

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022047Orig1s000

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

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

DATE RECEIVED: December 4, 2006

DESIRED COMPLETION DATE:

OSE Review #: 2006-1182

DATE OF DOCUMENT:

March 10, 2007

OSE Review #: 2006-975

November 30, 2006

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
Seroquel XR (alternate)
(Quetiapine Fumarate Extended- release) Tablets
50 mg, 200 mg, 300 mg, and 400 mg

NDA#: 22-047

NDA SPONSOR: AstraZeneca

RECOMMENDATIONS:

1. DMETS remains unconvinced that SR is an appropriate modifier for the product, and thus maintains that the proprietary name, Seroquel SR, should not be used.
2. DMETS concludes that the XR modifier is an acceptable choice for the proposed product, and does not object to the use of the proprietary name, Seroquel XR.
3. DMETS believes that it is likely that errors will occur as a result of Seroquel and Seroquel XR confusion. The ideal approach to minimizing this type of confusion would be to request the sponsor reformulate so that the product strengths do not overlap. DMETS believes that the risks inherent to the use of a modifier for this product line extension should be addressed by the actions proposed by the sponsor in the submissions dated November 30, 2006 and December 19, 2005 including: actions to educate health care practitioners about the differences between immediate- and the extended-release formulation of Seroquel; the use of a "Once-A-Day-Dosing" descriptor on package labels, the intagliation of the Seroquel XR tablets with 'XR' and strength. DMETS will also provide recommendations in OSE review# 2006-658 for modifications that could improve the label, labeling and packaging from a medication errors perspective.
4. DDMAC finds the proprietary name, Seroquel XR, acceptable from a promotional perspective.
5. 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 (see section D-3).

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**

REBUTTAL AND ALTERNATE PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 1, 2007

NDA#: 22-047

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

NDA HOLDER: AstraZeneca

I. INTRODUCTION:

This consult is in response to a November 1, 2006, submission from AstraZeneca requesting reconsideration of the proprietary name, Seroquel SR. The Division of Medication Errors and Technical Support (DMETS) previously objected to the use of the proprietary name, Seroquel SR, because the SR modifier is ambiguous and may not convey the dosing or formulation differences between the immediate-release (two to three times a day) and extended-release (once daily) Seroquel products (OSE Consult # 06-0022).

AstraZeneca also requests consideration of Seroquel XR as an alternative candidate to Seroquel SR for the proposed product. The Sponsor has provided a Drug Safety Institute study of the proposed proprietary name, Seroquel XR, for review. In response to a request from the Division of Psychiatry Products (HFD-130), DMETS will assess the proprietary name "Seroquel XR" at this time for potential confusion with other proprietary or established drug names. A separate review (OSE# 2006-658) of the proposed labeling and packaging for Seroquel SR/Seroquel XR is forthcoming and will be forwarded to the Division.

II. BACKGROUND:

In OSE Consult 06-0022, DMETS did not recommend use of the proprietary name, Seroquel SR,

DMETS' primary concern with the proprietary name, Seroquel SR, was that SR modifier is ambiguous and may not convey the dosing or formulation differences between the immediate-release (two to three times a day) and extended-release (once daily) Seroquel products. At the time of the review, DMETS identified nine prescription products that utilized the SR modifier, and noted that the products had a range of dosing intervals. On this basis, DMETS concluded that the SR modifier is ambiguous, and does not convey to healthcare practitioners that the product should be dosed on a daily basis.

Additionally, DMETS recommended against the use of the SR modifier for the once-daily dosage formulation of Seroquel based on concern that use of the SR modifier for a once-daily product may undermine the initiatives set forth by the Institute of Medicine (IOM)¹ and the National Coordinating

¹ Institute of Medicine, "Preventing Medication Errors." July 20 2006.

Council for Medication Error Reporting and Prevention (NCC MERP)². In a report issued by the IOM, FDA was urged to standardize abbreviations, acronyms, and terms to the extent possible (see recommendation number four in the report for detail). FDA participated in a meeting sponsored by NCC MERP entitled “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. Interested stakeholders, including representatives from industry, also participated in the NCC MERP meeting. Together, FDA, industry, and other stakeholders heard from practicing health care practitioners at this meeting to stop approving drug name modifiers that are ambiguous and error prone. The use of SR for the once-daily formulation of Seroquel is ambiguous, and therefore counterproductive towards FDA’s efforts to integrate the recommendations and initiatives set forth by the IOM and the NCC MERP into regulatory decisions.

Therefore, DMETS recommended that the Sponsor propose a suffix that would communicate to healthcare practitioners that this product is to be dosed once a day (see section D-2 of OSE Consult 06-0022). Specifically, DMETS recommended that the Sponsor propose a modifier that has been used only for once daily dosing. The Sponsor has proposed the suffix ‘XR,’ which this review will analyze (see Section III, page 5)

Lastly, DMETS expressed concern in the review regarding the established name for the Seroquel SR/Seroquel XR product. DMETS requested that the Division consult Richard Lostritto of the CDER Labeling and Nomenclature Committee (LNC), on the correct nomenclature for this product. The sponsor proposes to utilize "sustained-release" to describe the formulation (i.e., Quetiapine sustained-release tablet). However, this is not a recognized dosage form in the United States Pharmacopeia.

PRODUCT INFORMATION

Seroquel

Seroquel was approved on September 26, 1997. It is indicated for the treatment of bipolar disorder and the treatment of schizophrenia. Currently, Seroquel is marketed in 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, and 400 mg oral tablet strengths. The effective therapeutic target dose range is 300 mg to 300 mg in two or three divided doses.

Seroquel SR/Seroquel XR

Seroquel SR is an addition to the currently marketed product line. Seroquel SR is an atypical psychotropic agent proposed to treat schizophrenia. The available marketed strengths will be 50 mg, 200 mg, 300 mg, and 400 mg sustained-release tablets. The effective therapeutic target dose range is 400 mg to 800 mg once daily.

III. REBUTTAL

DMETS re-reviewed the data submitted with the December 19, 2005 submission along with the additional measures proposed in the November 1, 2006 submission that the Sponsor believed would help to assure Seroquel SR is differentiated from Seroquel in the marketplace. However, DMETS remains unconvinced that SR is an appropriate modifier for the product, and thus maintains that the proprietary name, Seroquel SR, should not be used.

DMETS also noted that the Sponsor proposed additional measures to differentiate the products in the marketplace including health care practitioner education, using a “Once-A-Day-Dosing” descriptor on

² NCC MERP: The First Ten Years, “Defining the Problem and Developing Solutions.” December 2005, page 11.

package labels, and intagliating the tablet with the modifier and strength, appear to be worthwhile endeavors from a medication safety perspective, though they do not help establish ‘SR’ as an appropriate modifier for this product. DMETS believes that these additional measures should be pursued by the Sponsor regardless of the modifier employed to help ensure clear differentiation of the extended-release product and Seroquel in the marketplace.

When product lines are extended, a current practice is to add a modifier to the root name to convey differences in product formulation or to introduce a different proprietary name to the new formulation and use dual tradenames for the same active ingredient in the marketplace. From a medication errors perspective, both of these practices have known risks which must carefully be considered when evaluating a product line extension. In this situation, the Sponsor states that they have chosen to use a modifier for the product line extension instead of using dual tradenames for the quetiapine products to avoid a situation in which patients could inadvertently receive two products containing the same active ingredient.³ DMETS agrees that the use of a modifier instead of dual tradenames should help to minimize this potential error. However, in doing so, the Sponsor has accepted risks that may be introduced by the use of a modifier. Specifically, it is common for modifiers to be omitted from prescriptions or medication,⁴ and, when included, modifiers can be overlooked by practitioners. For the proposed Seroquel SR product, the omission or oversight of the SR modifier would almost certainly result in the dispensing or administration of Seroquel because of the overlapping product characteristics.

