CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022047Orig1s000

ENVIRONMENTAL ASSESSMENT

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

SEROQUEL® SUSTAINED RELEASE TABLETS
(quetiapine fumarate)

NDA 22-047
Treatment of Schizophrenia and Acute Mania

Food and Drug Administration
Center for Drug Evaluation and Research

Office of New Drug Quality Assessment

November 9, 2006

Environmental Assessment Review #1， NDA 22-047
Seroquel® Sustained Release Tablets (quetiapine fumarate)
Treatment of Schizophrenia and Acute Mania

EXECUTIVE SUMMARY

Seroquel is currently approved for treatment of schizophrenia and acute mania (NDA 20-639). This environmental assessment dated June 6, 2006, supports the new drug application (NDA 22-047) for a new dosage form, a sustained release tablet. The EA was prepared in accordance with 21 CFR Part 25 by AstraZeneca Pharmaceuticals LP.

The environmental fate and effects data submitted in this EA were previously submitted in an EA for related application, NDA 20-639/S-016 and S-017 (December 30, 2002), which was reviewed and found adequate by Florian Zielinski (January 28, 2003). This EA is an update to reflect an increase in usage associated with the new dosage form.

The maxiumum quantity of quetiapine fumarate required for the new indication and all other products manufactured by AstraZeneca in any of the next 5 years is expected to be NMT (b) (4) kg/yr. The EIC of quetiapine is (b) (4)

Data previously submitted in the related EA (NDA 20-639/S-016 and S-017, December 30, 2002) included ecotoxicological studies of fish, daphnia, and algae, and showed that the most sensitive species tested is the bluegill sunfish. The EC_{50}/EIC ratio for the bluegill sunfish is 7423, which is greater than 100 (the tier 2 assessment factor). In addition the EIC is lower than the NOEC for each of the species tested. This assessment indicates that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

A FONSI is recommended.

Environmental Assessment Review #1， NDA 22-047
Seroquel® Sustained Release Tablets (quetiapine fumarate)
Treatment of Schizophrenia and Acute Mania

I. DATE: EA dated June 6, 2006, submitted July 17, 2006
EA dated June 6, 2006, re-submitted September 19, 2006

Note regarding submissions: The EA submitted July 17, 2006 failed to contain the referenced Confidential Appendix VIII. This was discussed with Mr. Norbert Ealer of AstraZeneca on August 28, 2006. On September 19, 2005 the EA was re-submitted with Confidential Appendix VIII attached.

II APPLICANT: AstraZeneca Pharmaceuticals LP

III ADDRESS: 1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

IV DESCRIPTION OF PROPOSED ACTION:

a. Requested Approval: AstraZeneca Pharmaceuticals LP filed an NDA pursuant to section 505 (b) of the FDA Act for Seroquel (quetiapine fumarate), 50 mg, 200 mg, 300 mg and 400 mg sustained release (SR) tablets packaged in bottles and hospital unit dose packages. An EA has been submitted pursuant to 21 CFR part 25.
b. Need for Action: This NDA provides for a sustained release tablet. Seroquel Tablets (quetiapine fumarate) are currently approved for treatment of schizophrenia and acute mania.
c. Locations of Use: Hospitals and households.
d. Disposal Sites: Empty or partially empty containers from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy or clinic procedures. (Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed in the sewer system.)

ADEQUATE

V IDENTIFICATION OF CHEMICALS

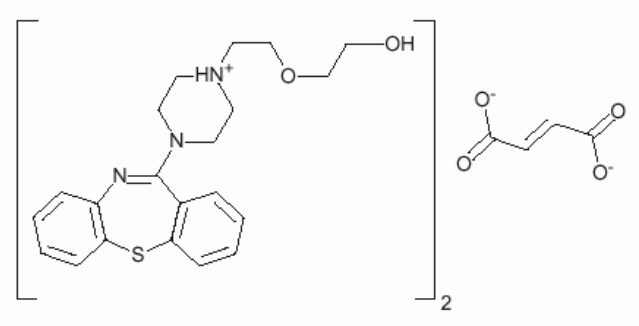
USAN Name: quetiapine fumarate

Brand Name: Seroquel Tablets

CAS Name: Ethanol[2-(2-[4-(dibenzo[b,f][1,4]-thiazepin-11-yl-1)piperazinyl)ethoxy]-(E)-2-butenedioate (2:1)

