CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-721

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

LEVAQUIN (levofloxacin) Oral Solution, 25 mg/mL

NDA 21-721
(New Formulation for all Indications)

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Special Pathogens and
Immunological Drug Products
(HFD-590)

May 6, 2004

FINDING OF NO SIGNIFICANT IMPACT

NDA 21-721
(New formulation for all indications)

LEVAQUIN (levofloxacin) Oral Solution, 25 mg/mL

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.

This NDA requests approval of a new formulation of Levaquin (levofloxacin), namely Oral Solution, 25 mg/mL, for treatment of community-acquired pneumonia, nosocomial pneumonia, acute exacerbation of chronic bronchitis, acute maxillary sinusitis, uncomplicated and complicated urinary tract infections, acute pylonephritis, uncomplicated and complicated skin and skin structure infections, and chronic bacterial prostatitis. In support of its new drug application for Levaquin Oral Solution, 25 mg/mL, Johnson & Johnson R & D, LLC 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.

Levofloxacin is a chemically synthesized drug currently approved for use in the treatment of several types of infections noted above.

Levofloxacin may enter the aquatic and terrestrial environment from patient use and disposal and is expected to degrade rapidly when exposed to light. Although degradation mechanisms were demonstrated for the aquatic and terrestrial environment, the toxicity of levofloxacin to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to 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
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Keith Webber
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Moheb Nasr.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

1. DATE

16 March 2004

2. NAME OF APPLICANT

Johnson & Johnson Pharmaceutical Research and Development, L.L.C.

3. ADDRESS

920 US Route 202 South
PO Box 300
Raritan, NJ 08869

4. PROPOSED ACTION

New Drug Application (NDA # 21-721) for LEVAQUIN® Oral Solution for all indications that LEVAQUIN (levofloxacin) Tablets and LEVAQUIN (levofloxacin) Injection are approved. An environmental assessment (EA), as required by 21 CFR Part 25.20 (l) was submitted on December 18 2003. The current document is an update.

Levofloxacin Tablets are the subject of NDA 20-634, approved 20 December 1996. In addition, an injectable formulation of levofloxacin is the subject of NDA 20-635, approved 20 December 1996. Both the tablet and injection are approved for treatment of community-acquired pneumonia, nosocomial pneumonia, acute exacerbation of chronic bronchitis, acute maxillary sinusitis, uncomplicated and complicated urinary tract infections, acute pylonephritis, uncomplicated and complicated skin and skin structure infections, and chronic bacterial prostatitis. This NDA is a new formulation of LEVAQUIN Oral Solution for all the above approved indications.

The maximum expected environmental concentration (MEEC) given in Section 6 of this environmental assessment is based on the total projected fifth year demand for the drug substance. The drug substance remains unchanged. Environmental fate and effects information for levofloxacin was submitted previously, and consequently, a cross-reference to NDA 20-634 is provided in lieu of much of the information typically found in Sections 5 and 6 of the Environmental Assessment.

LEVAQUIN® (levofloxacin) Oral Solution will be used primarily by patients in their homes and in hospitals and clinics, through physician prescription. Disposal of prescribed product will be through use, with returned product disposed via high temperature incineration at licensed disposal facilities. US hospitals, pharmacies, and clinics will dispose of empty or partially empty

packages according to their internal handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills, incineration, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

Cross-refer to Levofloxacin Tablets NDA 20-634 (Volume 1.014, Page 03 03077), submitted 21 December 1995, and to the revised data submitted on 31 October 1996, 27 November 1996, and 05 November 1999.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The manufacture and use of LEVAQUIN® (levofloxacin) Oral Solution are not expected to result in significant environmental releases of the active ingredient or excipients, and no potential adverse environmental effects resulting from the manufacture and use of levofloxacin have been identified.