In an ideal situation, FDA would have guidance available to assist in the selection of modifiers. The Sponsor is accurate in noting that, in fact, there is no existing guidance to serve this function. However, DMETS’ evaluation of modifiers must continue on a case by case basis, and, in the interim, is informed by the initiatives set forth for FDA by National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), and the Institute of Medicine (IOM). With respect to modifiers, members of the NCC MERP along with industry heard the requests of practicing healthcare practitioners for FDA to stop approving modifiers that are ambiguous and error-prone,⁵ and the IOM has urged the Agency to standardize abbreviations, acronyms and terms to the extent possible.⁶

In light of these initiatives, DMETS believes that the SR modifier is not appropriate for this product because the modifier is ambiguous. The Sponsor’s assertion that “most currently used modifiers are linked to specific characteristics of dosage form, and not the dosing frequency” is incorrect and fails to take into account the practitioners’ point of view. Currently, there are a number of modifiers used to denote “extended-release” dosage forms of various products marketed. In many cases, DMETS believes that these modifiers link to specific characteristics of dosage form and dosing frequency. ‘SR’, ‘XR’, ‘XL,’ and ‘LA’ are examples of modifiers used to describe extended-release product formulations marketed in the U.S. While ‘XR,’ ‘XL,’ and ‘LA’ appear to mainly be associated with extended-release products that are dosed once daily, ‘SR’ is a modifier more often used for extended-release formulations of products dosed several times daily (e.g., BID, TID, QID). In this instance, the most notable difference from the practitioners’ point of view is the products release *and* the dosing interval: Seroquel SR/Seroquel XR is an extended release formulation with once-daily dosing, while Seroquel is an immediate release formulation dosed two or three times daily.

Because DMETS does not believe that the ‘SR’ modifier clearly conveys the difference in the product formulation (extended-release) and dosing interval (once-daily), DMETS concludes that the ‘SR’ modifier is ambiguous. As such, DMETS maintains that the SR modifier is not an appropriate choice for the proposed product, and recommends against the approval, of the proprietary name Seroquel SR.

³ Refer to November 30, 2006 submission for detail.

⁴ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

⁵ NCC MERP meeting “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. October 2005.

⁶ July 20, 2006, Institute of Medicine (IOM) Report “Preventing Medication Errors” recommendation number four

DMETS believes that the Sponsor should employ a modifier that best indicates the extended release formulation and once daily dosing, in recognition of the medication safety initiatives set forth by the IOM and NCC MERP.

IV. RISK ASSESSMENT OF SEROQUEL XR:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{7,8}, as well as several FDA databases^{9,10} for existing drug names which sound-alike or look-alike to Seroquel XR to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted¹¹. The Saegis¹² Pharma-In-Use database was searched for drug names with potential for confusion.

An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Seroquel XR. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Seroquel XR, acceptable from a promotional perspective.
2. Ten product names were identified in the Expert Panel Discussion (EPD) that was thought to have potential for confusion with Seroquel SR. However, Serpasil, Ser-Ap-Es, Ser-a-Gen-Seromycin, Serophene, Symmetrel, and Serocalm will not be reviewed further because there are no documented cases of name confusion with the currently marketed Seroquel product, and the addition of the XR modifier is not thought to increase the potential for name confusion. Although there is one documented case of name confusion with Seroquel in AERS (see page 7 for detail), the name Serentil will not be reviewed further. DMETS does not believe the addition of the XR modifier will exacerbate the existing name confusion with Serentil, which is also no longer marketed in the U.S.¹³. The remaining products identified,

⁷ MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

⁸ Facts and Comparisons, 2007, Facts and Comparisons, St. Louis, MO.

⁹ The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.

¹⁰ Phonetic and Orthographic Computer Analysis

¹¹ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

¹² WWW location <http://www.uspto.gov/tmdb/index.html>.

¹³ According to drugs@fda (accessed 2/5/2007), the product Serentil (Mesoridazine besylate) is discontinued and there are no generic products available.

Seroquel and Serzone, are listed in table 1 (see below) with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by EPD

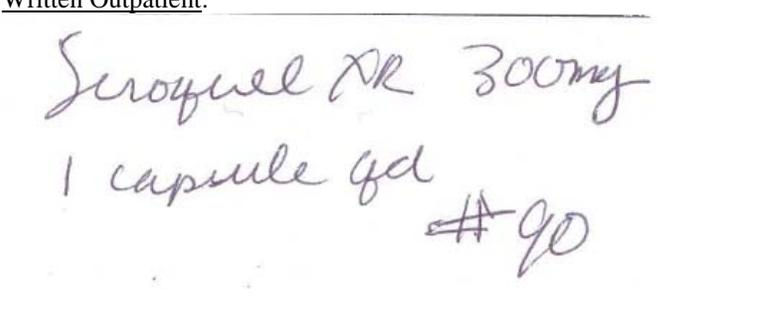
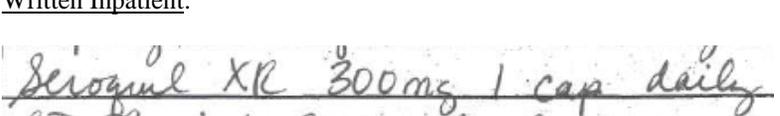
Product Name	Established name, Dosage form(s)	Usual adult dose*	Other
Seroquel XR	Quetiapine Fumarate Extended-release Tablets, 50 mg, 200 mg, 300 mg, and 400 mg	Dose range is 400 mg to 800 mg once daily	
Seroquel	Quetiapine Fumarate Tablets, 25 mg, 50 mg, 200 mg, 300 mg, 400 mg	Initially 25 mg twice daily. Increase by 25 – 50 mg two to three times per day on the 2 nd and 3 rd day to a target range of 300 – 400 mg per day given in 2 to 3 divided doses.	Look-alike, Sound-alike
Serzone (Discontinued, generic products still marketed)	Nefazodone Hydrochloride Tablets, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	Usual dose is 50-600 mg, given once or twice daily.	Look-alike

*Frequently used, not all-inclusive.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Seroquel XR with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). These exercises were conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Seroquel XR (see page 7). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Written Outpatient:</u></p> 	<p>Seroquel XR 300 mg One capsule by mouth qd. Dispense 90.</p>
<p><u>Written Inpatient:</u></p> 	

2. Results:

Of the 36 respondents in the prescription analysis studies, a total of two respondents (one from the written inpatient study, one from the written outpatient study) misinterpreted the name as Seroquel, omitting the modifier from the proposed proprietary name. Seroquel is currently marketed in the U.S. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Seroquel XR is an addition to the Seroquel product line. The immediate-release tablet formulation of Seroquel was approved on September 26, 1997. Therefore, the Adverse Event Reporting System (AERS) was searched for post-marketing safety reports concerning medication errors associated with Seroquel from February 1, 2006 to February 28, 2007. This time-period was chosen to identify new issues with Seroquel that were not available for analysis for the previous DMETS consult (OSE consult # 06-0022). The MedDRA Preferred Term (PT) “Medication Error” and the product name “Seroquel” were used as search criteria. A total of four new reports of medication errors concerned name confusion between Seroquel and Serzone. The narratives are listed in Appendix B.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Seroquel XR, the primary concern relating to look-alike and sound-alike confusion with Seroquel XR is with the existing immediate-release tablet of quetiapine called Seroquel.

DMETS conducted prescription studies to simulate the prescription ordering process. Although most of the responses were misspelled phonetic variations of Seroquel XR there were two respondents from the written inpatient study who misinterpreted the name as Seroquel.

The AERS search identified 4 new cases of name confusion between Serzone and Seroquel. This issue was previously reviewed by DMETS, and therefore will not be re-reviewed in this consult. However, it is important to note that while the marketing of Serzone was discontinued as of June 14, 2004, the generic “Nefazodone” is still available in the US and many prescribers may continue to order the drug by the proprietary name “Serzone”. Because the use of the name “Serzone” when prescribing has continued, name confusion between Seroquel and Serzone persists (see Appendix B). Given the existing confusion between Seroquel and Serzone, DMETS believes that it is possible that confusion may occur between Serzone and Seroquel XR may occur, despite the addition of the modifier. The product characteristics of Seroquel XR and Serzone (oral tablets in both 50 mg and 200 mg strengths) overlap, and there is a risk of omitting or overlooking the modifier. However, DMETS does not believe that the addition of the modifier is likely to exacerbate the existing name confusion, since neither Serzone nor Nefazodone are currently marketed in extended-release forms.