CAS Number: 111974-72-2 (quetiapine fumarate) Molecular Wt of $C_{46}H_{54}N_6O_8S_2$ is 883.1
111974-69-7 (free base) Molecular Wt of $C_{21}H_{25}N_3O_2S$ is 767
(quetiapine = 2 x base)

Molecular structure of quetiapine fumarate



ADEQUATE

VI ENVIRONMENTAL ISSUES / Assessing Toxicity to Environmental Organisms

Environmental Fate of Released Substances:
The data submitted in this section was previously submitted to an EA for an related application, NDA 20-639, S-016 and S-017, December 30, 2002 (reviewed and found adequate by Florian Zielinski on January 28, 2003). No new data is provided in this EA. In summary, it is predicted that most of the active moiety (quetiapine) is partitioned into the aqueous phase during wastewater treatment. Only 43%, however, is present in potentially active forms, since it is known that the two major metabolites show no pharmacological activity when tested *in vitro*.

Environmental Effects of Released Substances:
A summary of environmental fate and effects data is included in the EA. The complete environmental fate and effects data and related reports were previously submitted to an EA for a related application, NDA 20-639, S-016 and S-017, December 30, 2002 (reviewed and found adequate by Florian Zielinski on January 28, 2003). The toxicity of quetiapine fumarate to environmental organisms is summarized in the following table:

Test	Result
Microbial Growth Inhibition (ETAD Method 103)	No inhibition up to 100 ppm
Blue-green alga (M. aeruginosa) (21 day, TAD 4.01)	NOEC = 4 mg/L (max cell density) NOEC = 32 mg/L (growth rate)
Green alga (S. capricornutum)	NOEC = 2.5 mg/L

(14 day, TAD 4.01)	(max cell density & growth rate)
Rainbow Trout	NOEC = 1.0 ppm (96 hour) LC_{50} = 22.0 ppm (96 hour)
Bluegill Sunfish	NOEC = 1.8 ppm (96 hour) LC_{50} = 19.3 ppm (96 hour)
Daphnia magna (reproduction and length)	NOEC = 18 ppm (21 day) LOEC = 32 ppm (21 day)

Environmental Concentrations:
In this June 6, 2006 EA, the firm updated Confidential Appendix VIII for an increase in environmental concentration of the active moiety, to reflect an increase in usage of the drug associated with the new dosage form (SR tablets). The maximum quantity of quetiapine fumarate required for the new dosage form and all other products manufactured by AstraZeneca in any of the next 5 years is expected to be NMT (b) (4) kg/yr. In calculating the EIC, the firm appropriately assumed that all quetiapine ends up in the aquatic environment, but that only 43% is present in potentially active forms, since it is known that the two major metabolites are pharmacologically inactive. The firm calculated the EIC to be (b) (4).

The firm determined the Expected Environmental Concentration (EEC) of the active moiety by adjusting with a dilution factor of 10. The EEC is (b) (4) µg/L. The maximum expected environmental concentration (MEEC) is defined as the EIC or EEC, whichever is greater. In this case the MEEC is equal to the EIC.

Updated EC_{50}/EIC ratio:
Based on the NOECs for the different ecotoxicological studies, the most sensitive species is fish with an LC_{50} of 19.3 mg/L or 19,300 •g/L. Since data are available for fish, Daphnia, and algae, a Tier 2 assessment factor of 100 is justified (for the ratio of the LC_{50} or EC_{50} divided by the EIC). The LC_{50}/EIC is 19300/(b) (4) which is significantly greater than the assessment factor of 100. In addition the EIC ((b) (4) µg/L) is lower than the NOEC for each of the species tested. The data indicate that the compound is not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

ADEQUATE

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

ADEQUATE

IX PREPARERS

Names, job titles and qualifications were provided.

ADEQUATE

X REFERENCES

None provided.

XI APPENDICES

The firm provided Confidential Appendix VIII, which contains the maximum quantity of quetiapine estimated to be produced for direct use in any of the next five years, the EIC and the EEC.

For all other confidential appendices, the firm references the EA submitted December 30, 2002 for NDA 20-639/S-016.

