questions posed by AstraZeneca in an email sent to the Division on March 15, 2007. The questions concerned comments sent to AstraZeneca regarding the proposed Seroquel XR product, which originated from a DMETS review of the proprietary name, Seroquel XR (OSE Consult # 2006-1182 / 2006-975). DMETS has considered the Sponsor's questions from a medication errors perspective and offers the following responses as to how DMETS would like to see the company proceed.

Sponsor's Question: Within the section that provides comments from DMETS, there is a comment that we modify our tablet intagliation. Is this their preference, a recommendation, or a requirement?

DMETS Response: Preference. The intagliation of the tablet with the modifier and strength was proposed ***by the Sponsor*** as a measure to help ensure differentiation of the extended- and immediate- release formulations in the marketplace. DMETS acknowledges that the intagliation of the tablet requires modification from "**S**R" to "**X**R", but believes that this marking represents an

important safety measure. DMETS has also noted that mix-ups between Seroquel and Seroquel XR are likely to occur, and that the collective measures proposed by the Sponsor to ensure product differentiation are necessary to help to minimize these potential errors. As such, DMETS would strongly prefer that the Sponsor maintain this commitment.

Sponsor's Question: We already have tooling to produce tablets with the intagliation that is referenced within the NDA; this would require an additional investment of funds and time if this change is a requirement. If it is a requirement, can that be implemented as a post-approval commitment?

DMETS Response: The Sponsor notes that they have tools to produce tablets intagliated with "SR" (the previously proposed modifier) and the strength. DMETS acknowledges that the intagliation of the tablets with "XR" and strength may require an additional investment of funds and time, but believes that the efforts would be worthwhile. DMETS is not completely opposed to implementing this change as a post-approval commitment, though DMETS would prefer that the Sponsor meet this commitment prior to marketing the product for the following reasons:

1. DMETS is concerned that the launch of Seroquel XR will not have this safety measure in place, which might prevent errors of administration in the outpatient and inpatient setting. Although the intagliation of the tablet with "XR" will not prevent mix-ups between Seroquel and Seroquel XR, DMETS believes that it could help detect errors prior to administration by providing a visual means for patients and caregivers to readily identify the product formulation at the point of administration.

2. DMETS has concern that the change in tablet appearance in the post-marketing phase introduces a new source of confusion to the product line.

   - In an outpatient setting, tablet appearance and markings are routinely used by pharmacists and computer software programs in the final verification step when dispensing he product. Changing the markings post-approval would require some means of updating the software programs, and possibly alerting pharmacists to this change. This process could be complicated by the fact, that for some length of time, the markings on the Seroquel XR tablets could vary based on the date of manufacture.

   - Patients using Seroquel XR may become accustomed to the appearance and markings of the tablet at launch. Subsequent changes to the tablet appearance may be confusing and disconcerting to the patient population.

   If the Sponsor has just cause for not meeting this commitment prior to marketing the product, DMETS requests that they provide the Agency with the following information:

1) If the requirement is met as a post-approval commitment, would the tablets be intagliated with any information in the interim? If so, please specify in detail. DMETS is concerned that the Sponsor may proceed to intagliate the tablets with the old modifier (SR) and strength which would discordant with the proprietary name (Seroquel **XR**) and be a source of confusion.

2) When providing an expected timeline of implementation, please provide detail regarding the length of time required to achieve this change in manufacturing, along with the projected time to deplete the initial supply and the projected duration of overlap between the two tablets appearance.

3) Please indicate any additional measures that could be employed to minimize confusion resulting from this change in the post-marketing phase.

Sponsor's Question: Lastly, we are investigating ways to assure the 22-047 tablets are perceived to be different from the 20-639 immediate release tablets, and to improve the match between the XR trade name and drug name. Would the FDA agree with a change from 'quetiapine fumarate sustained release' to 'quetiapine fumarate extended release' tablets, which is a phrase DMETS use within their comments. It is our understanding that no technical aspects for tablet manufacture or drug release characteristics are represented by either concept, and they are basically equivalent in meaning.