The previous DMETS consult (OSE# 06-0022) also identified potential for name confusion with Seroquel SR and Zoloft or Sinequan based on a review of post-marketing medication errors reports. DMETS believes that this is also a concern with Seroquel XR. Zoloft is available as a 50 mg oral tablet which can be dosed once a day and Sinequan is available as a 50 mg oral capsule which can be dosed once a day. These product characteristics overlap with Seroquel XR which is proposed to have a 50 mg oral tablet strength and will be dosed once daily. Even though both Zoloft and Sinequan share overlapping product characteristics with Seroquel, the Agency has only received one error report to date involving Seroquel and either Zoloft or

Sinequan. Therefore, at this time we do not believe that the addition of the extended-release product will increase the risk for error between these products.

1. Extension of an Existing Product Line

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. Medication errors with product line extensions also result from the nomenclature of the product line. Specifically, it is common for modifiers to be omitted from prescriptions or medication,¹⁴ and, when included, modifiers can be overlooked by practitioners. In fact, two respondents of the written prescription study overlooked the XR modifier (see page 7).

For the proposed Seroquel XR product, the omission or oversight of the XR modifier would almost certainly result in the dispensing or administration of Seroquel because of the overlapping product characteristics. Seroquel XR and Seroquel overlap in established name (Quetiapine), indication (schizophrenia), product strength (50 mg, 200 mg, 300 mg, and 400 mg), route of administration (oral), and dosage form (tablet). In addition, both Seroquel XR and Seroquel share an overlapping target dose. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. However, the two drugs differ in dosing frequency (once daily vs. two to three times daily). DMETS is concerned with the potential consequences of a medication error if a prescription for Seroquel is filled with Seroquel XR or vice versa because the modifier may not adequately minimize confusion between these products. However, according to the sponsor, even if the two dosage forms (Seroquel given twice daily and Seroquel XR given once daily at the same daily dose) are inadvertently switched for one another, the total daily dose is comparable over a 24-hour time period and is unlikely to result in any untoward effects.

It is imperative that healthcare practitioners are educated about the existence of this extended-release formulation and understand the differences between the immediate-release and extended-release Quetiapine products. DMETS recommends that the Sponsor integrate the Seroquel XR tablets with 'XR' and the strength. It is also essential that the product labeling highlight the differences between the products to further reduce the potential for medication errors. Specific recommendations to improve the proposed labeling for Seroquel XR will be provided in OSE review # 2006-658. Even with practitioner education and labeling modification, we will likely see errors. Therefore, the ideal approach to minimizing this type of confusion would be to request the sponsor reformulate so that the product strengths do not overlap.

2. "XR" Modifier

DMETS has acknowledged that an accepted practice to convey differences in product formulation is to include an appropriate modifier. In this instance, the sponsor has proposed to modify the root name, Seroquel, with the modifier 'XR'.

Currently, there are nineteen prescription products listed in the Orange Book, drugs@FDA, and DSS that use the "XR" modifier [Adderall XR, Augmentin XR, (b) (4) XR, Cipro XR, Dilacor XR⁺, Dilt-XR⁺, Effexor XR, Focalin XR,

¹⁴ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

*** Proprietary and confidential information that should not be released to the public.

Glucophage XR, Lodrane XR⁺, (b) (4) Proquin XR⁺, Sanctura XR^{***}, Tanacof XR⁺, Tegretol XR, Tusso-XR⁺, Voltaren XR, Xanax XR, and Zerit XR (discontinued)]. For six of these drug products⁽⁺⁾, no immediate release product is available on the market. For the remaining drug products, the immediate release products were dosed twice daily (n=7), three times daily (n=5), or “q 4 to 6 hours” (n=1).

Most of the “XR” drugs that represent product line extensions are dosed once daily (n=14) with the remaining five dosed twice daily/three times daily (n=5). Of the five drug products not dosed once daily, three were monograph drug products (Tanacof XR, Tusso-XR, Lodrane XR), and one (Tegretol XR) was approved in 1996 and thus not reviewed by DMETS/OPDRA. The remaining name, Augmentin XR, was reviewed by DMETS and approved by the Agency in 2002. Unfortunately, the name Augmentin XR was reviewed prior to the release of the Institute of Medicine report “Preventing Medication Errors” (2006)¹⁵ or the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) meeting on “Drug Name Suffixes and Medication Errors” (2005)¹⁶ which identified safety concerns with ambiguous modifiers and these concerns are being addressed in DMETS’s current review practices.

Despite the fact that 5 products have twice-daily dosing and use the ‘XR’ modifier, in DMETS opinion, the XR modifier adequately captures the most notable differences between Seroquel XR and Seroquel from a healthcare practitioner’s standpoint: the extended release formulation and the dosing interval (once-daily). As such, DMETS concludes that the XR modifier is an acceptable choice for the proposed product, and does not object to the use of the proprietary name, Seroquel XR.

3. Potential for the XR modifier misinterpretation

When considering the use of the “XR” modifier for Seroquel XR, DMETS also considered whether the modifier could be misinterpreted. A review of post-marketing medication errors found that “XR” has been misinterpreted as “x 2.”¹⁷ This would involve an inpatient order and to adhere to JCAHO requirements, the practitioner would need to indicate strength. The order of the prescription would most likely be presented as name-modifier-strength (e.g. Seroquel XR 50 mg) not name-strength-modifier (e.g. not Seroquel 50 mg XR); thus, minimizing the potential for confusion.

4. Established Name

As we noted in a previous review (see OSE #06-0022), the Sponsor proposes to utilize “sustained-release” to describe this formulation (i.e., Quetiapine sustained-release tablet). However, this is not a recognized dosage form in the United States Pharmacopeia. We recommend consulting Richard Lostritto of the CDER Labeling and Nomenclature Committee (LNC), on the correct nomenclature for this product.

¹⁵ July 20, 2006, Institute of Medicine (IOM) Report “Preventing Medication Errors” recommendation number four

¹⁶ NCC MERP meeting “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. October 2005.

¹⁷ “Safety brief” in *ISMP Medication Safety Alert! Acute Care Edition*. Volume 1, Issue 21. October 23, 1996. See Appendix C for full text.

E. BRAND INSTITUTE NAME ANALYSIS

The Drug Safety Institute (DSI) division of the Brand Institute conducted an analysis of the proprietary name, Seroquel XR, from a safety perspective. Based on the findings of their analysis, DSI supported the use of the name, Seroquel XR, for the extended-release formulation of Queitapine Fumarate.

The analysis conducted by DSI identified the following names that were not identified as potential sound or look-alike products by DMETS: Effexor XR, Elavil, Ferro-Sequels, Serophene, Serostim, Sinemet CR, Tegretol XR, and Wellbutrin XL. Following review of these proprietary names, DMETS agrees with DSI that the aforementioned names do not pose a significant safety risk due to lack of convincing sound-alike and look-alike properties and product differences.

The analysis also identified the following names that were identified as potential sound or look-alike products by DMETS: Sinequan, Seroquel, and Serzone. Following review of the proprietary name, Sinequan, DMETS concurs with DSI that the name does not pose a significant safety risk due to sound-alike and look-alike properties and because the Agency has only received one report of Seroquel and Sinequan confusion to date.

However, DMETS does believe that there is potential for confusion with Seroquel XR and Serzone or Seroquel. Despite discontinuation of the product Serzone, confusion is still occurring between Serzone and Seroquel. Label revisions and an education program were implemented to help reduce error. The introduction of Seroquel XR may impact further on this existing confusion, though at this time DMETS has no reason to believe the introduction of the modifier will exacerbate the existing confusion.

In addition, DMETS believes it is likely that we will see errors resulting from Seroquel and Seroquel XR confusion, because the modifier could be omitted or overlooked and a majority of the products characteristics for these products overlap. However, DMETS has concluded that the XR modifier is an acceptable choice for the proposed product, and did not object to the use of the proprietary name, Seroquel XR. In order to counteract the potential risk of confusion with Seroquel XR and Seroquel, DMETS provided several recommendations aimed to minimize the potential for confusion with Seroquel XR and Seroquel (refer to Safety Evaluator Risk Assessment for detail, and forthcoming OSE consult # 2006-658). Therefore, DMETS concurs with the overall findings of the DSI study.