ADEQUATE

Review by: Ruth Ganunis, Ph. D. on November 9, 2006
Chemist, Center for Drug Evaluation and Research

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/s/

Raanan Bloom
1/18/2007 05:19:07 PM
ENV ASSESSMENT

Moheb Nasr
1/19/2007 08:56:37 AM
CHEMIST

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

SEROQUEL® SUSTAINED RELEASE TABLETS
(quetiapine fumarate)

NDA 22-047
Treatment of Schizophrenia and Acute Mania

Food and Drug Administration
Center for Drug Evaluation and Research

Office of New Drug Quality Assessment

November 9, 2006

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-047

Seroquel® Sustained Release Tablets (quetiapine fumarate)
Treatment of Schizophrenia and Acute Mania

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

NDA 22-047 requests approval of Seroquel® Sustained Release Tablets (quetiapine fumarate) for treatment of schizophrenia and acute mania. In support of its new drug application, AstraZeneca Pharmaceuticals LP prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts from the use and disposal of this product.

Quetiapine fumarate is a chemically synthesized drug currently approved for treatment of schizophrenia and acute mania. This application provides for a new dosage form, a sustained release tablet.

Quetiapine fumarate and its metabolites and conjugates may enter the aquatic environment from patient use and disposal. Quetiapine fumarate is not degraded by aerobic and anaerobic, hydrolytic and photolytic mechanisms. The toxicity of quetiapine fumarate to environmental organisms was characterized. The results indicate that the compound and its metabolites and conjugates are not expected to be toxic to aquatic organisms at the expected environmental introduction concentration.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital or clinic procedures. Empty or partially empty containers from home use typically will be disposed by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY

Ruth Ganunis, Ph.D.
Chemist, Center for Drug Evaluation and Research

CONCURRED BY

Raanan A. Bloom, Ph.D.
Senior Environmental Officer, Office of Pharmaceutical Science, Center for Drug Evaluation and Research

CONCURRED BY

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment, Office of Pharmaceutical Science, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

AstraZeneca

Environmental Assessment	
Drug Substance	Quetiapine
Document No.	CNS.000-139-123
Date	9 June 2006

Environmental Assessment of Quetiapine

Author: Gisela Holm, PhD
Ecotoxicologist
Global SHE Operations

TABLE OF CONTENTS PAGE

1. DATE

6 June 2006

2. NAME OF APPLICANT/PETITIONER

AstraZeneca Pharmaceuticals LP

3. ADDRESS

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

4. DESCRIPTION OF PROPOSED ACTION

4.1 Requested approval

AstraZeneca LP is filing an NDA pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Seroquel® 50 mg, 200 mg, 300 mg and 400 mg sustained release (SR) tablets packaged in bottles and hospital unit dose packages. An environmental assessment (EA) is being submitted pursuant to 21 CFR part 25. The EA is compiled in accordance with 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

4.2 Need for action

Seroquel is currently marketed for the treatment of schizophrenia and acute mania. An application has been filed to register Seroquel SR tablets.

4.3 Locations of use

Usage of Seroquel SR tablets will occur in households, but also in hospitals throughout the United States.

4.4 Disposal sites

Empty or partially empty packages from U.S. hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy, or clinic procedures.

5. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

5.1 Nomenclature

See CMC module, Nomenclature and Structure.

5.1.1 Established name (U.S. Adopted name - USAN)

Quetiapine fumarate

5.1.2 Brand/Proprietary name/tradename

Seroquel

5.1.3 Chemical names or genus/species of biologic product (e.g., virus)

5.1.3.1 Chemical abstracts (CA) index name

Ethanol[2–(2–[4–(dibenzo[b,f][1,4]– thiazepin–11–yl–1) piperazinyl)ethoxy]– (E)–2–butenedioate(2:1)

5.1.3.2 Systematic chemical name

IUPAC name:

Bis[2–(2–[4–(dibenzo[b,f][1,4]– thiapin –11–yl)piperazin–1–yl] ethoxy) ethanol]fumarate

5.2 Chemical abstracts service (CAS) registration number

Quetiapine fumarate: 111974-72-2

Base: 111974-69-7

5.3 Molecular formula

Quetiapine fumarate consists of two base components and one acid component.