DMETS Response: DMETS does not believe that relying on the Sponsor's "understanding" is prudent regarding the nomenclature of the proposed formulation. The Sponsor's assumption that the sustained- and extended-release terms are "basically equivalent in meaning" is presumptuous; "extended-release" is a recognized dosage form in the United States Pharmacopeia while "sustained-release" is not. In DMETS's opinion, this matter should be resolved by consulting Richard Lostritto of the CDER Labeling and Nomenclature Committee (LNC) on the proper designation of the established name for the modified-release product.

Sponsor's Question: If the FDA agrees with this change, how do we initiate this? Would this be a change we would include in our updated draft label?

DMETS Response: We do not agree with this revision. So we have no further comments to offer.

If you have any other questions or need further clarification, please contact Angela Robinson, Project Manager, at 301-796-2284.

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/s/

Kellie Taylor
3/22/2007 08:42:55 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/22/2007 08:57:55 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/22/2007 09:01:42 AM
DRUG SAFETY OFFICE REVIEWER

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

CLINICAL INSPECTION SUMMARY

DATE: February 12, 2007

TO: Kimberly Updegraff, Regulatory Project Manager
Michelle Chuen, M.D., Clinical Reviewer
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-047

APPLICANT: AstraZeneca Pharmaceuticals LP

DRUG: Seroquel (quetiapine) sustained-release tablets

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment for Schizophrenia

CONSULTATION REQUEST DATE: September 14, 2006

DIVISION ACTION GOAL DATE: March 1, 2007

PDUFA DATE: May 17, 2007

I. BACKGROUND:

Seroquel immediate release (IR) tablet is approved for the treatment of acute manic episodes associated with bipolar I disorder and the treatment of schizophrenia. Seroquel was studied to evaluate the efficacy and safety/tolerability profile of a new sustained release (SR) formulation. The sponsor has submitted a new drug application (NDA # 22-047) for marketing approval of Seroquel SR for the treatment of schizophrenia.

Drs. Efren Reyes' and Evelyn Belen's sites were selected for inspection due to insufficient domestic data. The goals of the inspections were to assess adherence to FDA regulatory requirements: specifically, investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. Protocol D1444C00132 entitled "A 6-week, International, Multicenter, Double-Blind, Double-Dummy, Randomized Comparison of the Efficacy and Safety of Sustained-Release Formulation Quetiapine Fumarate (SEROQUEL) and Placebo in the Treatment of Acutely Ill Patients with Schizophrenia" was inspected.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City	Country	Protocol	Inspection Date	EIR Received Date	Final Classification
Dr. Efren Reyes/ Site 501	Mandaluyong	Philippines	D1444C00132	Jan. 22-26, 2007	EIR Pending	Pending
Dr. Evelyn Belen/ Site 505	Pasig	Philippines	D1444C00132	Jan. 29-Feb. 2, 2007	EIR Pending	Pending

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable.

A. Protocol #D1444C00132

Observations noted below for Drs. Reyes and Belen are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

1. Dr. Efren Reyes, Site 501
National Center for Mental Health
Training Office (Medical)
9 De Pebrero Street
Mandaluyong City, Philippines

a. What was inspected: Dr. Reyes randomized 67 subjects. The inspection encompassed an audit of 20 subjects' records. Primary endpoint efficacy data were verified for 20 subjects.

b. Limitations of inspection: None

c. General observations/commentary: No significant deviations from FDA regulations were observed.

d. Data appear acceptable.

2. Dr. Evelyn Belen, Site 505
Metropsych Facility
520 Don Sixto Avenue
Maybunga Street
Pasig City 1605, Philippines

a. What was inspected: Dr. Belen randomized 50 subjects. The inspection encompassed an audit of 26 subjects' records. Primary endpoint efficacy data were verified for 26 subjects.

b. Limitations of inspection: None

c. General observations/commentary: No significant deviations from FDA regulations were observed.

d. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As mentioned above, the inspections of Dr. Reyes and Dr. Belen found no significant deviations from FDA regulations. The data from these sites appear acceptable in support of the respective indication.

