CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204353Orig1s000

ENVIRONMENTAL ASSESSMENT

Finding of No Significant Impact

NDA 204-353
INVOKAMET— Canagliflozin/Metformin Hydrochloride Immediate Release Fixed Dose Combination

Food and Drug Administration
Center for Drug Evaluation and Research

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

Janssen Research & Development, LLC (JRD or sponsor) on behalf of Janssen Pharmaceuticals, Inc., requests approval of NDA 204-353, INVOKAMET, to be used as an adjunct to diet and exercise in the management of type 2 diabetes mellitus (T2DM) patients who are not adequately controlled on a regimen containing metformin or canagliflozin. In support of its application, JRD prepared an environmental assessment (EA; attached), in accordance with 21 CFR Part 25, which evaluates the potential environmental impact from the use and disposal of this product.

The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and other information and has carefully considered the potential environmental impact due to approval of this application. Based on the CDER review and information available to date, FDA has determined that approval of the present application for INVOKAMET (canagliflozin/metformin) is not expected to have a significant impact on the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

Attachment: November 13, 2012, Environmental Assessment

Janssen Research & Development, L.L.C.

Environmental Assessment

NDA Environmental Assessment for Canagliflozin and Metformin Fixed Dose Combination

JNJ-28431754-ZAE and JNJ-1156196-AAC

Department:	Chemistry, Manufacturing & Controls
Document No.:	EDMS-ERI-42522740
Report No.:	EAUS-FA-JNJ28431754-JNJ1158196-NDA-TAB-V02

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NDA Environmental Assessment for Canagliflozin and Metformin Fixed Dose Combination

SUMMARY

Potential environmental impacts of canagliflozin and metformin drug substances have been evaluated in this environmental assessment according to 21 CFR Part 25.

The calculated Maximum Expected Environmental Concentration (MEEC, Expected Introduction Concentration, or EIC-aquatic based on use) was more than 1 part per billion (ppb, based on the fifth year projection forecast), therefore, fate and acute effects testing results are reported.

In accordance with the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications*{1}, if no rapid, complete depletion mechanisms are known, then a microbial inhibition test should be done; and if the Log K_{ow} <3.5, then an acute toxicity study should be done. If the results demonstrate that the acute EC_{50} (Median Effective Concentration) or the acute LC_{50} (Median Lethal Concentration), divided by the MEEC is ≥1,000, then no further testing should be conducted unless sublethal effects are observed at the MEEC.

For canagliflozin, no rapid, complete depletion mechanisms are known. A microbial inhibition test showed canagliflozin EC_{50} of >1000 mg/L. The Log K_{ow} is <3.5. The calculated assessment factors for algae, daphnids, and zebra fish were each greater than 1,000 according to the calculation described above, and sublethal effects were not seen at the MEEC; therefore additional testing is not required. No potential adverse environmental effects resulting from the manufacture and use of canagliflozin have been identified.

For metformin, no rapid, complete depletion mechanisms are known. A microbial inhibition test showed metformin EC_{50} of >750 mg/L. The Log K_{ow} is <3.5. The calculated assessment factors for algae, daphnids, and zebra fish were each greater than 1,000 according to the calculation described above, and sublethal effects were not seen at the MEEC; therefore additional testing is not required. No potential adverse environmental effects resulting from the manufacture and use of metformin have been identified.

1. Guidance for industry-environmental assessment of human drugs and biologics applications. US FDA - Food and Drug Administration, Washington, DC, July 1998.

1. DATE

13 November 2012

2. NAME

Janssen Research & Development, L.L.C.

3. ADDRESS OF APPLICANT

920 Route 202
Raritan, NJ 08869, U.S.A.

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Requested Approval

Janssen Research & Development, L.L.C., is submitting an NDA pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for canagliflozin and metformin drug substances. An environmental assessment (EA) is being submitted pursuant to 21 CFR Part 25.

4.2. Need for Action

This EA supports a New Drug Application (NDA) for the management of Type 2 Diabetes using canagliflozin and metformin fixed dose combination in the following canagliflozin/metformin fixed dose combination therapies: 50mg/500mg, 50mg/1000mg, 150mg/500mg, and 150mg/1000mg.

4.3. Locations of Use

This drug combination will be used in hospitals and private homes across the US. It will be available by prescription only.

4.4. Disposal Sites

Disposal of prescribed product will be through use, with returned product disposed of through high temperature incineration at licensed disposal facilities. US hospitals, pharmacies, or 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. Where available, disposal of unused medicines could also be through take-back programs in local community waste disposal systems or pharmacies.

5. IDENTIFICATION OF SUBSTANCES: CANAGLIFLOZIN

5.1. Nomenclature

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

Canagliflozin

5.1.2. Brand/Proprietary Name/Trade Name

Not applicable

5.1.3. Chemical Name

(1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate

5.2. Chemical Abstracts Service (CAS) Registration Number

928672-86-0

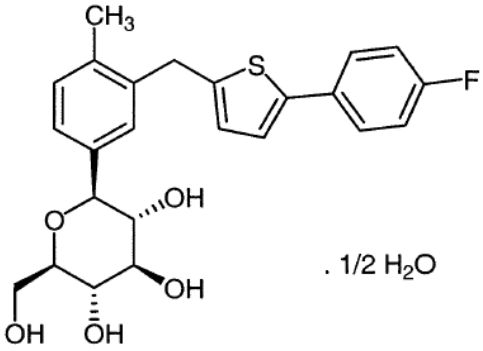
5.3. Molecular Formula

$C_{24}H_{25}FO_5S \bullet ½H_2O$

5.4. Molecular Weight

453.53

5.5. Structural (Graphic) Formula



6. ENVIRONMENTAL ISSUES: CANAGLIFLOZIN

The manufacture and use of canagliflozin tablets are not expected to result in significant environmental releases of the active ingredient or excipients. No potential adverse environmental effects resulting from the manufacture and use of canagliflozin have been identified.

The partition coefficient (log K_{ow}) indicates the tendency of an organic chemical to partition into lipids or fats, sorb to particulates such as soils or sediments, sorb to biomass and sludge, and distribute among the various environmental compartments. According to the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998), chemicals with log K_{ow} <3.5 do not have potential to bioaccumulate.{1} The log K_{ow} for canagliflozin is 1.95, which is below 3.5, therefore, canagliflozin does not show a potential to bioaccumulate.{2}

The adsorption coefficient (K_{oc}) indicates the tendency of an organic chemical to mobilize in the environment. The K_{oc} for canagliflozin was evaluated in a study according to OECD Guideline 121. Based on the results of this study, the K_{oc} was 5.9.{3}

Information related to the Maximum Expected Environmental Concentration (MEEC, Expected Introduction Concentration, or EIC-Aquatic, based on use) calculation is confidential and is provided in Confidential Appendices, Section 14, APPENDIX 1.