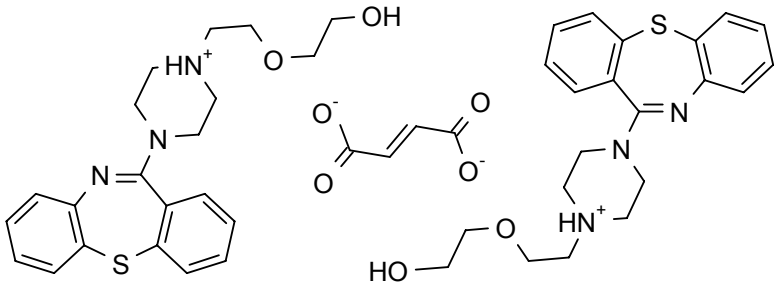
$C_{46}H_{54}N_6O_8S_2$ (quetiapine fumarate)
$C_{21}H_{25}N_3O_2S$ (base)

5.4 Molecular weight

Quetiapine fumarate consists of two base components and one acid component.

883.1 (quetiapine fumarate)
767 (quetiapine = 2 x base)

5.5 Structural (graphic) formula/amino acid sequence



Quetiapine fumarate

6. ENVIRONMENTAL ISSUES

6.1 Assessing Toxicity to Environmental Organisms

6.1.1 Environmental Fate of Released Substances

6.1.1.1 Identification of Substances of Interest

After oral administration, quetiapine is eliminated almost completely by metabolism, as <1% of the excreted dose can be recovered in urine and faeces as the parent compound (quetiapine) (Appendix I – **Confidential**). Approximately 73% of the dose is excreted as metabolites in urine and 20% is excreted in faeces (Appendix I – **Confidential**). Eleven of the metabolites have been identified, some of which are conjugates of either the metabolites or the parent compound. The conjugates of the parent compound accounts for approximately 1.4% of the given dose. There are two main excreted human metabolites of quetiapine; the sulfoxide acid metabolite (M 289,886) (Fig. 1), and the parent acid metabolite (M 289,663) (Fig. 2). Both metabolites are mainly excreted via urine, but a small amount of each metabolite is also excreted via the faeces. The excretion of M 289,886 altogether represents approximately 28% (24% via urine + 4% via faeces) of the given dose, whereas the excretion of M 289,663 represents approximately 29% (27% + 2%) of the given dose.

The remaining identified excreted metabolites each account for less than 5% of the given dose, except for the sulfoxide (ICI 213,841), which accounts for approximately 6% of the given dose (Appendix I – **Confidential**).

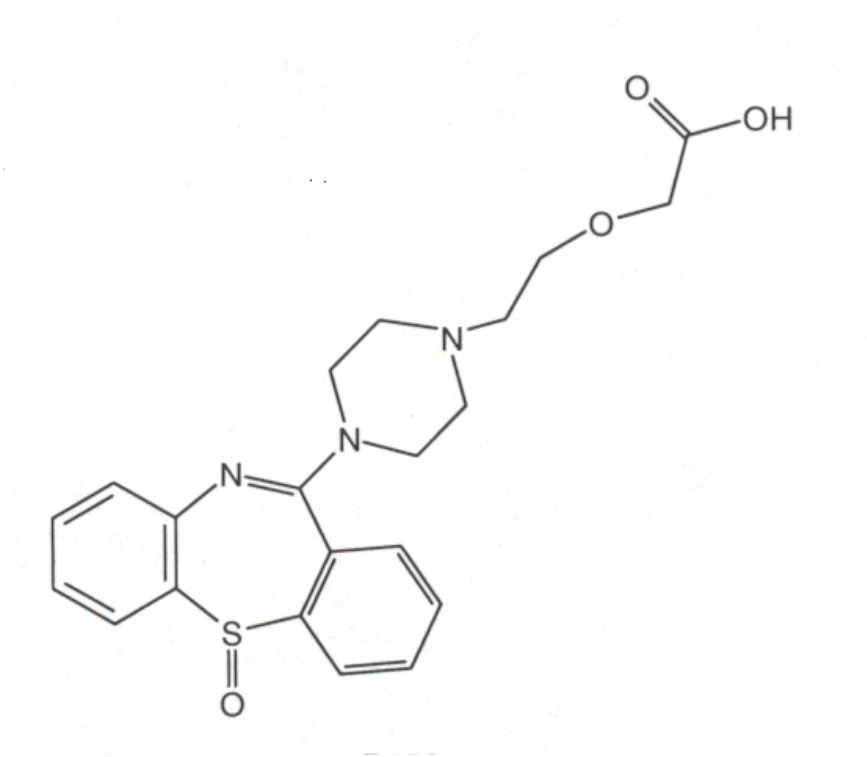


Figure 1. Structural formula for the sulfoxide acid metabolite (M 289,886).