As previously mentioned, observations noted above are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Sherbert Samuels
2/12/2007 11:44:11 AM
CSO

Constance Lewin
2/13/2007 12:28:12 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22; Mail Stop 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE Review #:** 2006-658
July 26, 2006	March 17, 2007	
DATE OF DOCUMENT:	**PDUFA DATE:**	
July 17, 2006	May 17, 2007	

TO: Thomas Laughren, MD
Director, Division of Psychiatry Products (HFD- 130)

THROUGH: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support (HFD-420)

FROM: Kellie Taylor, PharmD, MPH
Division of Medication Errors and Technical Support (HFD-420)

PRODUCT NAME: **Seroquel SR**
(Quetiapine Fumarate Extended- release) Tablets
50 mg, 200 mg, 300 mg, and 400 mg

NDA#: 22-047
NDA SPONSOR: AstraZeneca

RECOMMENDATIONS:

1. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of Seroquel SR.

2. DMETS recommends consulting Richard Lostritto of the CDER Labeling and Nomenclature Committee (LNC) on the proper designation of the established name for the modified-release product. Sustained-release is not a recognized dosage form in the United States Pharmacopeia.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Angela Robinson, project manager, at 301-796-2284.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

LABEL & LABELING REVIEW

DATE OF REVIEW: November 24, 2006

NDA#: 22-047

NAME OF DRUG: **Seroquel SR**
(Quetiapine Fumarate) Extended-release Tablets
50 mg, 200 mg, 300 mg, and 400 mg

IND HOLDER: AstraZeneca

I. INTRODUCTION:

This consult was written in response to a request from the Division of Psychiatry Products (HFD-130), to evaluate the proposed draft container labels, carton, unit-dose, and insert labeling for Seroquel SR from a medication errors perspective.

Seroquel was approved on September 26, 1997. It is marketed in 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg oral tablet strengths and is prescribed two to three times per day. Seroquel SR is an addition to the currently marketed product line. Previously, DMETS forwarded an assessment of the proprietary name, Seroquel SR, to the Division. DMETS did not recommend the use of the modifier 'SR' for this product (OSE# 06-0022, dated March 6, 2006). Subsequent to this review, the Sponsor has requested reconsideration of the name Seroquel SR and submitted an alternate name, Seroquel XR, for review. The rebuttal and review of the new proposed name, Seroquel XR, was forwarded under a separate consult (OSE# 2006-1182/2006-975, dated February 1, 2007)

PRODUCT INFORMATION

Seroquel SR is an atypical psychotropic agent intended to be used in the treatment of schizophrenia. The immediate release formulation is also indicated for the treatment of depressive and manic episodes associated with bipolar disorder. The available marketed strengths of Seroquel SR will be 50 mg, 200 mg, 300 mg, and 400 mg extended-release tablets. The effective therapeutic target dose range is 400 mg to 800 mg once daily.

II. RISK ASSESSMENT:

A. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed packaging and labeling for Seroquel SR, the two primary safety concerns relate to confusion with the existing immediate release bottles of Seroquel, and intra-brand confusion between the various strengths of the proposed extended-release product line of Seroquel SR.

Post-marketing experience has shown that the introduction of product line extensions result in medication errors especially when there is an overlap in strengths, dosing interval, and a knowledge deficit with respect to the introduction of the new extended-release formulation. Errors introduced by product line extensions are known to occur at all points in the medication

use process. In ordering or prescribing, it is common for modifiers to be omitted[1]. In transcribing and interpreting prescriptions and orders, modifiers have been overlooked. If the 'SR' modifier is omitted or overlooked at any point in the process, it is almost certain that Seroquel will be dispensed because of the overlapping product characteristics (see Table 1; **bolded text** used to represent overlapping characteristics).