The environmental assessment dated 28 October 1998 (which was added to the supplement to NDA 20-634, filed on 04 June 1998, for uncomplicated urinary tract infection) is the most recent document addressing fate and effects information for levofloxacin. The lowest minimum inhibitory concentration (MIC) found was 0.06 mg/L for the soil bacteria, *Bacillus subtilis*. The median effective concentration (EC_{50}) for *Daphnia magna* was 320 mg A.I./L, and the median lethal concentration (LC_{50}) for bluegill sunfish was >950 mg A.I./L. In accordance with the Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications, July 1998 related to *Environmental Effects of Release Substances, Tiered approach to environmental effects testing*, no further testing should be conducted if the EC_{50} (Median Effective Concentration) or the LC_{50} (Median Lethal Concentration) divided by the MEEC (Maximum Expected Environmental Concentration). is greater than or equal to 1000 for the Test Tier 1 Assessment Factor. As the MEEC resulting from this action will be well below the MIC and the Test Tier 1 results are significantly greater than the assessment factor of 1000, the original conclusion, that no environmental impact is expected, is still valid.

7. MITIGATION MEASURES

Section 7, Mitigation Measures, is not required when there have been no adverse environmental effects identified.

8. ALTERNATIVES TO THE PROPOSED ACTION

Section 8, Alternatives to the Proposed Action, is not required when there have been no adverse environmental effects identified.

9. PREPARER

Edward Nowak, QEP, CHMM
Staff Environmental Engineer
Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
1000 US Route 202 South
Raritan, NJ 08869-0602

More than 25 years of environmental experience; 15 years with the telecommunications research and development industry, 8 years with the United States Environmental Protection Agency, and over 2 years with pharmaceutical research and development.

Holds a Bachelor of Science in Civil Engineering and a Master of Science in Environmental Engineering, both from the New Jersey Institute of Technology.

10. CERTIFICATION

I certify that the information presented is true and accurate and complete to the best of the knowledge of the firm responsible for the preparation of the Environmental Assessment.

Date 16 March 2004

Signature Edward Nowak

Edward Nowak

Title Staff Environmental Engineer

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

/s/

Keith Webber
7/7/04 11:01:13 AM

Moheb Nasr
7/13/04 12:07:09 PM

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

LEVAQUIN® (levofloxacin) Oral Solution, 25 mg/mL

NDA 21-721

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Special Pathogens and
Immunological Drug Products
(HFD-590)

May 6, 2004

Environmental Assessment Review #1, NDA 21-721
LEVAQUIN® (levofloxacin) Oral Solution, 25 mg/mL

Executive Summary

A FONSI is recommended

Section 5 of the EA dated Oct 15, 2003 includes cross-reference to environmental information in NDA 20-634 (Volume 1.014, page 03 03077) for Levaquin Tablets submitted Dec 21, 1995 and to revised environmental data submitted on Oct 31, 1996, Nov 27, 1996 and Nov 5, 1999.

The environmental assessment (EA) dated Oct 15, 2003 (submitted on Dec 18, 2003) was updated on March 16, 2004. The updated EA replaces the one dated Oct 15, 2003. The updated EA supports the new drug application submitted by Johnson & Johnson Pharmaceutical R and D, LLC for Levaquin® (levofloxacin) Oral Solution, 25 mg/mL (NDA 21-721). The EA was prepared in accordance with 21 CFR Part 25.

The updated EA does not contain new environmental information. It includes a very brief description of the new formulation, Oral Solution, 25 mg/mL, clarifies data from the Daphnia Magna toxicity test (Section 6), and projects the highest production estimate to be — year for all indications in any of the next 5 years — $ppb_{(aq)}$ reported in Confidential Appendix, #11)

Previous EA submissions evaluated the potential environmental impacts from the use and disposal of levofloxacin, the active pharmaceutical ingredient in Levaquin (levofloxacin) Oral Solution. The previous reviews of the previous EAs resulted in FONSIs dated 12/5/96, 12/1/98, 1/4/00, 3/21/02, 7/16/02, 8/28/02 and 1/15/03.

Levofloxacin may enter the aquatic and terrestrial environment from patient use and disposal and is expected to degrade rapidly when exposed to light. Although degradation mechanisms were demonstrated for the aquatic and terrestrial environment, the toxicity of levofloxacin to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at the expected environmental introduction concentration.