6.1. Assessing Toxicity to Environmental Organisms

The following environmental effect studies have been conducted with canagliflozin drug substance; the results are summarized in Table 1: Toxicity Testing of Canagliflozin Drug Substance with Representative Environmental Organisms.

A. Microbial growth inhibition (activated sludge respiration inhibition){4}

B. Algae (*Pseudokirchneriella subcapitata)* acute toxicity{5}

C. Daphnids (*Daphnia magna*) acute toxicity{6}

D. Rainbow Trout (*Oncorhynchus mykiss*) acute toxicity{7}

Table 1: Toxicity Testing of Canagliflozin Drug Substance with Representative Environmental Organisms

Test Organism	Conditions	Results	Source
Microbial Inocula	Microbial growth inhibition	NOEC = 368 mg/L EC_{50} > 1000 mg/L	Report {4}
Algae (*Pseudokirchneriella subcapitata)*	Acute toxicity	NOEC = 8.0 mg/L EC_{50} > 8.0 mg/L (72 h)	Report {5}
Daphnids *(Daphnia magna)*	Acute toxicity	NOEC = 9.1 mg/L EC_{50} > 9.1 mg (48 h)	Report {6}
Rainbow Trout (*Oncorhynchus mykiss*)	Acute toxicity	NOEC = 9.3 mg/L LC_{50} > 9.3 mg/L (96 h)	Report {7}

EC_{50} = median effective concentration
NOEC = no observed effect concentration
LC_{50} = median lethal concentration

6.1.1. Microbial Inhibition Test

The influence of canagliflozin on microorganisms was determined by measuring the respiration rate under defined conditions in a 3-hour respiration inhibition-activated sludge study according to OECD Guideline 209.

Based on the results of this test, the EC_{50} (Median Effective Concentration) was calculated to be greater than 1000 mg/L. The No-Observed-Effect Concentration (NOEC, determined as the calculated 3-hour EC_{15}) was 368 mg/L.{4}

6.1.2. Acute Toxicity to Freshwater Green Algae

The influence of canagliflozin on the green algal species *Pseudokirchneriella subcapitata* was investigated in a 72-hour static test, according to OECD Guideline 201.

Based on the results, the EC_{50} for growth rate and yield was determined to be greater than 8.0 mg/L. The NOEC was determined to be 8.0 mg/L.{5}

6.1.3. Acute Toxicity to the Water-Flea (*Daphnia magna*)

The acute toxicity of canagliflozin to *Daphnia magna* was determined in a 48-hour static test according to OECD Guideline 202.

The 48-hour EC_{50} value was determined to be greater than 9.1 mg/L. The NOEC was determined to be 9.1 mg/L.{6}

6.1.4. Acute Toxicity to Fish

The acute toxicity of canagliflozin to rainbow trout (*Oncorhynchus mykiss*) was determined in a 96-hour static test, according to OECD Guideline 203.

Based on the results from this study, the 96-hour LC_{50} (Median Lethal Concentration) was estimated to be greater than 9.3 mg/L. The NOEC was determined to be 9.3 mg/L.{7}

7. IDENTIFICATION OF SUBSTANCES: METFORMIN

7.1. Nomenclature

7.1.1. Established Name (U.S. Adopted Name-USAN)

metformin hydrochloride

7.1.2. Brand/Proprietary Name/Trade Name

Not applicable

7.1.3. Chemical Name

1,1-Dimethylbiguanide hydrochloride, N,N-dimethyl-, monochloride, Imidodicarbonimidic diamide

7.2. Chemical Abstracts Service (CAS) Registration Number

1115-70-4

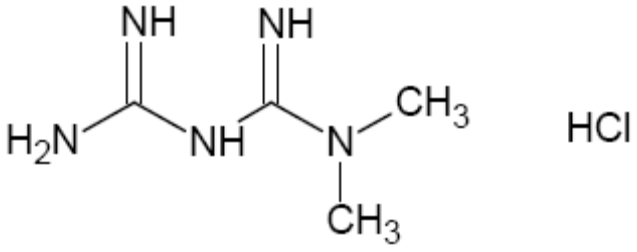
7.3. Molecular Formula

$C_4H_{11}N_5 \bullet HCl$

7.4. Molecular Weight

165.62

7.5. Structural (Graphic) Formula



8. ENVIRONMENTAL ISSUES: METFORMIN

The manufacture and use of canagliflozin tablets are not expected to result in significant environmental releases of the active ingredient or excipients. No potential adverse environmental effects resulting from the manufacture and use of canagliflozin have been identified.

The partition coefficient (log K_{ow}) indicates the tendency of an organic chemical to partition into lipids or fats, sorb to particulates such as soils or sediments, sorb to biomass and sludge, and distribute among the various environmental compartments. According to the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998), chemicals with log K_{ow} <3.5 do not have potential to bioaccumulate.{1} The log K_{ow} for metformin is -2.48, which is below 3.5, therefore, metformin does not show a potential to bioaccumulate.{8}

The adsorption coefficient (K_{oc}) indicates the tendency of an organic chemical to mobilize in the environment. The K_{oc} for metformin was evaluated in a study according to OECD Guideline 106. Based on the results of this study, the K_{oc} for activated sludge was 39.2.{9}

Information related to the Maximum Expected Environmental Concentration (MEEC, Expected Introduction Concentration, or EIC-Aquatic, based on use) calculation is confidential and is provided in Confidential Appendices, Section 14, APPENDIX 1.

8.1. Assessing Toxicity to Environmental Organisms

The following environmental effect studies have been conducted with metformin drug substance; the results are summarized in Table 2: Toxicity Testing of Metformin Drug Substance with Representative Environmental Organisms.