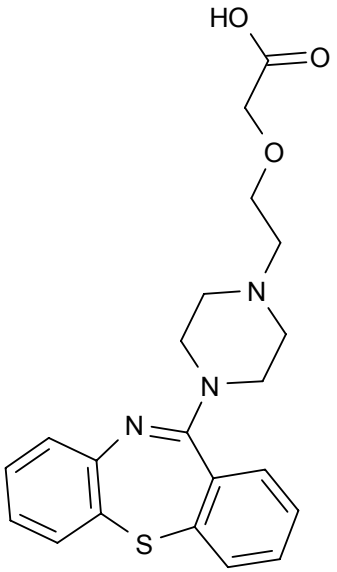


Figure 2. Structural formula for the parent acid metabolite (M 289,663).

The pharmacological effect of the two main excreted metabolites (M 289,886 and M 289,663) was tested *in vitro* (Appendix I – **Confidential**). Neither of these metabolites showed any pharmacological activity in terms of binding affinity and behavioural tests of dopamine antagonism. Regarding the remaining metabolites, four of them showed potencies similar to or greater than the parent compound. The unconjugated forms of these metabolites represent 4.5% of a given dose.

6.1.1.2 Physical and Chemical Characterization

Water solubility

1600 mg/L at pH 7 (Appendix II - **Confidential**)

Dissociation constants (pKa) (22°C)

(Appendix III – **Confidential**)

$pKa_1 = 6.8$
$pKa_2 = 3.3$

Octanol/Water Partition Coefficient (25°C)

log K_{ow} = 1.4 at pH 5 (Appendix IV - **Confidential**)

log K_{ow} = 2.7 at pH 7 (Appendix IV - **Confidential**)
log K_{ow} = 2.6 at pH 9 (Appendix IV - **Confidential**)

Vapour pressure

Not determined. Quetiapine is a solid and hence its vapour pressure is assumed to be very low ($<10^{-6}$ Pa).

6.1.1.3 Environmental Depletion Mechanisms

Photolysis
No data.

Biodegradation

Aerobic degradation
The aerobic biodegradation of quetiapine fumarate was assessed according to guideline OECD 301F (Appendix V - **Confidential**). In this test, aerobic micro-organisms from a sewage treatment works are used to investigate their potential to readily degrade a substance. The results showed that quetiapine fumarate is not readily biodegradable (BOD_{28}/ThOD <0.6).

Anaerobic degradation
The anaerobic biodegradation was assessed according to the UK Department of the

Environment test method (Appendix VI - **Confidential**). The results showed that quetiapine fumarate is not anaerobically biodegradable under the conditions of the test.

Hydrolysis

The stability of quetiapine fumarate in aqueous buffer solutions was assessed according to the US FDA Environmental Assessment (EA) Technical Assistance Document 3.09 (Appendix III – **Confidential**). The extent of hydrolysis at 50°C, at pH 5, 7 and 9, was <10% after 5 days. These data indicate that quetiapine fumarate is hydrolytically stable, with an estimated half-life of ≥1 year at 25°C.

Adsorption to soil

The soil sorption and desorption of quetiapine was assessed according to the US FDA EA Technical Assistance Document 3.08 (Appendix VII – **Confidential**).

Soil type	% organic carbon	% clay	pH	Mean Kd	Mean Koc	% recovery from soil
Nebo	1.6	28	4.9	3600	220,000	1
East Jubilee	2.2	13	5.8	180	8,000	6
Kenny Hill	3.1	14	7.7	45	1,400	19

From the results on the three soils tested, it is evident that the Kd may vary in different soils. However, the data suggests that quetiapine will be essentially immobile.

It should be noted that the Kd values are not proportional to the carbon content, so the Koc is not likely to be a reliable predictor of adsorption to soil (or sewage sludge). It is more likely that the adsorption is dependent on pH, with higher adsorption in more acidic soils. There is also evidence to suggest that the adsorption of quetiapine is irreversible, especially in more acidic soils.

6.1.1.4 Environmental Concentrations

The Expected Introduction Concentration (EIC) is based on all AstraZeneca Pharmaceuticals LP drug products containing quetiapine fumarate. See Appendix VIII – **Confidential**.