Table 1: Comparative product information

Proprietary name:	**Seroquel**	**Seroquel** SR
Established name:	**Quetiapine Fumarate**	**Quetiapine Fumarate**
Manufacturer:	**AstraZeneca**	**AstraZeneca**
Form:	**Tablets**	**Tablets**
Strengths:	25 mg **50 mg** 100 mg **200 mg** **300 mg** **400 mg**	- **50 mg** - **200 mg** **300 mg** **400 mg**
Route of administration:	**Oral**	**Oral**
Frequency:	Two to three times daily	Once daily
Target dose:	300 mg to **400 mg** (in divided doses)	**400 mg** to 800 mg
Prescriber:	**General Practitioner/Psychiatrist**	**General Practitioner/Psychiatrist**
Indication:	**Treatment of schizophrenia,** Treatment of depressive and manic episodes associated with bipolar disorder	**Treatment of schizophrenia** _

The Sponsor has chosen to develop a extended-release formulation of Quetiapine Fumarate tablets that overlaps four strengths of the currently marketed immediate-release formulation (50 mg, 200 mg, 300 mg, 400 mg), and in doing so, the Sponsor has eliminated a potentially valuable error-reduction strategy that has been employed in other product line extensions. For example, GlaxoSmithKline markets Paxil CR in strengths of 12.5 mg, 25 mg, 37.5 mg while Paxil is available in strengths of 10 mg, 20 mg, 30 mg, and 40 mg. Thus, if the "CR" modifier is omitted or overlooked, the difference introduced by the strength offer an opportunity for an error to be caught before it reaches the patient.

In addition to errors that could result from the omission or oversight of a modifier in prescriptions and medication orders, there is also a significant risk for product selection errors when both items are stocked. Typically, pharmaceutical products are organized alphabetically by proprietary name, established name, or sorted by manufacturer. Since these attributes are identical with Seroquel and Seroquel SR, it is likely that the products will be stored near one another in virtually any organization carrying both product lines. Given the number of characteristics that overlap with the products (refer to Table 1 for detail), the close proximity of the products increases the risk of product selection errors. In order to minimize this potential source of confusion, differentiation in the packaging and labeling of Seroquel and Seroquel SR is essential.

Moreover, differentiation in the packaging of the various strengths within the Seroquel SR product line is also essential to minimize wrong strength selection errors. DMETS is aware of some errors resulting from product selection within the immediate-release Seroquel product line.

[1] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

The Seroquel labels have colored highlights on the primary container labels to differentiate the various strengths. However, the packaging for the 100 mg and 200 mg bottles both utilize shades of blue and at least two mix-ups have been reported between these two strengths (ISR 5013536-5, 5/26/2005, ISR4853314-7, 12/20/2005). Fortunately, neither patient experienced adverse outcomes as a result of the reported error.

Overall, DMETS believes that labeling and packaging differentiation will help to minimize the potential for product selection errors, but will not be able to fully avoid confusion between Seroquel and Seroquel SR. Therefore, DMETS has focused on safety issues relating to possible medication errors in the review of the container labels, carton, unit-dose, and insert labeling, and identified several areas of possible improvement that might minimize potential user error.

III. PACKAGING, LABEL, LABELING, AND SAFETY RELATED ISSUES:

A. GENERAL COMMENTS

1. See comments in Safety Evaluator Risk Assessment (Section II, A; pages 2,3,4).

2. DMETS submitted to the Division a proprietary name review of Seroquel SR and Seroquel XR (OSE Review # 2006-1182/2006-975) that recommended that Richard Lostritto of the CDER Labeling and Nomenclature Committee (LNC) be consulted on the proper designation of the established name for the modified-release product. "Sustained-release" is not a recognized dosage form in the United States Pharmacopeia. DMETS believes that "extended-release" *may* be the proper designation of the dosage form for this proposed product, but will defer to the advice of Richard Lostritto of the CDER Labeling and Nomenclature committee.

B. CONTAINER LABEL

1. Container Closure

a) The immediate-release Seroquel product line utilizes a blue container closure on all of the retail bottles and bulk bottles (1000 count) of 25 mg and 50 mg tablets (see image below, from: http://www.seroquel.com/prof_asp/dispensing/).