Test	Result
Microbial Growth Inhibition (MIC)	Clostridium perfringens = — Nostoc sp. = — Bacillus subtilis = 0.06 — Trichoderma virde — Aspergillus niger —
Daphnia Magna	EC_{50} = 320 —
Bluegill Sunfish	NOEC = — EC_{50} = 950 —

REVIEW #1 OF EA FOR NDA 21-721

New Formulation of Levofloxacin

I. DATE: March 16, 2004

II APPLICANT: Johnson & Johnson Pharmaceutical R & D, LLC

III ADDRESS: 920 US Route 202 South
PO Box 300
Raritan, New Jersey 08869

IV PROPOSED ACTION:

This original NDA 21-721 requests approval of a new formulation of levofloxacin, namely, an oral solution containing 25 mg/mL of the active pharmaceutical ingredient.

The additional quantity of levofloxacin required for this new formulation will increase the total amount of levofloxacin manufactured for all indications in any of the next 5 years. New information in Confidential Appendix 1 indicates that the total amount of drug substance manufactured for all indications is expected to be NMT [redacted] yr. This production estimate does not include [redacted]. The maximum production estimate corresponds to EIC = [redacted] ppb in the aquatic environment.

Appropriate environmental information was provided in the Original NDA 20-634 dated 12/21/95 (Volume 1.014, page 0303077) and revised data submitted on 10/31/96, 11/27/96 and 11/5/99. All submissions pertain to potential environmental impacts from the use and disposal of levofloxacin. The previous reviews of the previous EAs resulted in FONSIs dated 12/5/96, 12/1/98, 1/4/00, 3/21/02, 7/16/02, 8/28/02 and 1/15/03.

ADEQUATE

V IDENTIFICATION OF CHEMICALS

Information about levofloxacin is provided by cross-reference to NDA 20-634 (Volume 1.014, page 0303077) submitted Dec 21, 1995 and revised data submitted Oct 31, 1996, Nov 27, 1996 and Nov 5, 1999.

ADEQUATE

VI ENVIRONMENTAL ISSUES

Environmental fate & effects data are provided by cross-reference to the EA dated Oct 28, 1998 submitted to the "uncomplicated urinary tract infection" supplement to NDA 20-634 / S-003.

Briefly, the lowest minimum inhibitory concentration (MIC) found was 60 — for the soil bacteria, *Bacillus subtilis*. EC_{50} for daphnia magna is 320 — The LC_{50} is > 950 — and the NOEC is — for blue gill sunfish. The EIC, namely — ppb, is more than 1000 times lower than values reported above. Therefore, no significant environmental impact is expected. (Ref: Guidance for Industry; Environmental Assessment of Human Drug & Biologics Applications, July 1998, p 14)

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 PREPARER

Name, job title and qualifications provided.

ADEQUATE

X CERTIFICATION

Provided by Staff Environmental Engineer, Edward Nowak

ADEQUATE

XI APPENDIX

Production estimate provided in Confidential Appendix I: $EIC_{aquatic}$ = — ppb

ADEQUATE

SUMMARY

A Package Insert for Levaquin (NDA 20-634 / S-028 and NDA 20-635 / S-027) was approved recently on October 23, 2003 by Dr. Renata Albrecht. Indications and Usage are stated on pages 16 and 17 of the Package Insert. Levofloxacin is currently approved for treatment of:

(a) acute maxillary sinusitis
(b) acute bacterial exacerbation of chronic bronchitis
(c) nosocomial pneumonia
(d) community acquired pneumonia
(e) complicated skin and skin structure infections
(f) uncomplicated skin and skin structure infections
(g) chronic bacterial prostatitis
(h) complicated urinary tract infections
(i) acute pylonephritis
(j) uncomplicated urinary tract infections

This original NDA 21-721 requests approval of a new formulation of levofloxacin, namely, an oral solution containing 25 mg/mL of the active pharmaceutical ingredient.

The additional quantity of levofloxacin required for this new formulation will increase the total amount of levofloxacin manufactured in any of the next 5 years. New information in Confidential Appendix 1 indicates that the total amount of drug substance manufactured for all indications is expected to be NMT — yr. This corresponds to EIC = — ppb in the aquatic environment.

New ecotoxicity data are not provided in the EA dated March 16, 2004.

The conclusion from the previous submissions that a FONSI is appropriate is still valid.

Review by: Florian Zielinski on May 6, 2004
Chemist, Center for Drug Evaluation and Research

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/s/

Florian Zielinski
6/14/04 11:25:40 AM
ENV ASSESSMENT

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