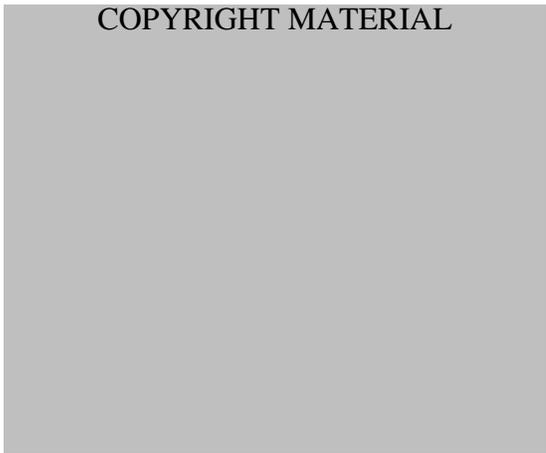
Appendix B: AERS Cases for Seroquel

ISR NUMBER FDA RECEIVED DATE SETTING LOCATION OUTCOME	Type of Error	Summary
5196828-3 12/29/2006 Community pharmacy Not provided Crying, "sick feeling" vertigo	Wrong drug	A 39 year-old female presented a hand-written prescription for Serzone 100 mg to a pharmacy. The name was misinterpreted as Seroquel. The patient took Seroquel 100 mg for approximately 2 weeks, and suffered adverse effects that the physician attributed to withdrawal of Nefazodone. The error was discovered when the patient returned to the pharmacy with a new prescription for Serzone.
5082313-5 08/16/2006 Community pharmacy (b) (4) Error discovered prior to ingestion	Wrong drug	A 61 year-old male submitted a prescription for Serzone 100 mg but the pharmacy dispensed Seroquel 100 mg. The patient discovered the error.
5126734-1 06/07/2006 Outpatient (b) (4) Unknown	Wrong drug	A 50 year-old male patient was ordered for Serzone 100 mg bid. The order was typed and dispensed as Seroquel 25 mg bid in October of 2005. The following day, a nurse called and said the patient did not receive the Serzone. Every four weeks until October of 2006 the patients medication were reordered and dispensed, perpetuating the Seroquel error. The error was discovered in October 2006 by a visiting nurse that noted Seroquel was not on the med sheet.
4900028-9 02/03/2006 Outpatient Unknown Muscle pain, weakness, fatigue, diarrhea, headaches	Wrong drug	A 58 year-old female patient was ordered for Serzone 600 mg qhs. The patient routinely took three tablets of Serzone 200 mg. The pharmacy dispensed Seroquel 200 mg, and the patient took one dose of 3 tablets (600 mg) at bedtime. The patient awoke at 11 pm with pains in the legs (muscle spasms), found herself unable to stand, and felt she was 'dying'. The patient also reported having overall weakness, fatigue, diarrhea, and posterior headaches for 10 days following the error.

Appendix C: Misinterpretation of the XR modifier

“Safety brief” in *ISMP Medication Safety Alert! Acute Care Edition*. Volume 1, Issue 21. October 23, 1996.

COPYRIGHT MATERIAL



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

/s/

Kellie Taylor
3/2/2007 04:00:34 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/2/2007 04:09:15 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): HFD-420 Division of Medication Errors and Technical Support (DMETS) Attention: Diane Smith			FROM: HFD-130/ Division of Psychiatry Products Kim Updegraff, Regulatory Project Manager		
DATE December 4, 2006	IND NO.	NDA NO. 22-047	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT November 30, 2006	
NAME OF DRUG Seroquel SR Seroquel XR (quetiapine sustained-release tablets)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Schizophrenia	DESIRED COMPLETION DATE March 10, 2007	
NAME OF FIRM: AstraZeneca					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review	
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
<p>AstraZeneca has responded to the comments we sent in a letter dated 11/1/06 (the letter and the DMETs consult are attached). Please review the submission. The sponsor mentions two names, Seroquel SR and Seroquel XR. This was an electronic submission and can be accessed in the EDR via the following link \\CDSESUB1N22047\N_000\2006-11-30, the labeling is listed under SR-Rtl_Lbls. If you have any questions, please contact Kim Updegraff (32201) PDUFA date: 5/17/07. THANK YOU !!!</p>					
SIGNATURE OF REQUESTER Kimberly Updegraff, BSP, MS, RPh Regulatory Project Manager 301-796-2201 Kimberly.Updegraff@fda.hhs.gov			METHOD OF DELIVERY (Check one) X MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

CONSULTATION RESPONSE

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

DATE RECEIVED: January 23, 2006	DESIRED COMPLETION DATE: April 20, 2006	OSE Review #: 06-0022
DATE OF DOCUMENT: December 19, 2005		
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:	Nora Roselle, PharmD, Team Leader 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	
IND#:	45,456	
IND SPONSOR:	AstraZeneca	
RECOMMENDATIONS:	<ol style="list-style-type: none">1. DMETS does not recommend use of the modifier ‘SR’ for this product. DMETS recommends that the sponsor propose a suffix that would communicate to healthcare practitioners that this product is to be dosed once a day (see section D-2). Despite the addition of a suitable modifier, the sponsor will need to educate healthcare professionals and patients on the appropriate use of this once daily extended-release formulation, in relation to the other approved dosage formulations of quetiapine fumarate, to avoid confusion between the immediate-release and this extended-release product. DMETS recommends a “usual dosage” statement be included on the extended-release formulation container label that reads “ONCE DAILY”. Ideally to avoid confusion between these two dosage forms, consideration should be given to reformulation so that the doses do not overlap (see sections D1 – D2).2. DMETS requests that upon receipt, the labels and labeling be submitted for review and comment.3. DDMAC finds the proprietary name, Seroquel SR, acceptable from a promotional perspective.4. DMETS recommends consulting Guiragos Poochikian 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 (see section D-3). <p>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 Diane Smith, project manager, at 301-796-0538.</p>	

**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**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 6, 2006
IND#: 45,456
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), for assessment of the proprietary name “Seroquel SR”, regarding potential name confusion with other proprietary or established drug names. Seroquel was approved on September 26, 1997. It is marketed in 25 mg, 50 mg, 100 mg, 150 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. A Drug Safety Institute study, draft container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Seroquel SR is an atypical psychotropic agent being developed for the treatment of schizophrenia and other mental illnesses. The available marketed strengths will be 50 mg, 200 mg, 300 mg, and 400 mg sustained-release tablets. The effective therapeutic target dose range is 400 mg to 800 mg once daily.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Seroquel SR to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient)

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2006, Facts and Comparisons, St. Louis, MO.

³ The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis

⁵ Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at www.thomson-thomson.com

⁶ WWW location <http://www.uspto.gov/tmdb/index.html>.

and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Seroquel SR. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Seroquel SR, acceptable from a promotional perspective.
2. One product name was identified in the Expert Panel Discussion (EPD) that was thought to have potential for confusion with Seroquel SR. This product is listed in table 1 (see below), along with the dosage forms available and usual dosage.

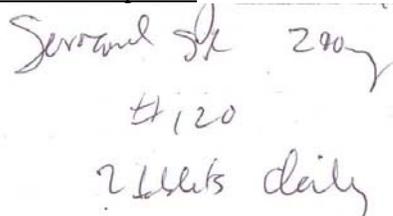
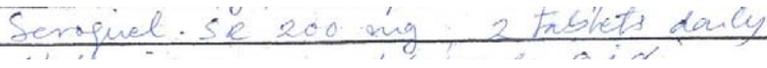
Table 1: Potential Sound-Alike/Look-Alike Names Identified by EPD

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other
Seroquel SR	Quetiapine Fumarate Extended-release Tablets, 50 mg, 200 mg, 300 mg, and 400 mg	Dose range is 400 mg to 800 mg once daily	
Seroquel	Quetiapine Fumarate Immediate-release Tablets, 25 mg, 50 mg, 200 mg, 300 mg, 400 mg (the 50 mg and 400 mg strengths are recently approved and not yet marketed)	Initially 25 mg twice daily. Increase by 25 – 50 mg two to three times per day on the 2 nd and 3 rd day to a target range of 300 – 400 mg per day given in 2 to 3 divided doses.	Look-alike, Sound-alike
*Frequently used, not all-inclusive.			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Seroquel SR with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). These exercises were conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Seroquel SR (see page 4). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Written Outpatient:</p>  <p>Seroquel SR 200mg #120 2 tablets daily</p>	<p>Seroquel SR 200 mg Two tablets daily. Dispense one twenty.</p>
<p>Written Inpatient:</p>  <p>Seroquel SR 200mg 2 tablets daily</p>	

2. Results:

One respondent from the written inpatient study misinterpreted the name as Seroquel, omitting the modifier from the proposed proprietary name. Seroquel is currently marketed in the U.S. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Seroquel SR is an addition to the Seroquel product line. The immediate-release tablet formulation of Seroquel was approved on September 26, 1997. Therefore, the Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports concerning medication errors associated with Seroquel. The MEDDRA Preferred Term (PT) “Medication Error” and the product name “Seroquel” were used as search criteria. A number of reports involving Serzone and Seroquel were retrieved. Many of these were previously reviewed by DMETS, and therefore will not be re-reviewed in this consult. However, it is important to note that while the marketing of Serzone was discontinued as of June 14, 2004, the generic “Nefazodone” is still available in the US and many prescribers may continue to order the drug by its’ proprietary name. Therefore, it is possible to ascertain that confusion may occur between Serzone and Seroquel SR despite the addition of the modifier due to overlapping product characteristics (oral tablets in both 50 mg and 200 mg strengths) and the risk of omitting the modifier.