The Sponsor has proposed [redacted] (b) (4)

[redacted] (b) (4)

(b) (4) DMETS believes that Seroquel SR and Seroquel have an increased risk for selection errors because of the similar nomenclature of the products, overlapping strengths, net quantity of containers, primary container label's color scheme.

Therefore, DMETS recommends that the Sponsor utilize white container closures for the Seroquel SR product line to help lessen the potential for product selection errors with Seroquel SR and Seroquel.

b) DMETS also noted that the Seroquel SR product line is packaged in "unit of use quantities" of 60 tablets. DMETS recommends that the Sponsor employ Child Resistant Closures for all strengths of Seroquel SR tablets in the 60 count bottles.

The use of Child Resistant Closures would increase the pharmacist's opportunity to directly label and dispense the manufacturers' stock bottle. From a medication errors perspective, this may have several benefits. Direct labeling of the pharmacy container decreases the number of steps in the dispensing process, which inherently decreases the opportunity for error. Since there are multiple opportunities for the Seroquel SR to be confused with Seroquel throughout the medication use process, minimizing the number of opportunities could help improve the safe use of the product. Direct labeling of the manufacturer stock bottle ensures that the pharmacist has the original container at the point of final verification, thus enhancing the likelihood to catch product selection errors. Lastly, direct labeling of the manufacturer bottle gives patients the opportunity to verify the contents, and potential identify errors prior to ingestion.

2. Container Label

a) DMETS is concerned that the proposed color scheme for the Seroquel SR may increase the potential for selection errors and confusion with the Seroquel product line. (b) (4) DMETS recommends that the Sponsor employ a different color for Seroquel SR container labels that does not overlap with the Seroquel product line, in order to help minimize the potential for selection errors.

Table 1. Proposed Seroquel SR container labels and Seroquel container labels

(b) (4)	

(b) (4)

[redacted]

b) DMETS is concerned that the proposed color scheme for the 300 mg strength of Seroquel SR may lead to selection errors. For the 300 mg strength of Seroquel SR, the sponsor has proposed using a brightly [redacted] (b) (4) DMETS recommends that the Sponsor employ a different color for Seroquel SR container labels that does not overlap with the Seroquel product line, in order to help minimize the potential for selection errors.

Table 2. Proposed container label for Seroquel SR 300mg compared to Seroquel 25 mg and 300 mg

(b) (4)

[redacted]

	(b) (4) [redacted]

c) DMETS recommends the established dosage form (extended-release tablets) follow the established name, and not the strength of the product as proposed by the Sponsor. In addition, DMETS recommends that the dosage form be displayed in black.

d) Normally, DMETS would recommend that the Sponsor display the root name (i.e. "Seroquel") and established name (i.e. "Quetiapine Fumarate") using upper and lower case letters, since the use of all capitalized letters decreases the readability of information. However, in this instance, DMETS does not object to the use of all capitalized letters for the proprietary name (i.e. SEROQUEL SR), since this may help to differentiate the product from Seroquel. DMETS does recommend that the Sponsor use upper and lower case letters for the established name, to improve readability.

e) DMETS recommends the Sponsor increase the size and prominence of "ONCE DAILY" on the primary display panel. DMETS also recommends that the sponsor reference the "Once daily" dosage frequency of the product on the secondary display panel under "USUAL DOSAGE" to reinforce this message.

f) Remove the (b) (4) [redacted] graphic from the primary display panel from all strengths of the Seroquel SR product line. (b) (4) [redacted]

g) DMETS recommends that the sponsor display the strength and dosage form in colors that provide good visual contrast to increase readability and prominence of this information. (b) (4) [redacted]

B. PROFESSIONAL SAMPLES

1. Carton Label
   a) See CONTAINER LABEL comments 2a, 2b, 2c, 2d, 2e, 2f, 2g.

2. Container Label
   a) See CONTAINER LABEL comments 2a, 2b, 2c, 2d, 2e, 2f, 2g.

   b) Include a descriptor to indicate how the product should be dosed (e.g. "Once-A-Day Dosing") on the primary display panel of the Seroquel SR container bottle label for the samples. DMETS believes that this statement may, to some degree, lessen confusion

with the existing Seroquel products.