E. Microbial growth inhibition (activated sludge respiration inhibition){10}

F. Algae (*Pseudokirchneriella subcapitata)* acute toxicity{11}

G. Daphnids (*Daphnia magna*) acute toxicity{12}

H. Zebra fish (*Brachydanio rerio*) acute toxicity{13}

Table 2: Toxicity Testing of Metformin Drug Substance with Representative Environmental Organisms

Test Organism	Conditions	Results	Source
Microbial Inocula	Microbial growth inhibition	NOEC = 1.5 mg/L EC_{50} > 750 mg/L	Report {10}
Algae (*Pseudokirchneriella subcapitata)*	Acute toxicity	NOEC = 99 mg/L EC_{50} > 99 mg/L (72 h)	Report {11}
Daphnids *(Daphnia magna)*	Acute toxicity	NOEC = 110 mg/L EC_{50} > 110 mg (48 h)	Report {12}
Zebra Fish (*Brachydanio rerio*)	Acute toxicity	NOEC = 110 mg/L LC_{50} > 110 mg/L (96 h)	Report {13}

EC_{50} = median effective concentration
NOEC = no observed effect concentration
LC_{50} = median lethal concentration

8.1.1. Microbial Inhibition Test

The influence of metformin on microorganisms was determined by measuring the respiration rate under defined conditions in a 3-hour respiration inhibition-activated sludge study according to OECD Guideline 209.

Based on the results of this test, the EC_{50} (Median Effective Concentration) was calculated to be greater than 750 mg/L. The No-Observed-Effect Concentration (NOEC, determined as the calculated 3-hour EC_{15}) was 1.5 mg/L.{10}

8.1.2. Acute Toxicity to Freshwater Green Algae

The influence of tapentadol hydrochloride on the green algal species *Pseudokirchneriella subcapitata* was investigated in a 72-hour static test, according to OECD Guideline 201.

Based on the results, the EC_{50} for growth rate and yield was determined to be greater than 99 mg/L. The NOEC was determined to be 99 mg/L.{11}

8.1.3. Acute Toxicity to the Water-Flea (*Daphnia magna*)

The acute toxicity of metformin to *Daphnia magna* was determined in a 48-hour static test according to OECD Guideline 202.

The 48-hour EC_{50} value was determined to be greater than 110 mg/L. The NOEC was determined to be 110 mg/L.{12}

8.1.4. Acute Toxicity to Fish

The acute toxicity of metformin to zebra fish (*Brachydanio rerio*) was determined in a 96-hour static renewal test, according to OECD Guideline 203.

Based on the results from this study, the 96-hour LC_{50} (Median Lethal Concentration) was estimated to be greater than 110 mg/L. The NOEC was determined to be 110 mg/L.{13}

9. CONCLUSION

In accordance with the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998){1}, no further testing is required. The microbial inhibition test found canagliflozin to have an EC_{50} of greater than 1000 mg/L, the log K_{ow} was determined to be <3.5, after which acute ecotoxicity studies were reported. The calculated assessment factor for each of the 3 acute toxicity studies is >1,000. No observed effects were seen at the MEEC, therefore no further testing is required. The original assumption that canagliflozin has no known environmental effects remains valid.

In accordance with the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998){1}, no further testing is required. The microbial inhibition test found metformin to have an EC_{50} of greater than 750 mg/L, the log K_{ow} was determined to be <3.5, after which acute ecotoxicity studies were reported. The calculated assessment factor for each of the 3 acute toxicity studies is >1,000. No observed effects were seen at the MEEC, therefore no further testing is required. The original assumption that metformin has no known environmental effects remains valid.

Information related to the tiered approach to environmental effects testing is confidential and is provided in Confidential Appendices.

10. MITIGATION MEASURES

Mitigation measures are not required when there have been no adverse environmental effects identified.

11. ALTERNATIVES TO THE PROPOSED ACTION

Alternatives to the proposed action are not required when there have been no adverse environmental effects identified.

12. LIST OF PREPARERS

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7 years of environmental experience with the pharmaceutical industry.

Bachelor of Science in Environmental Science, Rutgers University

Master of Science in Environmental Science, Rutgers University

13. REFERENCES

1. Guidance for industry-environmental assessment of human drugs and biologics applications. US FDA - Food and Drug Administration, Washington, DC, Jul 1998.

2. Van Meter D. JNJ-28431754 – Determination of n-Octanol/Water Partition Coefficient Following OECD Guidelines, Section 117. Springborn Smithers Study No. 13674.6198. JNJ Study No. RMD 1092. 4 August 2010.

3. Van Meter D. JNJ-28431754 – Determination of the K_{oc} Coefficient Following OECD Guideline 121 (Sewage Sludge). Springborn Smithers Study No. 13674.6197. JNJ Study No. RMD 1091. 3 August 2010.

4. Turk R. JNJ-28431754 – Activated Sludge Respiration Inhibition Test Following OECD Guideline 209. Springborn Smithers Study No. 13674.6202. JNJ Study No. RMD 1096. 26 May 2010.

5. Soucy K. JNJ-28431754 – 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following OECD Guideline 201. Springborn Smithers Study No. 13674.6199. JNJ Study No. RMD 1093. 15 December 2010.

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7. Fournier A. JNJ-28431754 – Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline # 203. Springborn Smithers Study No. 13674.6201. JNJ Study No. RMD 1095. 17 November 2010.

8. Reibach P. Metformin Hydrochloride – Determining the Partitioning Coefficient (*n*-Octanol/Water) by the Fask-Shaking Method Following OECD Guideline 107. Smithers Viscient Study No. 13674.6227. JNJ Study No. RMD 1152. 3 November 2011.

9. Kang S. [^{14}C]Metformin Hydrochloride – Determining the Adsorption Coefficient (K_{oc}) Following OECD Guideline 106. Smithers Viscient Study No. 13674.6225. JNJ Study No. RMD 1151. 8 September 2011.

10. Griffith A. Metformin Hydrochloride – Activated Sludge Respiration Inhibition Test Following OECD Guideline 209. Smithers Viscient Study No. 13674.6228. JNJ Study No. RMD 1153. 6 March 2012.

11. Kirkwood A. Metformin Hydrochloride – 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following

OECD Guideline #201 and the Official Journal of the European Communities L220/36, Method C.3. Springborn Smithers Study No. 13751.6179. Janssen Study No. RMD 1146. 7 January 2011.

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13. Sayers L. Metformin Hydrochloride – Acute Toxicity to Zebra Fish (*Brachydanio rerio*) Under Static Conditions, Following OECD Guideline Number 203 and The Official Journal of the European Communities L 142/446, Method C.1. Springborn Smithers Study No. 13751.6181. Janssen Study No. RMD 1148. 14 January 2011.