In addition, the AERS search revealed a total of seven medication error reports concerning name confusion between Seroquel and other products [Serentil (n=1), Zoloft (n=1), Seoquil (n=1), Ferro-Sequels (n=1), and Sinequan (n=1)]. The final error involved the established name for Seroquel, Quetiapine, and Quinidine (n=1). The narratives are listed in Appendix B.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Seroquel SR, the primary concern relating to look-alike and sound-alike confusion is with the existing immediate-release tablet of quetiapine called Seroquel. Additionally, a review of postmarketing medication error reports with Seroquel identified Zoloft and Sinequan as having the potential for confusion. Zoloft is available as a 50 mg oral tablet which can be dosed once a day and Sinequan is available as a 50 mg oral capsule which can be dosed once a day. These product characteristics overlap with Seroquel SR which is proposed to have a 50 mg oral tablet strength and will be dosed once daily. Even though both Zoloft and Sinequan share overlapping product characteristics with Seroquel, the Agency has only received one error report involving Seroquel and either Zoloft or Sinequan. Therefore, at this time we do not believe that the addition of the extended-release product will increase the risk for error between these products.

DMETS conducted prescription studies to simulate the prescription ordering process. Although most of the responses were misspelled phonetic variations of Seroquel SR there was one respondent from the written inpatient study who misinterpreted the name as Seroquel.

1. Extension of an Existing Product Line

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. Moreover, it is common for modifiers to be omitted⁷. In this case, if the SR modifier is omitted it is almost certain that Seroquel will be dispensed because of the overlapping product characteristics. Seroquel SR and Seroquel overlap in established name (Quetiapine), indication (schizophrenia), product strength (50 mg, 200 mg, 300 mg, and 400 mg), route of administration (oral), and dosage form (tablet).

In addition, both Seroquel SR and Seroquel share an overlapping target dose. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. However, the two drugs differ in dosing frequency (once daily vs. two to three times daily). DMETS is concerned with the potential consequences of a medication error if a prescription for Seroquel is filled with Seroquel SR or vice versa because the modifier may not adequately minimize confusion between these products. However, according to the sponsor, even if the two dosage forms (Seroquel given twice daily and Seroquel SR given once daily at the same daily dose) are inadvertently switched for one another, the total daily dose is comparable over a 24-hour time period and is unlikely to result in any untoward effects. DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation and understand the differences between the immediate-release and extended-release Quetiapine products. Moreover, all product labeling should include a descriptor indicating how the product should be dosed (e.g., “Once-A-Day Dosing” and “Twice-A-Day Dosing”) for the existing products to minimize the potential for confusion. Even with this labeling, we will likely see errors. Therefore, the ideal approach to minimizing this type of confusion would be to request the sponsor reformulate so that the product strengths do not overlap.

2. “SR” Modifier

With respect to the use of the modifier SR, DMETS is concerned that the modifier may be ambiguous and not convey the dosing or formulation differences between the immediate-release (two to three times a day) and extended-release (once daily) products.

We recognize that the accepted practice to convey differences in product formulations is to include an appropriate modifier. We also acknowledge there are nine prescription products listed in the Orange Book which use the “SR” modifier (Wellbutrin SR, Indocin SR, Dilatrate-SR, Ritalin-SR, Oramorph SR, Cardene SR, Pronestyl SR, Rythmol SR, and Isoptin SR). Three of these products (Indocin SR, Dilatrate SR, and Isoptin SR) can be dosed once a day, while the other products are dosed either two or more times a day. Since, the currently marketed products have a wide range of dosing intervals, this suffix is ambiguous and does not convey to healthcare practitioners that the product should be dosed on a daily basis. Furthermore, this confusion can be compounded because Seroquel and Seroquel SR have overlapping product strengths (50 mg, 200 mg, 300 mg,

⁷ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

and 400 mg), dosage forms (tablet) and target doses. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. There is postmarketing evidence of modifier confusion between Wellbutrin/Wellbutrin SR, Cardene/Cardene SR, and Ritalin/Ritalin SR which all have similar overlapping product profiles as Seroquel and Seroquel SR and utilize the SR modifier.

Additionally, FDA participated in a meeting sponsored by NCCMERP entitled “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. We heard from practicing health care practitioners at this meeting to stop approving drug name modifiers that are ambiguous and error prone. Moreover, the July 20, 2006, IOM Report “Preventing Medication Errors” recommendation number four, urges FDA to standardize abbreviations, acronyms, and terms to the extent possible. Because the modifier SR can have several meanings it may be beneficial to use a modifier that has been reserved for only once a day dosing.

Therefore, DMETS does not recommend the use of the proposed suffix “SR” to represent this once-a-day product. A modifier that has been used only for once daily dosing should be employed. Furthermore, because modifiers can be omitted from prescriptions, we recommend that the product labels and labeling include a descriptor indicating how the product should be dosed (e.g., “Once-A-Day Dosing” and “Twice-A-Day Dosing”) for the existing products to minimize the potential for confusion.

3. Established Name

In addition, the sponsor proposes to utilize "sustained-release" to describe this formulation (i.e., Quetiapine sustained-release tablet). However, this is not a recognized dosage form in the United States Pharmacopeia. We recommend consulting Guiragos Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC), on the correct nomenclature for this product.

E. BRAND INSTITUTE NAME ANALYSIS

The analysis conducted by the Drug Safety Institute (DSI) division of the Brand Institute identified the following names that were not identified as potential sound or look-alike products by DMETS: Elavil, Indocin SR, Insulin, Sermorelin, Serophene, Serostim, Serzone, Sinequan, Sinumist SR, Tegretol SR, and Ferro-Sequels. Following review of these proprietary names, DMETS concurs with DSI that the aforementioned names do not pose a significant safety risk due to lack of convincing sound-alike and look-alike properties and product differences. However, we note that despite discontinuation of the product Serzone, confusion is still occurring between Serzone and Seroquel. Label revisions and an education program were implemented to help reduce error. The introduction of Seroquel SR may impact further on this existing confusion. We concur with the overall findings of the study.

III. COMMENTS TO THE SPONSOR:

DMETS is concerned with the potential for confusion between the proposed extended-release tablet called Seroquel SR and the existing immediate-release tablet of quetiapine called Seroquel. Additionally, DMETS does not recommend use of the modifier ‘SR’ for this product.

1. Extension of an Existing Product Line

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. Moreover, it is common for modifiers to be omitted⁸. In this case, if the SR modifier is omitted it is almost certain that Seroquel will be dispensed because of the overlapping product characteristics. Seroquel SR and Seroquel overlap in established name (Quetiapine), indication (schizophrenia), product strength (50 mg, 200 mg, 300 mg, and 400 mg), route of administration (oral), and dosage form (tablet).

In addition, both Seroquel SR and Seroquel share an overlapping target dose. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. However, the two drugs differ in dosing frequency (once daily vs. two to three times daily). DMETS is concerned with the potential consequences of a medication error if a prescription for Seroquel is filled with Seroquel SR or vice versa because the modifier may not adequately minimize confusion between these products. However, according to the sponsor, even if the two dosage forms (Seroquel given twice daily and Seroquel SR given once daily at the same daily dose) are inadvertently switched for one another, the total daily dose is comparable over a 24-hour time period and is unlikely to result in any untoward effects. DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation and understand the differences between the immediate-release and extended-release Quetiapine products. Moreover, all product labeling should include a descriptor indicating how the product should be dosed (e.g., “Once-A-Day Dosing” and “Twice-A-Day Dosing”) for the existing products to minimize the potential for confusion. Even with this labeling, we will likely see errors. Therefore, the ideal approach to minimizing this type of confusion would be to request the sponsor reformulate so that the product strengths do not overlap.