C. HOSPTIAL UNIT-DOSE

1. Unit-dose blister Label

a) GENERAL COMMENTS

The labels used for the unit-dose Seroquel SR appear very similar to Seroquel and may increase confusion between the products if both are stocked within an institution (see images below).

(b) (4)

The similar appearance of the labels could lead to product confusion when stocking, dispensing, and administering the products. DMETS recommends that the Sponsor explore different layouts and formats to improve differentiation of these products.

If the Sponsor is unable to pursue alternative formats, DMETS believes that mix-ups are likely to occur in facilities that stock both products. To help minimize the potential for confusion, DMETS recommends the following to improve the safety of the current proposed labels:

1) The dosage form ("extended-release tablets") is missing. Add the dosage form to the label after the established name.

2) Normally, DMETS would recommend that the Sponsor display the root name (i.e. "Seroquel") and established name (i.e. "Quetiapine Fumarate") using upper and lower case letters, since the use of all capitalized letters decreases the readability of information. However, in this instance, DMETS does not object to the use of all capitalized letters for the proprietary name (i.e. SEROQUEL SR), since this may help to differentiate the product from Seroquel. DMETS does recommend that the Sponsor use upper and lower case letters for the established name, to improve readability. Additionally, if the unit-dose label has adequate space, DMETS recommends increasing the size of the type used to display the established name and dosage form to further improve the readability of the established name and dosage form, as this information may be used frequently as the primary product identifier in an inpatient settings.

3) Consider displaying the Proprietary Name in reverse block print, maintaining bolded "SR" (see sample below). Although bolded, the barcode on the label decreases the prominence of the SR modifier, which could lead to errors.

SEROQUEL **SR**

4) DMETS recommends that the placement of the strength be left justified. The proposed placement decreases the prominence of the strength, and DMETS has concern that it could lead to confusion between the various strengths of Seroquel SR.

5) Left-justify the Lot and Expiration, and Manufacturer information, and mover the barcode to the right. DMETS believes that this will improve the overall readability of the information, and help to provide some differentiation from the immediate-release unit dose Seroquel tablets.

2. Carton Label

a) See CONTAINER LABEL comments 2a, 2b, 2c, 2d, 2e, and 2f. (b) (4)

b) Remove the (b) (4) graphic from the primary display panel from all strengths of the Seroquel SR product line. (b) (4)

c) Include a descriptor to indicate how the product should be dosed (e.g. "Once-A-Day) Dosing" on the primary display panel of the Seroquel SR product line. DMETS believes that this statement may, to some degree, lessen confusion with the existing Seroquel products.

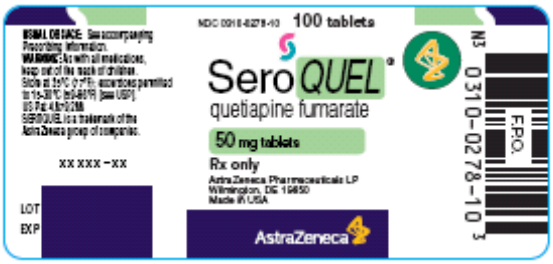
D. PRESCRIBING INFORMATION

1. Dosage and Administration

a) (b) (4)

Appendix A

Comparative Packaging and Labeling characteristics for Seroquel and Seroquel SR

Proprietary name:	Seroquel	Seroquel SR
Established name:	Quetiapine Fumarate	Quetiapine Fumarate
Manufacturer:	AstraZeneca	AstraZeneca
Form:	Tablets	Tablets
Strengths:	25 mg 50 mg 100 mg 200 mg 300 mg 400 mg	- 50 mg - 200 mg 300 mg 400 mg
50 mg		
Tablet description	White, round	Peach, capsule-shaped
Hospital (unit dose)	Cartons containing 100 unit dose	Cartons containing 100 unit dose
Bottle quantity	100 count, 1000 count	(b) (4)
Container label color scheme (bulk bottles, unit dose cartons)	Green/Purple  	
Bottle container closure color	Blue (all bottles)	
200 mg		
Tablet description	White, round	Yellow, capsule- shaped
Hospital (unit dose)	Cartons containing 100 unit dose	Cartons containing 100 unit dose
Bottle quantity	60 count	60 count, 500 count
Label color	Royal blue/purple	(b) (4)