14. CONFIDENTIAL APPENDICES

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/s/

JAMES P LAURENSON
10/18/2013

NAKISSA SADRIEH
10/18/2013

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: October 18, 2013

From: James P. Laurenson
OPS/IO/SRS

To: Rebecca McKnight
OPS/ONDQA

Through: Nakissa Sadrieh, Ph.D.
OPS/IO/SRS

Subject: Review of Environmental Assessment (EA) for NDA 204-353, Canagliflozin/Metformin Hydrochloride Immediate Release Fixed Dose Combination (INVOKAMET)

Sponsor: Janssen Research & Development, LLC (JRD) on behalf of Janssen Pharmaceuticals, Inc., 1125 Trenton-Harbourton Road, Titusville, NJ 08560

A. Summary

JRD has filed a new drug application (NDA) for INVOKAMET, which is a combination of canagliflozin and metformin in a fixed-dose combination tablet intended to be used as an adjunct to diet and exercise in the management of type 2 diabetes mellitus (T2DM) patients who are not adequately controlled on a regimen containing metformin or canagliflozin alone. Canagliflozin is relatively new, while metformin is used in a variety of other products. JRD provided an EA for canagliflozin/metforim, relying primarily on the Tier 1 testing described in the EA Guidance (USFDA 1998). This memorandum provides a review of this EA. The two key goals of this review are to (1) determine whether this EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) determine whether the proposed action will significantly affect the environment.

The JRD EA provided partition coefficient (log K_{ow}) and adsorption coefficient (K_{oc}) data, noting that chemicals with these levels do not have the potential to bioaccumulate or adsorb to biosolids, but rather will move primarily into the aquatic environment. JRD then used screening-level assumptions, such as no depletion, to develop maximum expected environmental concentrations (MEECs)—referred to as the expected introductory concentration (EIC) in the review portions of this memorandum—of (b) (4) µg/L ((b) (4) ppb) for

conagliflozin and (b) (4) µg/L ((b) (4) ppb) for metformin in the aquatic environment. Comparing these EICs to the lowest 50% effective concentration (EC_{50}) of >8 mg/L for canagliflozin and EC_{50} of >99 mg/L for metformin resulted in assessment factors (AFs) greater than 1,000. In addition, no sublethal effects were observed at the EICs. The microbial inhibition tests, which are primarily for assessing the potential for the compound to disrupt waste treatment processes, indicate that both canagliflozin and metformin from this application, as well as cumulatively for all uses of these substances, would have virtually no potential to disrupt waste treatment processes. As described in the EA Guidance, this information indicates that the application for conagliflozin/metformin would have no significant impact on the environment.

Additional confirmatory analysis was conducted for this review to assess the potential for these drugs to be highly active toxicologically (i.e., with aquatic toxicity affects below 1 µg/L). Specifically, a chronic toxicity value of (b) (4) µg/L for canagliflozin was developed based on the lowest acute no-observed-effects concentration (NOEC) of 8 mg/L and a screening-level adjustment factor of 1,000. The EIC of (b) (4) µg/L for canagliflozin is less than this chronic toxicity value by almost (b) (4). Similarly, a chronic toxicity value of 44 µg/L was found for metformin in the literature. The EIC of (b) (4) µg/L for metformin is less than this toxicity value by more than (b) (4). These comparisons indicate a low likelihood of adverse aquatic effects due to this application. Furthermore, the modes of action (MOAs) for these two products do not appear to be related to MOAs associated with highly active pharmaceuticals.

Cumulative impacts from all uses of this drug in the US, including due to this action, also appear to be low. The canagliflozin EIC represents all uses of this drug in the US, and the MOA appears to be somewhat unique. Thus the above assessment is complete with regard to cumulative (total additive) exposure to this substance. The metformin use from this application, however, is only about (b) (4)% of the total use of metformin. A worst-case EIC based on total use of metformin would be approximately (b) (4) µg/L. While this EIC is higher than measured concentrations in surface waters, applying conservative estimates of dilution to this EIC, as well as reductions due to human metabolism and wastewater treatment, results in an expected environmental concentration (EEC) of approximately (b) (4) µg/L. This concentration is almost (b) (4) lower than the chronic toxicity value of 44 µg/L. Thus, there does not appear to be a significant impact from cumulative (total additive) exposure to metformin in the aquatic environment.

In summary, the EA provided by the sponsor is adequate for approval because it contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment. Furthermore, the results of the risk characterizations in the EA and this review suggest that the specific use of INVOKAMET tablets will not significantly impact the environment. Based on the information available to date, therefore, a finding of no significant impact (FONSI) is recommended for this application.

B. Background

Canagliflozin/metformin is a fixed-dose combination tablet intended to be used as an adjunct to diet and exercise in the management of type 2 diabetes mellitus (T2DM) patients who are not adequately controlled on a regimen containing metformin or canagliflozin. Metformin is a biguanide whereas canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor; the two different mechanisms of action are expected to produce beneficial additive effect in the treatment of T2DM. The four strengths of the FDC tablet intended for marketing are 50/500 mg, 150/500 mg, 50/1000 mg, and 150/1000 mg (canagliflozin/metformin HCl).

Canagliflozin was approved for use in JRD products on February 28, 2013 under NDA 204-042. The IMS 2012 drug use database contains no data for canagliflozin. The total 5-year production amount for all formulations, however, as described in NDA 204-042, is estimated as less than a total of (b) (4) kg of canagliflozin per year.

Metformin is used in several generic products. The IMS 2012 drug use database contains estimates that total use of metformin was (b) (4) kg/year, (b) (4) (b) (4)

JRD provided an environmental assessment (EA) for canagliflozin/metformin because the product does not meet the requirements for a categorical exclusions (21 CFR Part 25). In particular, approval of this product would likely increase the use of canagliflozin, and the calculated expected introduction concentration for the aquatic environment (EIC) would be more than 1 part per billion (ppb, based on the fifth year projection forecast). Metformin use, however, is not expected to increase, and thus a categorical exclusion, while not requested by the sponsor, likely would have been acceptable. The information provided for metformin in the sponsor's EA has also been reviewed.

C. Environmental Assessment Review

A summary of the EA provided by the sponsor is provided below. Comments based on the FDA review of the EA are provided in italics.

1. **EA Date:** November 13, 2012; submitted December 12, 2012

2. **Author:** Janssen Research & Development, L.L.C. (JRD)

3. **Address:** 920 Route 202, Raritan, NJ 08869, U.S.A.

4. **Proposed Action:** JRD has submitted an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) for the management of Type 2 Diabetes using canagliflozin/metformin fixed dose combination in the following therapies: 50 mg/500 mg, 50 mg/1,000 mg, 150 mg/500 mg, and 150 mg/1,000 mg.