2. “SR” Modifier

With respect to the use of the modifier SR, DMETS is concerned that the modifier may be ambiguous and not convey the dosing or formulation differences between the immediate-release (two to three times a day) and extended-release (once daily) products.

We recognize that the accepted practice to convey differences in product formulations is to include an appropriate modifier. We also acknowledge there are nine prescription products listed in the Orange Book which use the “SR” modifier (Wellbutrin SR, Indocin SR, Dilatrate-SR, Ritalin-SR, Oramorph SR, Cardene SR, Pronestyl SR, Rythmol SR, and Isoptin SR). Three of these products (Indocin SR, Dilatrate SR, and Isoptin SR) can be dosed once a day, while the other products are dosed either two or more times a day. Since, the currently marketed products have a wide range of dosing intervals, this suffix is ambiguous and does not convey to healthcare practitioners that the product should be dosed on a daily basis. Furthermore, this confusion can be compounded because Seroquel and Seroquel SR have overlapping product strengths (50 mg, 200 mg, 300 mg, and 400 mg), dosage forms (tablet) and target doses. Seroquel SR will be

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

dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. There is postmarketing evidence of modifier confusion between Wellbutrin/Wellbutrin SR, Cardene/Cardene SR, and Ritalin/Ritalin SR which all have similar overlapping product profiles as Seroquel and Seroquel SR and utilize the SR modifier.

Moreover, the July 20, 2006, IOM Report “Preventing Medication Errors” recommendation number four, urges FDA to standardize abbreviations, acronyms, and terms to the extent possible. Because the modifier SR can have several meanings it may be beneficial to use a modifier that has been reserved for only once a day dosing.

Therefore, DMETS does not recommend the use of the proposed suffix “SR” to represent this once-a-day product. A modifier that has been used only for once daily dosing should be employed. Furthermore, because modifiers can be omitted from prescriptions, we recommend that the product labels and labeling include a descriptor indicating how the product should be dosed (e.g., “Once-A-Day Dosing” and “Twice-A-Day Dosing”) for the existing products to minimize the potential for confusion.

Appendix A. Seroquel SR

Written Outpatient

Seroquel SR
Seroquel SR
Seroquel SR
Seravul
Seroquel · SR
Seroquel SR
Sevacul SR
Seroquel SR
Seronavril
Seroquel SR
Seroquel SR
Serevant SR
Seroquel SR
Sevrاند SR
Seroquel SR

Written Inpatient

Seroquel SR
Seroquel SR
Seroquel SR
Serogiel
Seroquel SR
Seroquel SR
Senoquiel SR
Seroquel SR
Seroquel SR
Senoginal-SR
Seroquel SR
Seroquel
Seroquesl
Seroquel SR
Seroquel SR
Seroquel SR
Seroquel SR

Verbal

Seroquel SR
Seraquel SR
Seroquel SR
Seroquel SR
Seraquil
Seroquel SR
Seraquil SR
Seroquel SR
Seraquil SR

Appendix B: AERS Cases for Seroquel

ISR NUMBER FDA RECEIVED DATE LOCATION OUTCOME	Summary
3309984-6 7/23/99 United States Outcome not indicated	Two drugs, whose names sound very similar, were interchanged; Serentil was dispensed instead of Seroquel.
4035421-2 1/3/03 New York Outcome not indicated	A prescription was written for Seroquel and the nurse administered Zoloft.
4088688-9 4/10/03 Oregon Outcome not indicated	We had a prescription for Quetiapine 300 mg tablets filled with Quinidine 300 mg tablets. The patient took three tablets and had no problems. It looked like the prescription was entered electronically in our system correctly, but the pharmacist picked the wrong drug off the shelf. The drugs are not stored next to each other on the shelf. When the pharmacist saw the label of quetiapine, they thought Quinidine, and went to the Quinidine location. A technician could have been involved, but I'm not sure. I don't know whether or not patient counseling was provided. I'm not sure who discovered the error, whether it was the patient, his primary care provider, or the pharmacist.
4248696-1 12/8/03 Tennessee Pt found unresponsive and taken to ER.	A report has been received from a Pharmaceutical Sales Specialist concerning a male patient in his 40s. On 09-Jun-2003, the patient was found unresponsive. EMS responded and the patient was taken to the ER. The reporter states that the product name on the bottle was Seoquil 100 mg bid and asked whether this could be Seroquel or another product. Other drugs listed include Lithium, Ambien, and Lithobid 300.
4510527-X and 4510200-8 11/22/04 California Pt had confusion and needed a psychiatric consult.	An order was placed for Ferro-Sequel (ferrous fumarate) 500 mg. The handwritten transcription was "Serrosequel 500 mg" and the order was read as "Seroquel 500 mg". It was thought that this was the home dose prior to admission. The error was possibly caused by sound-alike names, legibility, and misunderstanding of "correct read-back (possible foreign accent)." The error did reach the patient and the patient exhibited confusion and symptoms requiring a psychiatric consult. The error occurred in a hospital and a nurse discovered the error. The nurse is also the one who noticed the symptoms. The patient recovered completely.
4827923-3 11/14/05 New York Pt experienced drowsiness.	Pharmacist in an inpatient facility for substance-abuse related services, received a medication order for Sinequan 50 mg tonight (8/19), Sinequan 100 mg at bedtime on 8/20 and 8/21, Sinequan 150 mg at bedtime, nightly starting 8/22. The pharmacist dispensed Seroquel 2 X 25 mg for the 50 mg dose of Sinequan on 8/19. The nurse administered the Seroquel in place of Sinequan. 8/20 the patient complained of drowsiness and the error was discovered. Look-alike, sound-alike potential. The physicians order was clearly written, but the pharmacist thought the Rx was for SeroQUEL instead of SINEquan.

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

/s/

Thomas Laughren
12/7/2006 02:44:31 PM

CONSULTATION RESPONSE

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

DATE RECEIVED: January 23, 2006	DESIRED COMPLETION DATE: April 20, 2006	OSE Review #: 06-0022
DATE OF DOCUMENT: December 19, 2005		

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: Nora Roselle, PharmD, Team Leader
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

IND#: 45,456

IND SPONSOR: AstraZeneca

RECOMMENDATIONS:

1. DMETS does not recommend use of the modifier ‘SR’ for this product. DMETS recommends that the sponsor propose a suffix that would communicate to healthcare practitioners that this product is to be dosed once a day (see section D-2). Despite the addition of a suitable modifier, the sponsor will need to educate healthcare professionals and patients on the appropriate use of this once daily extended-release formulation, in relation to the other approved dosage formulations of quetiapine fumarate, to avoid confusion between the immediate-release and this extended-release product. DMETS recommends a “usual dosage” statement be included on the extended-release formulation container label that reads “ONCE DAILY”. Ideally to avoid confusion between these two dosage forms, consideration should be given to reformulation so that the doses do not overlap (see sections D1 – D2).
2. DMETS requests that upon receipt, the labels and labeling be submitted for review and comment.
3. DDMAC finds the proprietary name, Seroquel SR, acceptable from a promotional perspective.
4. DMETS recommends consulting Guiragos Poochikian 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 (see section D-3).

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 Diane Smith, project manager, at 301-796-0538.

**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**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 6, 2006

IND#: 45,456

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), for assessment of the proprietary name “Seroquel SR”, regarding potential name confusion with other proprietary or established drug names. Seroquel was approved on September 26, 1997. It is marketed in 25 mg, 50 mg, 100 mg, 150 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. A Drug Safety Institute study, draft container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Seroquel SR is an atypical psychotropic agent being developed for the treatment of schizophrenia and other mental illnesses. The available marketed strengths will be 50 mg, 200 mg, 300 mg, and 400 mg sustained-release tablets. The effective therapeutic target dose range is 400 mg to 800 mg once daily.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Seroquel SR to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient)

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2006, Facts and Comparisons, St. Louis, MO.

³ The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis

⁵ Data provided by Thomson & Thomson’s SAEGIS™ Online Service, available at www.thomson-thomson.com

⁶ WWW location <http://www.uspto.gov/tmdb/index.html>.

and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Seroquel SR. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Seroquel SR, acceptable from a promotional perspective.
2. One product name was identified in the Expert Panel Discussion (EPD) that was thought to have potential for confusion with Seroquel SR. This product is listed in table 1 (see below), along with the dosage forms available and usual dosage.