scheme (bottles, unit-dose cartons)	(b) (4) [redacted]	(b) (4) [redacted]
Bottle container closure color	Blue (all bottles)	
300 mg		
Tablet description	White, capsule-shaped	Pale yellow, capsule-shaped
Hospital (unit dose)	Cartons containing 100 unit dose	Cartons containing 100 unit dose
Bottle quantity	60 count	60 count, 500 count
Label color scheme (bulk bottles, unit-dose cartons)	Yellow/ purple	(b) (4) [redacted]
	(b) (4) [redacted]	(b) (4) [redacted]
Bottle container closure color	Blue	
400 mg		
Tablet description	Yellow, capsule-shaped	White, capsule-shaped
Hospital (unit dose)	Cartons containing 100 unit dose	Cartons containing 100 unit dose
Bottle quantity	100 count	60 count
Label color scheme (bulk bottles, unit-dose carton)	Orange	(b) (4) [redacted]

	(b) (4)	(b) (4)
Bottle container closure color	Blue	

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/s/

Kellie Taylor
3/6/2007 12:29:12 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/6/2007 01:56:01 PM
DRUG SAFETY OFFICE REVIEWER

DSI CONSULT: Request for Clinical Inspections

Date: September 14, 2006

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Joseph Salewski, , Acting Director, DSI, HFD-45
Thomas Laughren, M.D., Director, HFD-130

From: Kimberly Updegraff, Regulatory Project Manager, HFD-130
Division of Psychiatry Products

Subject: **Request for Clinical Site Inspections**
NDA 22-047
AstraZeneca Pharmaceuticals LP
Seroquel (quetiapine) sustained-release tablets

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Dr. Efren Reyes National Center for Mental Health 9 de Pebrero Street Mandaluyong City 1553 Philippines Site # 501	D1444C00132	66	Schizophrenia
Dr. Evelyn Belen Metropsych Facility Maybunga Street, Pasig City 1605 Philippines Site # 505	D1444C00132	48	Schizophrenia

Domestic Inspections:

We have requested inspections because (please check all that apply):

____ Enrollment of large numbers of study subjects

____ High treatment responders (specify:)

____ Significant primary efficacy results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

____ Other: SPECIFY

International Inspections:

We have requested inspections because (please check all that apply):

__X__ There are insufficient domestic data

____ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by March 1, 2007. We intend to issue an action letter on this application by May 17, 2007.

Should you require any additional information, please contact Kimberly Updegraff at 301-796-2201.

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/s/

Thomas Laughren
9/14/2006 04:03:45 PM

DSI CONSULT: Request for Clinical Inspections

DATE: July 24, 2006

TO: Constance Lewin, M.D.
Division of Scientific Investigations, HFD-48

THROUGH: Thomas Laughren, M.D.
Division Director, Division of Psychiatry, HFD-130

FROM: LT Felecia Curtis, RN, Regulatory Project Manager, HFD-130

SUBJECT: **Request for Clinical Inspections**
NDA 22-047
Seroquel (quetiapine fumarate) Sustained-Release Tablets

Study/Site Identification:

We have received an original NDA from AstraZeneca Pharmaceuticals for Seroquel (quetiapine fumarate) Sustained-Release Tablets for the treatment of schizophrenia that will allow physicians to administer quetiapine once daily. Our 45-day filing meeting is scheduled for Thursday, August 31, 2006, and the filing date for this application is September 15, 2006. If the application is filed, the medical officer will identify the pivotal studies that need to be investigated, and I will inform you of these sites.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by March 1, 2007. We intend to issue an action letter on this application by May 17, 2007.

Should you require any additional information, please contact Felecia Curtis, RN.