5. Identification of Chemicals

(i) Established Name: Canagliflozin

a. Brand/Proprietary Name/Tradename: INVOKAMET (when combined with metformin)

b. Chemical Abstracts Names: canagliflozin (USAN)

Systematic Chemical Name: (1S)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate

Other Name(s): (2S,3R,4R,5S,6R)-2-[3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl]-6-(hydroxymethyl)oxane-3,4,5-triol;hydrate

(1S)-1,5-anhydro-1-C-(3-{[5-(4-fluorophenyl)thiophen-2-yl]methyl}-4-methylphenyl)-D-glucitol hemihydrate

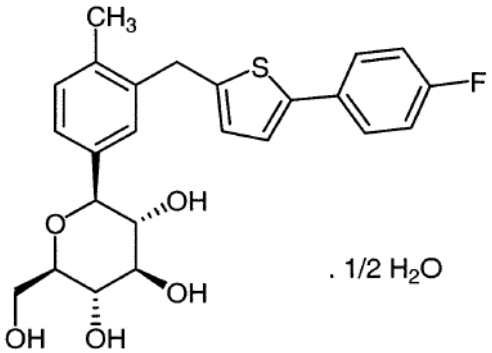
D-Glucitol, 1,5-anhydro-1-C-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-, hydrate (2:1), (1S)-

c. Chemical Abstract Services Number (CASN): 928672-86-0

d. Molecular Formula: $C_{24}H_{25}FO_5S \bullet \frac{1}{2}H_2O$

e. Molecular Weight: 453.53 g/mol

f. Chemical Structure:



(ii) Established Name: Metformin

a. Brand/Proprietary Name/Tradename: INVOKAMET (when combined with canagliflozin)

b. Chemical Abstracts Name: metformin hydrochloride (USAN)

Systematic Chemical Name: biguanide, 1,1-dimethyl-, hydrochloride

Other Name(s): N,N-dimethyl-imidodicarbonimidic diamide, monohydrochloride

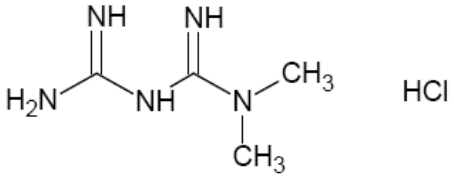
3-(diaminomethylidene)-1,1-dimethylguanidine;hydrochloride

c. CASN: 1115-70-4

d. Molecular Formula: C4H11N5 • HCl

e. Molecular Weight: 165.62 g/mol

f. Chemical Structure:



6. Environmental Characterization

A summary of the physical/chemical values, environmental depletion mechanisms, environmental fate and effects, and risk characterization for this product is provided in the following subsections. Additional discussion of potential cumulative impacts not intended to support the reviewer's conclusions for this proposed action are provided in Attachment 1.

Physical/Chemical Values

The sponsor did not provide data on water solubility, dissociation, or vapor pressure or Henry's Law constant, which would help determine if the compounds are most likely to amass predominantly in aquatic, terrestrial, and/or atmospheric environments. Nor was a scientific basis for not providing these data included in the EA, as recommended in the EA Guidance. The sponsor did, however, provide partition coefficients (log K_{ow}), which the sponsor notes indicate the tendency of an organic chemical to partition into lipids or fats, sorb to particulates such as soils or sediments, sorb to biomass and sludge, and distribute among the various environmental compartments. The sponsor further states that according to the Tier 1 Testing Criteria described in the EA Guidance, chemicals with log K_{ow} <3.5 do not have potential to bioaccumulate. Because the log K_{ow} for canagliflozin is 1.95 and for metformin is -2.48, therefore, these compounds are described as showing low potential to bioaccumulate. Similarly, the sponsor provides adsorption coefficient (K_{oc}) data, noting that these data are indicators of the tendency of an organic chemical to mobilize in the environment. The K_{oc} for canagliflozin and metformin are 5.9 and 39.2, respectively.

<u>Review Comments</u>: The sponsor only provides limited physical/chemical characteristic data, as noted above, and does not put the K_{oc} into context. FDA agrees, however, that per the EA Guidance the log K_{ow} values indicate a low bioaccumulation potential. Also per the EA Guidance, the K_{oc} values, being <<1,000, indicate that these compounds will not tend to adsorb to biosolids. Thus, assumptions used below regarding the movement of these drugs primarily into the aquatic environment are reasonable.

Environmental Depletion Mechanisms

The sponsor does not report any environmental depletion mechanisms or metabolites for either canangliflozin or metformin. Instead, the sponsor uses a screening-level scenario in which no such mechanisms exist (100% of the product will enter the aquatic environment) and that any metabolites are equivalent to the parent compounds.

<u>Review Comments</u>: These are reasonable assumptions for a screening-level EA such as this. Nevertheless, metabolism, treatment, dilution, and environmental degradation are depletion mechanisms that would be expected to reduce the environmental loading and concentration of these products. Also, metabolites, degradants, and other SRSs are expected to enter or exist in the environment. As noted in the EA Guidance, the majority of pharmaceuticals are metabolized to some extent in humans to SRSs that are more polar, less toxic, and less pharmacologically active than the parent compound. Exceptions exist, however, and therefore this review includes a brief assessment of the available clinical and nonclinical data provided to FDA (December 12, 2012 and October 23, 2012, respectively).

The nonclinical review notes that canagliflozin is extensively metabolized in humans to two prominent glucuronide metabolites, M5 and M7, and that both metabolites are inactive and highly water soluble and readily excreted into urine and feces, with no safety concern. Specifically, less than 1% of the administered canagliflozin dose is excreted unchanged in urine, approximately 7-10% is excreted in urine as M5, and approximately 21–32% is excreted as M7 (Devineni et al. 2013). Excretion in feces was mainly as canagliflozin (41.5%), M9 (7.0%), and M7 (3.2%), based on clinical data provided by the sponsor (November 12, 2012). Thus, potentially over 90% of conagliflozin, in the form of the parent compound and its conjugated metabolites, are released to WWTPs. No data could be found on the reduction of canagliflozin during treatment.

In contrast, metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. One estimate indicates that approximately 60% is excreted and enters WWTPs (Oosterhuis et al. 2013). Over 90% is either removed or converted to guanylurea during treatment, with final effluent ratios of guanylurea to metformin at approximately 10:1 (Scheurer et al. 2012, Oosterhuis et al. 2013).