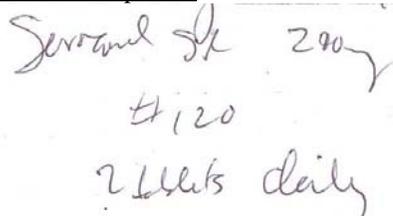
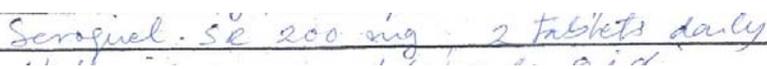
Table 1: Potential Sound-Alike/Look-Alike Names Identified by EPD

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other
Seroquel SR	Quetiapine Fumarate Extended-release Tablets, 50 mg, 200 mg, 300 mg, and 400 mg	Dose range is 400 mg to 800 mg once daily	
Seroquel	Quetiapine Fumarate Immediate-release Tablets, 25 mg, 50 mg, 200 mg, 300 mg, 400 mg (the 50 mg and 400 mg strengths are recently approved and not yet marketed)	Initially 25 mg twice daily. Increase by 25 – 50 mg two to three times per day on the 2 nd and 3 rd day to a target range of 300 – 400 mg per day given in 2 to 3 divided doses.	Look-alike, Sound-alike
*Frequently used, not all-inclusive.			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Seroquel SR with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). These exercises were conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Seroquel SR (see page 4). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Written Outpatient:</p>  <p>Seroquel SR 200mg #120 2 tablets daily</p>	<p>Seroquel SR 200 mg Two tablets daily. Dispense one twenty.</p>
<p>Written Inpatient:</p>  <p>Seroquel SR 200mg 2 tablets daily</p>	

2. Results:

One respondent from the written inpatient study misinterpreted the name as Seroquel, omitting the modifier from the proposed proprietary name. Seroquel is currently marketed in the U.S. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Seroquel SR is an addition to the Seroquel product line. The immediate-release tablet formulation of Seroquel was approved on September 26, 1997. Therefore, the Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports concerning medication errors associated with Seroquel. The MEDDRA Preferred Term (PT) “Medication Error” and the product name “Seroquel” were used as search criteria. A number of reports involving Serzone and Seroquel were retrieved. Many of these were previously reviewed by DMETS, and therefore will not be re-reviewed in this consult. However, it is important to note that while the marketing of Serzone was discontinued as of June 14, 2004, the generic “Nefazodone” is still available in the US and many prescribers may continue to order the drug by its’ proprietary name. Therefore, it is possible to ascertain that confusion may occur between Serzone and Seroquel SR despite the addition of the modifier due to overlapping product characteristics (oral tablets in both 50 mg and 200 mg strengths) and the risk of omitting the modifier.

In addition, the AERS search revealed a total of seven medication error reports concerning name confusion between Seroquel and other products [Serentil (n=1), Zoloft (n=1), Seoquil (n=1), Ferro-Sequels (n=1), and Sinequan (n=1)]. The final error involved the established name for Seroquel, Quetiapine, and Quinidine (n=1). The narratives are listed in Appendix B.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Seroquel SR, the primary concern relating to look-alike and sound-alike confusion is with the existing immediate-release tablet of quetiapine called Seroquel. Additionally, a review of postmarketing medication error reports with Seroquel identified Zoloft and Sinequan as having the potential for confusion. Zoloft is available as a 50 mg oral tablet which can be dosed once a day and Sinequan is available as a 50 mg oral capsule which can be dosed once a day. These product characteristics overlap with Seroquel SR which is proposed to have a 50 mg oral tablet strength and will be dosed once daily. Even though both Zoloft and Sinequan share overlapping product characteristics with Seroquel, the Agency has only received one error report involving Seroquel and either Zoloft or Sinequan. Therefore, at this time we do not believe that the addition of the extended-release product will increase the risk for error between these products.

DMETS conducted prescription studies to simulate the prescription ordering process. Although most of the responses were misspelled phonetic variations of Seroquel SR there was one respondent from the written inpatient study who misinterpreted the name as Seroquel.

1. Extension of an Existing Product Line

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. Moreover, it is common for modifiers to be omitted⁷. In this case, if the SR modifier is omitted it is almost certain that Seroquel will be dispensed because of the overlapping product characteristics. Seroquel SR and Seroquel overlap in established name (Quetiapine), indication (schizophrenia), product strength (50 mg, 200 mg, 300 mg, and 400 mg), route of administration (oral), and dosage form (tablet).

In addition, both Seroquel SR and Seroquel share an overlapping target dose. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. However, the two drugs differ in dosing frequency (once daily vs. two to three times daily). DMETS is concerned with the potential consequences of a medication error if a prescription for Seroquel is filled with Seroquel SR or vice versa because the modifier may not adequately minimize confusion between these products. However, according to the sponsor, even if the two dosage forms (Seroquel given twice daily and Seroquel SR given once daily at the same daily dose) are inadvertently switched for one another, the total daily dose is comparable over a 24-hour time period and is unlikely to result in any untoward effects. DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation and understand the differences between the immediate-release and extended-release Quetiapine products. Moreover, all product labeling should include a descriptor indicating how the product should be dosed (e.g., “Once-A-Day Dosing” and “Twice-A-Day Dosing”) for the existing products to minimize the potential for confusion. Even with this labeling, we will likely see errors. Therefore, the ideal approach to minimizing this type of confusion would be to request the sponsor reformulate so that the product strengths do not overlap.

2. “SR” Modifier

With respect to the use of the modifier SR, DMETS is concerned that the modifier may be ambiguous and not convey the dosing or formulation differences between the immediate-release (two to three times a day) and extended-release (once daily) products.

We recognize that the accepted practice to convey differences in product formulations is to include an appropriate modifier. We also acknowledge there are nine prescription products listed in the Orange Book which use the “SR” modifier (Wellbutrin SR, Indocin SR, Dilatrate-SR, Ritalin-SR, Oramorph SR, Cardene SR, Pronestyl SR, Rythmol SR, and Isoptin SR). Three of these products (Indocin SR, Dilatrate SR, and Isoptin SR) can be dosed once a day, while the other products are dosed either two or more times a day. Since, the currently marketed products have a wide range of dosing intervals, this suffix is ambiguous and does not convey to healthcare practitioners that the product should be dosed on a daily basis. Furthermore, this confusion can be compounded because Seroquel and Seroquel SR have overlapping product strengths (50 mg, 200 mg, 300 mg,

⁷ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

and 400 mg), dosage forms (tablet) and target doses. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. There is postmarketing evidence of modifier confusion between Wellbutrin/Wellbutrin SR, Cardene/Cardene SR, and Ritalin/Ritalin SR which all have similar overlapping product profiles as Seroquel and Seroquel SR and utilize the SR modifier.

Additionally, FDA participated in a meeting sponsored by NCCMERP entitled “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. We heard from practicing health care practitioners at this meeting to stop approving drug name modifiers that are ambiguous and error prone. Moreover, the July 20, 2006, IOM Report “Preventing Medication Errors” recommendation number four, urges FDA to standardize abbreviations, acronyms, and terms to the extent possible. Because the modifier SR can have several meanings it may be beneficial to use a modifier that has been reserved for only once a day dosing.

Therefore, DMETS does not recommend the use of the proposed suffix “SR” to represent this once-a-day product. A modifier that has been used only for once daily dosing should be employed. Furthermore, because modifiers can be omitted from prescriptions, we recommend that the product labels and labeling include a descriptor indicating how the product should be dosed (e.g., “Once-A-Day Dosing” and “Twice-A-Day Dosing”) for the existing products to minimize the potential for confusion.

3. Established Name

In addition, the sponsor proposes to utilize "sustained-release" to describe this formulation (i.e., Quetiapine sustained-release tablet). However, this is not a recognized dosage form in the United States Pharmacopeia. We recommend consulting Guiragos Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC), on the correct nomenclature for this product.