6.1.1.5 Summary

The use of quetiapine fumarate is likely to result mainly in metabolites and, to a lesser extent, the active moiety entering the environment, since it is almost completely metabolised after consumption. The metabolites are mainly excreted *via* urine (73%), and to a lesser extent *via* faeces (20%). Based on the physico-chemical properties of quetiapine fumarate (log K_{ow} 2.7,

water solubility = 1600 mg/L and vapour pressure $<10^{-6}$ Pa) it is predicted that most of the active moiety (quetiapine) will be partitioned into the aqueous phase during wastewater treatment. However, the log K_{ow} may not be a very reliable predictor of adsorption and some adsorption to sludge may occur depending on the pH. The aqueous streams containing quetiapine will then subsequently be passed to the aquatic environment. When estimating the Expected Introduction Concentration (EIC), it is assumed that all quetiapine ends up in the aquatic environment, but that only 43% is present in potentially active forms, since it is known that the two major metabolites showed no pharmacological activity when tested *in vitro*.

In the aquatic environment, quetiapine is not likely to be hydrolytically degraded, and there is no evidence to suggest that biodegradation will be significant. However, quetiapine is not likely to bioaccumulate in aquatic organisms.

6.1.2 Environmental Effects of Released Substances

The following ecotoxicological studies were performed with quetiapine fumarate:

Activated sludge, respiration inhibition test (NB screening test)

The respiration inhibition of activated sludge was assessed according to the Ecological and Toxicological Association of Dyestuffs Manufacturing Industries (ETAD) method 103 (Appendix IX - **Confidential**). No inhibition was observed at concentrations up to 100 mg/L.

Blue-green alga, *Microcystis aeruginosa*

The toxicity to the blue-green alga, *M. aeruginosa* was assessed according to the FDA Environmental Assessment (EA) Technical Assistance Document 4.01 (Appendix X – **Confidential**).

Based on the largest specific growth rates during the study (21 days):

No observed effect (P=0.05) concentration (NOEC)	= 32 mg/L
Lowest significant effect (P=0.05) concentration	= 64 mg/L

Based on maximum cell densities achieved (21 days):

NOEC (P=0.05)	= 4.0 mg/L
Lowest significant effect (P=0.05) concentration	= 8.0 mg/L

Green alga, *Selenastrum capricornutum*

The toxicity to green alga, (*Selenastrum capricornutum*) was assessed according to the FDA EA Technical Assistance Document 4.01 (Appendix XI – **Confidential**).

Based on the largest specific growth rates during the study (14 days):

NOEC (P=0.05) = 2.5 mg/L
Lowest significant effect (P=0.05) concentration = 5.0 mg/L

Based on maximum cell densities achieved (14 days):

NOEC (P=0.05) = 2.5 mg/L
Lowest significant effect (P=0.05) concentration = 5.0 mg/L

Water-flea, *Daphnia magna*

The long-term toxicity to *Daphnia magna* was assessed according to the FDA EA Technical Assistance Document 4.09 (Appendix XII - **Confidential**).

Based on reproduction (21 days):

NOEC = 18 mg/L
Lowest Observed Effect Concentration (LOEC) = 32 mg/L

Based on length (21 days):

NOEC = 18 mg/L
LOEC = 32 mg/L

Rainbow trout (*Oncorhynchus mykiss*)

The toxicity of quetiapine fumarate to rainbow trout was assessed according to the FDA EA Technical Assistance Document 4.11 (Appendix XIII - **Confidential**).

96 h LC_{50} = 22.0 mg/L
96 h NOEC = 1.0 mg/L

Bluegill sunfish (*Lepomis macrochirus*)

The toxicity of to rainbow trout was assessed according to the FDA EA Technical Assistance Document 4.11 (Appendix XIV - **Confidential**).

96 h LC_{50} = 19.3 mg/L
96 h NOEC = 1.8 mg/L

According to the short-term ecotoxicological tests, quetiapine fumarate shows low short-term toxicity to fish but no short-term toxicity to micoorganisms in activated sludge. The long-term ecotoxicological tests show toxicity to algae and blue-green algae at mg/L concentration levels. The long-term effect of quetiapine to the water-flea *D. magna* appears to be minor. In addition, there were no observed sublethal effects at the Maximum Expected Environmental Concentration (MEEC).

In summary, the available ecotoxicological data indicate that quetiapine is not very toxic to aquatic organisms.