Environmental Fate and Effects

The sponsor notes that disposal of prescribed product will be through use, with returned product disposed of through high temperature incineration at licensed disposal facilities. The sponsor otherwise does not report any environmental fate information for either canagliflozin or metformin. Instead, the sponsor uses a screening-level scenario in which 100% of the product will remain in the aquatic environment following wastewater treatment and discharge of effluents. The sponsor thus developed MEECs (EICs) of (b) (4) µg/L ((b) (4) ppb) for conagliflozin and (b) (4) µg/L ((b) (4) ppb) for metformin in the aquatic environment, using the mass balance method described in the EA Guidance for the EIC.

Review Comments: These are reasonable assumptions for a screening-level EA such as this. The canagliglozin EIC (MEEC) represents all uses of this drug in the US. The metformin EIC of (b) (4) µg/L, however, is only about (b) (4)% of the total concentration of metformin, based on IMS data noted in Section B above, i.e., approximately (b) (4) mg/L ((b) (4) µg/L). To confirm this level and assess actual environmental fate via a comparison of this total EIC to measured amounts, FDA conducted a literature search on metformin, with the following results:

- *Two US WWTPs were found to be associated with the following average concentrations of metformin: Plant A, 7.61 µg/L influent, 0.97 µg/L effluent; Plant B, 2.09 µg/L influent, 0.53 µg/L effluent (Ottmar et al. 2013). These influent and effluent concentrations are considerably lower—(b) (4)—than the total concentration EIC of (b) (4) µg/L noted above. The difference between the influents and the total concentration EIC can be explained to some extent by human metabolism of the drug and possibly the relatively high student populations in the two towns and thus the likely lower use of metformin compared to towns with older populations (Wysowski et al. 2003, Cheung et al. 2009). The lower effluent concentrations reflect the treatment and dilution occurring with the WWTP. For recipient waters, maximum concentrations of the parent drug metformin of 0.15 µg/L were reported in US streams (Scheurer et al. 2012).*

- *Concentration data for metformin also were found related to foreign WWTPs. In one study, a sample of WWTPs in Portugal were receiving waste from four hospitals. The influent averaged 0.72 µg/L, with a maximum of 1.57 µg/L, and the effluent averaged 0.164 µg/L, with a maximum of 0.299 µg/L (Santos et al. 2013). In a sample of WWTPs in Holland, the influent averaged 79 µg/L and the effluent averaged 1.5 µg/L (Oosterhuis et al. 2013).*

Tables 1 and 2, from the sponsor's EA, summarize the aquatic toxicity data for canagliflozin and metformin.

Table 1. Toxicity Testing of Canagliflozin with Representative Environmental Organisms

Test Organism	Conditions	Results
Microbial Inocula	Microbial growth inhibition	NOEC = 368 mg/L EC_{50} > 1000 mg/L
Algae (*Pseudokirchneriella subcapitata*)	Acute toxicity	NOEC = 8.0 mg/L EC_{50} > 8.0 mg/L (72 h)
Daphnids (*Daphnia magna*)	Acute toxicity	NOEC = 9.1 mg/L EC_{50} > 9.1 mg (48 h)
Rainbow Trout (*Oncorhynchus mykiss*)	Acute toxicity	NOEC = 9.3 mg/L LC_{50} > 9.3 mg/L (96 h)

EC_{50} = median effective concentration
NOEC = no observed effect concentration
LC_{50} = median lethal concentration

Table 2. Toxicity Testing of Metformin with Representative Environmental Organisms

Test Organism	Conditions	Results
Microbial Inocula	Microbial growth inhibition	NOEC = 1.5 mg/L EC_{50} > 750 mg/L
Algae (*Pseudokirchneriella subcapitata*)	Acute toxicity	NOEC = 99 mg/L EC_{50} > 99 mg/L (72 h)
Daphnids (*Daphnia magna*)	Acute toxicity	NOEC = 110 mg/L EC_{50} > 110 mg (48 h)
Zebra Fish (*Brachydanio rerio*)	Acute toxicity	NOEC = 110 mg/L LC_{50} > 110 mg/L (96 h)

EC_{50} = median effective concentration
NOEC = no observed effect concentration
LC_{50} = median lethal concentration

Review Comments: Based on these data, algae is the most sensitive species tested for canagliflozin, with a NOEC of 8 mg/L. For metformin, either microbial inocula or algae are the most sensitive species tested, depending on whether the NOEC or EC_{50} are used. A literature search did not result in any additional data for canagliflozin, but did result in a slightly lower EC_{50} for metformin—60 mg/L for daphnid—which was divided by 1,000 to obtain a chronic value of 60 µg/L (Santos et al. 2013). Another study developed a chronic toxicity value of 44 µg/L using the ECOSAR model developed by the US Environmental Protection Agency (EPA) (Dong et al. 2013).

As discussed in the nonclinical data overview provided by the sponsor (October 23, 2012), glucuronide conjugated metabolites are recognized as safe detoxification pathways for elimination of the compound from the body and render the compound more water soluble and pharmacologically inactive. M5 and M7 metabolites were approximately 800-fold less potent than the parent for inhibition of SGLT2 and are considered to be inactive metabolites. Furthermore, according to the data overview, there is a lack of activity against cytochrome P450 (CYP), and transporter activity studies for M5 and M7 at clinically relevant concentrations is consistent with a low

propensity for these metabolites to perpetrate drug-drug interactions (DDIs). The sponsor concludes that these results suggest that M5 and M7 are pharmacologically and toxicologically inactive. Nevertheless, due to the potential for deconjugation of metabolites during wastewater treatment or in the aquatic environment, these metabolites should be assumed to be equivalent to the parent compound.

Metformin's degradation product from wastewater treatment, guanylurea, showed no toxic effects on the bacterial community in a manometric respiratory test at a concentration of 11.9 mg/L (Scheurer et al. 2012).

Risk Characterization

The sponsor states that in accordance with the Tier 1 Testing Criteria described in the EA Guidance, no further testing is required. The microbial inhibition test found canagliflozin to have an EC_{50} of greater than 1,000 mg/L, the log K_{ow} was determined to be <3.5, after which acute ecotoxicity studies were reported. The calculated AF for each of the three acute toxicity studies is >1,000, and no observed effects were seen at the MEEC. Therefore, no further testing is required for canagliflozin. Similarly, the microbial inhibition test found metformin to have an EC_{50} of greater than 750 mg/L, the log K_{ow} was determined to be <3.5, after which acute ecotoxicity studies were reported. The calculated AF for each of the three acute toxicity studies is >1,000, and no observed effects were seen at the MEEC (EIC). Therefore, no further testing is required for metformin.