E. BRAND INSTITUTE NAME ANALYSIS

The analysis conducted by the Drug Safety Institute (DSI) division of the Brand Institute identified the following names that were not identified as potential sound or look-alike products by DMETS: Elavil, Indocin SR, Insulin, Sermorelin, Serophene, Serostim, Serzone, Sinequan, Sinumist SR, Tegretol SR, and Ferro-Sequels. Following review of these proprietary names, DMETS concurs with DSI that the aforementioned names do not pose a significant safety risk due to lack of convincing sound-alike and look-alike properties and product differences. However, we note that despite discontinuation of the product Serzone, confusion is still occurring between Serzone and Seroquel. Label revisions and an education program were implemented to help reduce error. The introduction of Seroquel SR may impact further on this existing confusion. We concur with the overall findings of the study.

III. COMMENTS TO THE SPONSOR:

DMETS is concerned with the potential for confusion between the proposed extended-release tablet called Seroquel SR and the existing immediate-release tablet of quetiapine called Seroquel. Additionally, DMETS does not recommend use of the modifier ‘SR’ for this product.

1. Extension of an Existing Product Line

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. Moreover, it is common for modifiers to be omitted⁸. In this case, if the SR modifier is omitted it is almost certain that Seroquel will be dispensed because of the overlapping product characteristics. Seroquel SR and Seroquel overlap in established name (Quetiapine), indication (schizophrenia), product strength (50 mg, 200 mg, 300 mg, and 400 mg), route of administration (oral), and dosage form (tablet).

In addition, both Seroquel SR and Seroquel share an overlapping target dose. Seroquel SR will be dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. However, the two drugs differ in dosing frequency (once daily vs. two to three times daily). DMETS is concerned with the potential consequences of a medication error if a prescription for Seroquel is filled with Seroquel SR or vice versa because the modifier may not adequately minimize confusion between these products. However, according to the sponsor, even if the two dosage forms (Seroquel given twice daily and Seroquel SR given once daily at the same daily dose) are inadvertently switched for one another, the total daily dose is comparable over a 24-hour time period and is unlikely to result in any untoward effects. DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation and understand the differences between the immediate-release and extended-release Quetiapine products. Moreover, all product labeling should include a descriptor indicating how the product should be dosed (e.g., “Once-A-Day Dosing” and “Twice-A-Day Dosing”) for the existing products to minimize the potential for confusion. Even with this labeling, we will likely see errors. Therefore, the ideal approach to minimizing this type of confusion would be to request the sponsor reformulate so that the product strengths do not overlap.

2. “SR” Modifier

With respect to the use of the modifier SR, DMETS is concerned that the modifier may be ambiguous and not convey the dosing or formulation differences between the immediate-release (two to three times a day) and extended-release (once daily) products.

We recognize that the accepted practice to convey differences in product formulations is to include an appropriate modifier. We also acknowledge there are nine prescription products listed in the Orange Book which use the “SR” modifier (Wellbutrin SR, Indocin SR, Dilatrate-SR, Ritalin-SR, Oramorph SR, Cardene SR, Pronestyl SR, Rythmol SR, and Isoptin SR). Three of these products (Indocin SR, Dilatrate SR, and Isoptin SR) can be dosed once a day, while the other products are dosed either two or more times a day. Since, the currently marketed products have a wide range of dosing intervals, this suffix is ambiguous and does not convey to healthcare practitioners that the product should be dosed on a daily basis. Furthermore, this confusion can be compounded because Seroquel and Seroquel SR have overlapping product strengths (50 mg, 200 mg, 300 mg, and 400 mg), dosage forms (tablet) and target doses. Seroquel SR will be

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

dosed as 400 mg to 800 mg once daily while the target dose range for Seroquel is 300 mg to 400 mg per day in two to three divided doses. There is postmarketing evidence of modifier confusion between Wellbutrin/Wellbutrin SR, Cardene/Cardene SR, and Ritalin/Ritalin SR which all have similar overlapping product profiles as Seroquel and Seroquel SR and utilize the SR modifier.

Moreover, the July 20, 2006, IOM Report “Preventing Medication Errors” recommendation number four, urges FDA to standardize abbreviations, acronyms, and terms to the extent possible. Because the modifier SR can have several meanings it may be beneficial to use a modifier that has been reserved for only once a day dosing.

Therefore, DMETS does not recommend the use of the proposed suffix “SR” to represent this once-a-day product. A modifier that has been used only for once daily dosing should be employed. Furthermore, because modifiers can be omitted from prescriptions, we recommend that the product labels and labeling include a descriptor indicating how the product should be dosed (e.g., “Once-A-Day Dosing” and “Twice-A-Day Dosing”) for the existing products to minimize the potential for confusion.

Appendix A. Seroquel SR

Written Outpatient

Seroquel SR
Seroquel SR
Seroquel SR
Seravul
Seroquel · SR
Seroquel SR
Sevacul SR
Seroquel SR
Seronavril
Seroquel SR
Seroquel SR
Serevant SR
Seroquel SR
Sevrاند SR
Seroquel SR

Written Inpatient

Seroquel SR
Seroquel SR
Seroquel SR
Serogiel
Seroquel SR
Seroquel SR
Senoquiel SR
Seroquel SR
Seroquel SR
Senoginal-SR
Seroquel SR
Seroquel
Seroquesl
Seroquel SR
Seroquel SR
Seroquel SR
Seroquel SR

Verbal

Seroquel SR
Seraquel SR
Seroquel SR
Seroquel SR
Seraquil
Seroquel SR
Seraquil SR
Seroquel SR
Seraquil SR

Appendix B: AERS Cases for Seroquel

ISR NUMBER FDA RECEIVED DATE LOCATION OUTCOME	Summary
3309984-6 7/23/99 United States Outcome not indicated	Two drugs, whose names sound very similar, were interchanged; Serentil was dispensed instead of Seroquel.
4035421-2 1/3/03 (b) (6) Outcome not indicated	A prescription was written for Seroquel and the nurse administered Zoloft.
4088688-9 4/10/03 (b) (6) Outcome not indicated	We had a prescription for Quetiapine 300 mg tablets filled with Quinidine 300 mg tablets. The patient took three tablets and had no problems. It looked like the prescription was entered electronically in our system correctly, but the pharmacist picked the wrong drug off the shelf. The drugs are not stored next to each other on the shelf. When the pharmacist saw the label of quetiapine, they thought Quinidine, and went to the Quinidine location. A technician could have been involved, but I'm not sure. I don't know whether or not patient counseling was provided. I'm not sure who discovered the error, whether it was the patient, his primary care provider, or the pharmacist.
4248696-1 12/8/03 (b) (6) Pt found unresponsive and taken to ER.	A report has been received from a Pharmaceutical Sales Specialist concerning a male patient in his 40s. On 09-Jun-2003, the patient was found unresponsive. EMS responded and the patient was taken to the ER. The reporter states that the product name on the bottle was Seoquil 100 mg bid and asked whether this could be Seroquel or another product. Other drugs listed include Lithium, Ambien, and Lithobid 300.
4510527-X and 4510200-8 11/22/04 (b) (6) Pt had confusion and needed a psychiatric consult.	An order was placed for Ferro-Sequel (ferrous fumarate) 500 mg. The handwritten transcription was "Serrosequel 500 mg" and the order was read as "Seroquel 500 mg". It was thought that this was the home dose prior to admission. The error was possibly caused by sound-alike names, legibility, and misunderstanding of "correct read-back (possible foreign accent)." The error did reach the patient and the patient exhibited confusion and symptoms requiring a psychiatric consult. The error occurred in a hospital and a nurse discovered the error. The nurse is also the one who noticed the symptoms. The patient recovered completely.
4827923-3 11/14/05 (b) (6) Pt experienced drowsiness.	Pharmacist in an inpatient facility for substance-abuse related services, received a medication order for Sinequan 50 mg tonight (8/19), Sinequan 100 mg at bedtime on 8/20 and 8/21, Sinequan 150 mg at bedtime, nightly starting 8/22. The pharmacist dispensed Seroquel 2 X 25 mg for the 50 mg dose of Sinequan on 8/19. The nurse administered the Seroquel in place of Sinequan. 8/20 the patient complained of drowsiness and the error was discovered. Look-alike, sound-alike potential. The physicians order was clearly written, but the pharmacist thought the Rx was for SeroQUEL instead of SINEquan.

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

/s/

Nora L. Roselle
8/4/2006 04:21:37 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/4/2006 04:23:14 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/4/2006 05:20:24 PM
DRUG SAFETY OFFICE REVIEWER