No rapid, complete depletion mechanism has been identified for quetiapine fumarate. However, the result from the microbial inhibition screening test above indicates that the drug substance does not inhibit respiration of activated sludge microorganisms. Therefore, it is not thought to disrupt wastewater treatment processes. Furthermore, as the log K_{ow} is <3.5 (see Physical and Chemical Characterization), the compound is not likely to bioaccumulate in aquatic organisms.

Based on the NOECs for the different ecotoxicological studies, the most sensitive species is fish. Since data are available for fish, *Daphnia* and algae, a Tier 2 assessment factor of 100 is justified. Hence a safety factor of 100 is applied to the lowest acute LC_{50} of 19.3 mg/L (bluegill sunfish).

96 h LC_{50} = 19.3 mg/L = 19300 µg/L

EC_{50}/EIC (Appendix VIII - **Confidential**) = 19300/EIC >100 (assessment factor), and no effects were observed at MEEC, i.e. no further testing is needed.

6.1.3 Summary

The intended use of quetiapine fumarate is likely to result mainly in metabolites entering the environment, since it is almost completely metabolised after consumption. Approximately 73% of the metabolites are excreted in the urine and 20% in the faeces. It is predicted that most of the active moiety (quetiapine) will be partitioned into the aqueous phase during wastewater treatment.

In the aquatic environment, quetiapine is not likely to be hydrolytically degraded, and there is no evidence to suggest that biodegradation will be significant. However, quetiapine is not likely to bioaccumulate in aquatic organisms.

Quetiapine fumarate shows short-term toxicity to fish but not to micoorganisms in activated sludge. The long-term studies indicate that quetiapine is not very toxic to aquatic organisms.

When estimating the Expected Introduction Concentration (EIC), it is assumed that all quetiapine ends up in the aquatic environment, but that only 43% is present in potentially active forms, since it is known that the two major metabolites are essentially inactive. The rest of the excreted metabolites were assumed to exhibit the same pharmacological effects as the parent compound, due to the insufficient information available.

The EIC is based on all AstraZeneca Pharmaceuticals LP drug products containing quetiapine (Appendix VIII – **Confidential**).

Comparing the EIC with the lowest LC_{50} from the most sensitive species (bluegill sunfish) using an assessment factor of 100 gives:

EC_{50}/EIC = 19300 / EIC >100 (assessment factor)

In conclusion, since the ratio of the EC_{50} for the most sensitive of the acute toxicity test organisms to the expected introduction concentration is over two orders of magnitude larger than the assessment factor, and no effects were observed at MEEC, no adverse environmental effects are anticipated as a consequence of the use of quetiapine.

7. MITIGATION MEASURES

No adverse environmental effects are anticipated due to the use of quetiapine fumarate. Therefore, no mitigation measures are needed.

8. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified for the proposed action. Therefore, no alternatives to the proposed action will be proposed.

9. LIST OF PREPARERS

Gisela Holm, Ecotoxicologist, Global SHE Operations, AstraZeneca, Södertälje, Sweden since six years, Ph.D. Stockholm University, 19 years of experience in environmental research and consulting.

Persons consulted:

Jill Bailey, Seroquel Global Demand Manager, Supply Chain & Logistics, AstraZeneca, Alderley Park, UK

Donna Caster, Manager, AstraZeneca Pharmaceuticals LP, Wilmington, USA

Norb Ealer, Associate Director, Technical Regulatory Affairs AstraZeneca Pharmaceuticals LP, Wilmington, USA

Richard Murray-Smith, BSc, AstraZeneca, Brixham, UK

Greg Rullo, CMC Regulatory Director, AstraZeneca Pharmaceuticals LP, Wilmington, USA

Helen Winter Ph.D. Associate Director, Clinical Pharmacokinetics, Experimental Medicine, AstraZeneca Pharmaceuticals LP, Wilmington, USA

Testing laboratory:

Brixham Environmental Laboratory, AstraZeneca, Brixham, UK

10. APPENDICES

10.1 Nonconfidential Appendices

10.1.1 Data Summary Table

All test results from the environmental effect studies are expressed as ppm of quetiapine fumarate.