<u>Review Comments</u>: The microbial inhibition tests are primarily for assessing the potential for the compound to disrupt waste treatment processes, as described in the EA Guidance. The sponsor does not conduct this assessment, however. Therefore, FDA compared the canagliflozin microbial NOEC of 368 mg/L noted above to the canagliflozin EIC (MEEC), as a surrogate for the waste treatment influent concentration, of (b) (4) µg/L (b) (4) mg/L). This difference of (b) (4) indicates that canagliflozin would have virtually no potential to disrupt waste treatment processes. Similarly, the (b) (4) difference between the metformin microbial NOEC of 1.5 mg/L and EIC of (b) (4) µg/L (b) (4) mg/L) indicates that this application for metformin also would have virtually no potential to disrupt waste treatment processes. Cumulatively, this assessment already includes all uses of canaglifozin. For metformin, however, this application would contribute only about (b) (4)% to the total amount of metformin used in the US, based on the IMS data noted in Section B above. The total amount of metformin in the US represents a total concentration of approximately (b) (4) mg/L. In terms of microbial disruption, this value is still (b) (4) below the metformin microbial NOEC of 1.5 mg/L, and thus metformin presents a low risk of disrupting waste treatment processes.

Regarding aquatic toxicity, the canagliflozin and metformin AFs of >1,000, along with the log K_{ow}s of <3.5 and no observed sublethal effects at the EICs, would indicate that no further testing is required, as described in the EA Guidance. To confirm this result, FDA conducted a literature search on the aquatic toxicity of these compounds. For canagliflozin, because it is a relatively new molecular entity, FDA conducted a screening

computational toxicology assessment. The results of these additional analyses are provided below:

- *Canagliflozin. No additional aquatic risk data were found on canagliflozin during a literature search. Given recent concerns about hormonally active compounds, canagliflozin nonclinical data for this application were reviewed for reproductive toxicity. These data noted that canagliflozin had no effects on the ability of rats to mate and sire or maintain a litter up to the high dose of 100 mg/kg (~14x and 18x the maximum recommended human dose (MRHD) in males and females, respectively), although there were minor alterations in a number of reproductive parameters (decreased sperm velocity, increased number of abnormal sperm, slightly fewer corpora lutea, fewer implantation sites, and smaller litter sizes) at the highest dosage administered. Nevertheless, these nonclinical doses are many orders of magnitude higher than those expected in the aquatic environment. A computational toxicology assessment also was performed on the canagliflozin chemical structure as a method to evaluate whether the molecule bears any known structural alerts for reproductive and developmental toxicity. Two complementary (quantitative) structure-activity relationship (Q)SAR methodologies were employed in the analysis; one expert rule-based SAR (Derek Nexus 3.0.1) and a statistical QSAR system (Leadscope 1.6.0-3). The results of the predictions from both computational programs were negative for reproductive toxicity (Attachments 2 and 3). In addition, canagliflozin is a sodium-dependent glucose co-transporter 2 (SGLT2) inhibitor, which is an MOA that does not appear on the list of MOAs described in a recent FDA response to a citizen petition on drugs in the environment (USFDA 2013). Together, these findings, along with the lack of observed effects at the EIC, support the default conclusion in the EA Guidance that an AF of greater than 1,000 provides sufficient confidence of no adverse effects at the EIC. (Note that this is equivalent to calculating a chronic toxicity value of (b) (4) µg/L using the lowest NOEC of 8 mg/L and a screening-level adjustment factor of 1,000, and then comparing the resulting (b) (4) µg/L chronic toxicity value to a EIC of (b) (4) µg/L, with the result that the EIC is less than the chronic toxicity value (b) (4).)*

- *Metformin. Comparing the metformin EIC of (b) (4) µg/L for this application with the lowest chronic toxicity value noted above, 44 µg/L, results in a ratio of (b) (4), indicating a low likelihood of adverse aquatic effects due to this application. A cumulative EEC (expected environmental concentration) of approximately (b) (4) µg/L was calculated for all uses of metformin by starting with the total metformin EIC of (b) (4) µg/L, applying a standard dilution factor of 10, a 40% reduction due to human metabolism, and a 90% reduction due to treatment. While (b) (4) µg/L is still larger than the measured effluent concentrations noted above for US WWTPs and the maximum measured surface water concentration (it should be lower), it is still almost (b) (4) lower than the chronic toxicity value of 44 µg/L. Thus, there does not appear to be a significant impact from cumulative (additive) exposure of metformin in the aquatic environment. Two recent*

assessments of metformin came to similar conclusions (Stockholm City Council 2011, Brausch et al. 2012).

7. Mitigation Measures and Alternatives

No significant adverse environmental impact is expected from this NDA based on the information available to date, and therefore no mitigation measures or alternatives are addressed other than the monitoring of scientific literature for potential environmental impacts.

8. Submitted Study Reports

The following study reports were submitted with or reference by the EA:

Van Meter D. JNJ-28431754 – Determination of n-Octanol/Water Partition Coefficient Following OECD Guidelines, Section 117. Springborn Smithers Study No. 13674.6198. JNJ Study No. RMD 1092. 4 August 2010.

Van Meter D. JNJ-28431754 – Determination of the Koc Coefficient Following OECD Guideline 121 (Sewage Sludge). Springborn Smithers Study No. 13674.6197. JNJ Study No. RMD 1091. 3 August
2010.

Turk R. JNJ-28431754 – Activated Sludge Respiration Inhibition Test Following OECD Guideline 209. Springborn Smithers Study No. 13674.6202. JNJ Study No. RMD 1096. 26 May 2010.

Soucy K. JNJ-28431754 – 72-Hour Acute Toxicity Test with Freshwater Green Alga, Pseudokirchneriella subcapitata, Following OECD Guideline 201. Springborn Smithers Study No. 13674.6199. JNJ Study No. RMD 1093. 15 December 2010.

Fournier A. JNJ-28431754 – Acute Toxicity to Water Fleas, (Daphnia magna), Under Static Conditions, Following OECD Guideline #202. Springborn Smithers Study No. 13674.6200. JNJ Study No. RMD 1094. 18 November 2010.

Fournier A. JNJ-28431754 – Acute Toxicity to Rainbow Trout (Oncorhynchus mykiss) Under Static Conditions, Following OECD Guideline # 203. Springborn Smithers Study No. 13674.6201. JNJ Study No. RMD 1095. 17 November 2010.