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/s/

Thomas Laughren
8/1/2006 08:31:56 AM

Study Endpoints and Label Development (SEALD) Team
Review of Physician Labeling Rule (PLR) Labeling

Subject: Proposed Labeling Format Review

Application Number: NDA 22-047

Applicant: AstraZeneca

Drug Names: Seroquel (quetiapine fumarate)

Receipt Date: 7/17/06
SEALD Review Date: 1/5/07

Project Manager: Kimberly Updegraff
Review Division: Division of Psychiatric Products

SEALD Reviewer: Robin Anderson, RN, MBA
SEALD Director Concurrence: Laurie Burke, RPh, MPH

Executive Summary

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

SEALD Comments

HIGHLIGHTS:

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(6) and (d)(8)]

- The "Initial US. Approval: pending" statement should not be in all capital letters. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Revise the Boxed Warning so that the title is in all capital letters. The required statement ***See full prescribing information for complete boxed warning*** should appear immediately after the title. Add cross-references to each bulleted statement. The Boxed Warning should read:

WARNING: MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA
See full prescribing information for complete boxed warning.

- **Atypical antipsychotic drugs may rarely lead to an increased risk of death (add cross-reference)**
- **Causes of death are variable (add cross-reference)**
- **Quetiapine is not approved for elderly patients with Dementia-Related Psychoses (add cross-reference).**

[See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Since there are no recent major changes, please delete this section heading. [See 21 CFR 201.56(d)(4)].

- Add a cross-reference after the bullet under Indications and Usage. [See 21 CFR 201.56(d)(3)]

- Create bulleted statements under Dosage and Administration and include cross-references for all statements. [See 21 CFR 201.56(d)(3)]

- Under Adverse Reactions, your proposed required statement currently reads:

  To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch (b) (4)

  The AstraZeneca phone number must connect callers directly to a location for voluntary reporting of adverse events. A general phone number that is not specifically designated for adverse event reporting should not be included. Also, (b) (4) should be deleted since it is not included in the required statement. [See 21 CFR 201.57(a)(11)]

- Add "Revised:" before the month/year after the required statement "**See 17 for PATIENT COUNSELING INFORMATION**". [See 21 CFR 201.57(a)(15)]

FULL PRESCRIBING INFORMATION: CONTENTS

- Add an asterisk and use all capital letters for the title "**Full Prescribing Information: Contents**".
  [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Limit contents to one-half page in length, in 8 point type, two-column format. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Unbold the section subheadings. Only section headings should be bolded. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

- Section and subsection headings can only be numbered. Do not number headings within a subsection (e.g. 2.3.1 Maintenance Treatment). Use headings without numbering (e.g., *Maintenance Treatment*). Please correct in Highlights, Contents and the FPI. [See 21 CFR 201.5(c)]

- The required subsections under 9 Drug Abuse and Dependence are named the following:

  9.1 Controlled Substance
  9.2. Abuse
  9.3 Dependence

  Please revise in both Contents and the FPI. [See CFR 201.57(c)(10)]

- Add the required footnote "*Sections or subsections omitted from the full prescribing information are not listed" at the end of Contents. [See http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.]

FULL PRESCRIBING INFORMATION

- Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use bold print or capitalize the section headings in cross-references. For example, *[see Clinical Pharmacology (12)]*, not [see **CLINICAL PHARMACOLOGY** (12)]. Please fix your cross-references throughout the FPI. [Implementation Guidance]

- Under Adverse Reactions, you refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise your Adverse Reactions section accordingly.

Recommendations

After the comments are conveyed to the applicant and revised labeling is submitted, please check to ensure that comments have been addressed and incorporated into the labeling. At the first labeling meeting, use the applicant's updated (revised) draft labeling for review.

Appendix A: Applicant's Proposed Labeling

Attached product labeling in WORD reviewed (structured product labeling (SPL) not submitted as of this date, to be submitted on 1/8/07).

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

Robin E Anderson
1/8/2007 09:57:14 AM
CSO

Laurie Burke
1/9/2007 07:02:01 PM
INTERDISCIPLINARY