DATA SUMMARY TABLE FOR QUETIAPINE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	1600 mg/L (ppm) at pH 7
Dissociation Constants (22°C)	$pKa_1 = 6.8$ $pKa_2 = 3.3$
Log Octanol/Water Partition Coefficient (log K_{ow}) (25°C)	log K_{ow} = 1.4 at pH 5 log K_{ow} = 2.7 at pH 7 log K_{ow} = 2.6 at pH 9
Vapour Pressure or Henry's Law Constant	No data
Sorption / Desorption (K_{oc})	K_{oc} = 220,000 (Nebo) K_{oc} = 8,000 (East Jubilee) K_{oc} = 1,400 (Kenny Hill)
DEPLETION MECHANISMS	
Hydrolysis	t½ at 25°C ≥ 1 year
Aerobic Biodegradation	Not readily biodegradable (BOD_{28}/ThOD <0.6).
Anaerobic degradation	Not degradable
Soil Biodegradation	No data
Photolysis	No data
Metabolism	Almost completely metabolised, <1% of the dose can be recovered as quetiapine

ENVIRONMENTAL EFFECTS	
Microbial Inhibition	No inhibition up to 100 ppm
Acute toxicity	**Rainbow trout** (*Oncorhynchus mykiss*) 96 h LC50 = 22.0 ppm 96 h NOEC = 1.0 ppm **Bluegill sunfish** (*Lepomis macrochirus*) 96 h LC50 = 19.3 ppm 96 h NOEC = 1.0 ppm
Chronic Toxicity	**Green alga** (*Selenastrum capricornutum*): Max. cell densities (MCD) 14 d NOEC = 2.5 ppm MCD 14 d lowest significant effect = 5.0 ppm Growth rate 14 d NOEC = 2.5 ppm Growth rate 14 d lowest significant effect = 5.0 ppm **Blue-green alga** (*Microcystis aeruginosa*) MCD 14 d NOEC = 4.0 ppm MCD 14 d lowest significant effect = 8.0 ppm Growth rate 14 d NOEC = 32 ppm Growth rate 14 d lowest significant effect = 64 ppm **Water flea** (*Daphnia magna*): 21 d reproduction NOEC = 18 ppm 21 d reproduction LOEC = 32 ppm 21 d length NOEC = 18 ppm 21 d length LOEC = 32 ppm

10.2 Confidential Appendices

A revised Confidential Appendix VIII is attached.

For all other appendices please refer to NDA 20-639, S-016 submitted December 30, 2002.

Appendix I. Investigator's Brochure Seroquel™ (Quetiapine fumarate; ICI 204,636 fumarate). AstraZeneca Pharmaceuticals, Mereside, Alderley Park, UK. 7th edition, January 2002.

Appendix II. ICI 204,636 solubility measurements in partial fulfillment of FDA environmental-assessment requirements. Pharmaceutical research & development report no. SP3010/B. Zeneca Pharmaceuticals, Wilmington, USA. 22 September 1995.

Appendix III. Data generated in the US to support the environmental assessment report for ICI 204,636. Pharmaceutical research & development report no. SP2900/B. Zeneca Pharmaceuticals Group, Wilmington, USA. 29 March 1995.

Appendix IV. ICI 204,636 log partition coefficient measurements in partial fulfillment of FDA environmental assessment requirements. Pharmaceutical research & development report no. SP3011/B. Zeneca Pharmaceuticals, Wilmington, USA. 3 October 1995.

Appendix V. Seroquel: Determination of 28 day ready biodegradability. Report no. BL5078/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VI. Seroquel: Determination of anaerobic biodegradability. Report no. BL5077/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VII. Seroquel: Soil sorption and adsorption. Report no. BL5062/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix VIII. Environmental concentrations of quetiapine. AstraZeneca Global SHE Operations, 2 March, 2006.

Appendix IX. ICI 204636 PURE: Inhibition of the respiration rate of activated sludge by ETAD method 103. Report no. BLS1461/B. Brixham Environmental Laboratory (Former ICI Group Environmental Laboratory), Brixham, UK. December 1992.

Appendix X. Seroquel: Toxicity to the blue-green alga *Microcystis aeruginosa*. BL5018/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XI. Seroquel: Toxicity to the green alga *Selenastrum capricornutum*. BL5017/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XII. Seroquel: Chronic toxicity to *Daphnia magna*. BL5232/B. Brixham Environmental Laboratory, Brixham, UK. September 1994.

Appendix XIII. Seroquel: Acute toxicity to rainbow trout *Oncorhynchus mykiss*. BL5084/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

Appendix XIV. Seroquel: Acute toxicity to bluegill sunfish *Lepomis macrochirus*. BL5085/B. Brixham Environmental Laboratory, Brixham, UK. February 1994.

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