Reibach P. Metformin Hydrochloride – Determining the Partitioning Coefficient (n-Octanol/Water) by the Fask-Shaking Method Following OECD Guideline 107. Smithers Viscient Study No. 13674.6227. JNJ Study No. RMD 1152. 3 November 2011.

Kang S. [14C]Metformin Hydrochloride – Determining the Adsorption Coefficient (Koc) Following OECD Guideline 106. Smithers Viscient Study No. 13674.6225. JNJ Study No. RMD 1151. 8 September 2011.

Griffith A. Metformin Hydrochloride – Activated Sludge Respiration Inhibition Test Following OECD Guideline 209. Smithers Viscient Study No. 13674.6228. JNJ Study No. RMD 1153. 6 March 2012.

Kirkwood A. Metformin Hydrochloride – 72-Hour Acute Toxicity Test with Freshwater Green Alga, Pseudokirchneriella subcapitata, Following OECD Guideline #201 and the Official Journal of the European Communities L220/36, Method C.3. Springborn Smithers Study No. 13751.6179. Janssen Study No. RMD 1146. 7 January 2011.

Sayers L. Metformin Hydrochloride – Acute Toxicity to Water Fleas, (Daphnia magna) Under Static Conditions, Following OECD Guideline #202 and The Official Journal of the European Communities L142/456, Method C.2. Springborn Smithers Study No. 13751.6180. Janssen Study No. RMD 1147. 11 January 2011.

Sayers L. Metformin Hydrochloride – Acute Toxicity to Zebra Fish (Brachydanio rerio) Under Static Conditions, Following OECD Guideline Number 203 and The Official Journal of the European Communities L 142/446, Method C.1. Springborn Smithers Study No. 13751.6181. Janssen Study No. RMD 1148. 14 January 2011.

D. Additional Literature Considered by Reviewer

Beck, B. H. and S. A. Fuller. 2012. The Impact of Mitochondrial and Thermal Stress on the Bioenergetics and Reserve Respiratory Capacity of Fish Cell Lines. Journal of Aquatic Animal Health **24**:244-250.

Brausch, J. M., K. A. Connors, B. W. Brooks, and G. M. Rand. 2012. Human Pharmaceuticals in the Aquatic Environment: A Review of Recent Toxicological Studies and Considerations for Toxicity Testing. Pages 1-99 *in* D. M. Whitacre, editor. Reviews of Environmental Contamination and Toxicology. Springer US.

Cheung, B. M. Y., K. L. Ong, S. S. Cherny, P.-C. Sham, A. W. K. Tso, and K. S. L. Lam. 2009. Diabetes Prevalence and Therapeutic Target Achievement in the United States, 1999 to 2006. The American Journal of Medicine **122**:443-453.

Devineni, D., C. R. Curtin, D. Polidori, M. J. Gutierrez, J. Murphy, S. Rusch, and P. L. Rothenberg. 2013. Pharmacokinetics and Pharmacodynamics of Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, in Subjects With Type 2 Diabetes Mellitus. The Journal of Clinical Pharmacology.

Dong, Z., D. B. Senn, R. E. Moran, and J. P. Shine. 2013. Prioritizing Environmental Risk of Prescription Pharmaceuticals. Regulatory Toxicology and Pharmacology **65**:60-67.

Garceau, N., N. Pichaud, and P. Couture. 2010. Inhibition of goldfish mitochondrial metabolism by< i> in vitro</i> exposure to Cd, Cu and Ni. Aquatic Toxicology **98**:107-112.

Lerebours, A., C. Adam-Guillermin, D. Brèthes, S. Frelon, M. Floriani, V. Camilleri, J. Garnier-Laplace, and J.-P. Bourdineaud. 2010. Mitochondrial energetic metabolism perturbations in skeletal muscles and brain of zebrafish (< i> Danio rerio</i>) exposed to low concentrations of waterborne uranium. Aquatic Toxicology **100**:66-74.

Nesci, S., V. Ventrella, F. Trombetti, M. Pirini, and A. Pagliarani. 2011. Tributyltin (TBT) and mitochondrial respiration in mussel digestive gland. Toxicology In Vitro **25**:951-959.

Oosterhuis, M., F. Sacher, and T. L. ter Laak. 2013. Prediction of concentration levels of metformin and other high consumption pharmaceuticals in wastewater and regional surface water based on sales data. Science of the Total Environment **442**:380-388.

Ottmar, K. J., L. M. Colosi, and J. A. Smith. 2013. Evaluation of a Prediction Model for Influent Pharmaceutical Concentrations. Journal of Environmental Engineering **In press**.

Rena, G., E. R. Pearson, and K. Sakamoto. 2013. Molecular mechanism of action of metformin: old or new insights? Diabetologia:1-9.

Santos, L. H. M. L. M., M. Gros, S. Rodriguez-Mozaz, C. Delerue-Matos, A. Pena, D. Barceló, and M. C. B. S. M. Montenegro. 2013. Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals. Science of the Total Environment **461-462**:302-316.

Scheurer, M., A. Michel, H.-J. Brauch, W. Ruck, and F. Sacher. 2012. Occurrence and fate of the antidiabetic drug metformin and its metabolite guanylurea in the environment and during drinking water treatment. Water Research **46**:4790-4802.

Shen, R. 2013. Potential of Pharmaceuticals and Personal Care Products (PPCPs) as Nitrosamine Precursors during Drinking Water Disinfection. University of Toronto.

Shen, R. and S. A. Andrews. 2011. Demonstration of 20 Pharmaceuticals and Personal Care Products (PPCPs) as Nitrosamine Precursors during Chloramine Disinfection. Water Research **45**:944-952.

Stockholm City Council. 2011. Environmentally Classified Pharmaceuticals. Stockholm City Council, Stockholm, Sweden.

USFDA. 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. Page 39 *in* Center for Biologics Evaluation and Research, editor. US Food and Drug Administration, Rockville, MD.

USFDA. 2013. Response to citizen petition to the FDA commissioner under the national environmental policy act and administrative procedure act requesting an amendment to a FDA rule regarding human drugs and biologics. Page 16.

Wysowski, D. K., G. Armstrong, and L. Governale. 2003. Rapid increase in the use of oral antidiabetic drugs in the United States, 1990–2001. Diabetes Care **26**:1852-1855.

E. Conclusions

The EA is adequate for approval of the NDA. It contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and supporting reports, in FDA guidance, and of the scientific validity of the "no significant effects" conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA for INVOKAMET tablets.

Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application.

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/s/

JAMES P LAURENSON
10/18/2013

NAKISSA SADRIEH
10/18/2013