CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366/S-016

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEP – HFD 510	21-366
3. NAME AND ADDRESS OF APPLICANT		**4. SUPPLEMENT NUMBER, DATE**
IPR Pharmaceuticals, Inc. P.O. Box 1967 Carolina, PR 00984-1967	Authorized U.S. Agent AstraZeneca Pharmaceuticals LP 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355	S-016, 08-Apr-2009

5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	7. AMENDMENTS, REPORT, DATE
Crestor (rosuvastatin calcium) Tablets	rosuvastatin calcium	SE1-016QR, 04-Dec-2009 SE1-016, 15-Jun-2010

8. SUPPLEMENT PROVIDES FOR:

The reduction of total mortality and the risk of major cardiovascular events in adult patients with an increased risk of cardiovascular disease.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Lipid lowering agent	Rx	

12. DOSAGE FORM	13. POTENCY
Oral	5mg, 10mg, 20mg, 40mg

14. CHEMICAL NAME AND STRUCTURE

See Chemistry Review #1

15. COMMENTS

Since the approval of this indication would increase the use of Crestor, Dr. Egan, Deputy Director for Safety DMEP requested additional information to support the categorical exclusion. The following information request was conveyed to the applicant:

- Please provide an accurate projection of the expected use of CRESTOR based on the JUPITER indication. In addition, please include the sales forecast numbers (number of patients) used to calculate the data to support the Categorical Exclusion statement from the 4 December response and recalculate the Categorical exclusion calculations to reflect the current amount (based on the 2009 CRESTOR NDA Annual Report Distribution Data) plus the amount of use based on the projected forecast.

The applicant has revised their expected environmental concentration from(b) (4) µg/L (ppb) to(b) (4) µg/L (ppb) which is below the EA threshold of 1 ppb. Therefore, the request for the categorical exclusion under 21 CFR 25.31(b) is granted.

16. CONCLUSION AND RECOMMENDATION

The applicant's revised request for a categorical exclusion from preparing an environmental assessment is granted. From a CMC standpoint, this supplement can be approved.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
JANICE T. BROWN	See attached electronic signature sheet	19-Jan-2010

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

Attachment 1: Categorical Exclusion Request

A claim for a Categorical Exclusion of rosuvastatin from an Environmental Assessment (EA) (per 21 CFR Parts 25.30 and 25.31) is made based on the assertion that the use of the active moiety and/or the estimated concentration of the substance at the point of entry into the aquatic environment will not be greater than 1 ppb (1 μg/L). To support the claim for a Categorical Exclusion, the Expected Introduction Concentration (EIC) of rosuvastatin calcium at the point of entry into the aquatic environment was calculated using the procedure outlined in the Food and Drug Administration's (FDA) guidance. In addition, the assumptions which underlie the projected production forecast volumes for direct use for years 2009 through 2015 (7-year projection) are shown below.

Crestor (rosuvastatin) and Certriad (rosuvastatin/fenofibric acid) will be promoted by AstraZeneca according to the approved indications at the time. The forecast provided is an optimum view, and assumes approval of the Crestor JUPITER NDA 21-366 (S-016) submission in February 2010 and expected approval of Certriad NDA(b) (4) in March 2010. November 2009 IMS National Prescription Audit data shows that Crestor accounted for(b) (4) of all statin scripts in the United States and (b) (4)of all statin volume sales (i.e. Standard Units) at the same period (Refs 1 and 2).

The current forecast assumes that approximately(b) (4)of patients treated with a statin will receive Crestor or Certriad in the US by 2015. This forecast is based on the assumptions that existing guidelines on the prevention, detection, evaluation, and treatment of high cholesterol /dyslipidemia (ATP III) will be updated through the Adult Treatment Panel IV (ATP IV) by the National Lung and Blood Institute in 2H'2010 and 39% of statin eligible patients under ATP IV are treated with a statin (Ref 3).

1.EXPECTED INTRODUCTION CONCENTRATION (EIC)

The Expected Introduction Concentration (EIC) describes the amount of an active moiety that is expected to enter the aquatic environment in the United States after use. The calculation, as described below, assumes that:

- All drug products produced in a year are used and enter the publicly owned treatment works (POTWs) system;
- Drug product usage occurs throughout the USA in proportion to the population and amount of waste water generated, and;
- There is no metabolism. However, the EIC calculation can consider the extent of metabolism of the active moiety to less pharmacologically active or inactive compounds, if that information is available.

The following EIC is based on all AstraZeneca LP drug products containing rosuvastatin. The calculation includes the largest projected production forecast for direct use, per year, in the US market for the years 2009 to 2015 inclusive. Based on these assumptions, the maximum quantity of rosuvastatin is estimated to be produced in year 2015. The EIC calculation is based on a worst-case scenario, i.e. no metabolism or degradation is taken into account.

EIC Aquatic (ppb) = A × B × C × D

(b) (4)

Based on the sales estimates and using the highest quantity of the active moiety expected to be produced for direct use through to 2015, the EIC for rosuvastatin was calculated to be (b) (4) µg/liter (ppb). Thus, the claim for an exemption from an environmental assessment for this application is supported.

2. EXPECTED ENVIRONMENTAL CONCENTRATION (EEC)

The Expected Environmental Concentration (EEC) of the active moiety is calculated by dividing the EIC with a dilution factor of 10, which is the dilution factor for POTWs available from the U.S. Environmental Protection Agency.
EEC = EIC/10 = (b) (4) µg/L

3. REFERENCES

1. 2009 Crestor TRx Data: November 2009 IMS NPA Data plus estimate for December demand and inventory sales.

2. 2009 Extended Units / TRx Data: November 2009 IMS NPA Data

3. Statin Eligibility Data: NHANES 1999 – 2004 Data (Data is based on 2004 population; therefore data has been forecast at a 1.16% per year growth rate per US Census Population Bureau Forecast)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICALS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

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

/s/

JANICE T BROWN
01/19/2010

JAMES D VIDRA
01/19/2010

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEP – HFD 510	21-366
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
IPR Pharmaceuticals, Inc. P.O. Box 1967 Carolina, PR 00984-1967	Authorized U.S. Agent AstraZeneca Pharmaceuticals LP 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355	S-016, 08-Apr-2009
5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	7. AMENDMENTS, REPORT, DATE
Crestor (rosuvastatin calcium) Tablets	rosuvastatin calcium	SE1-017QR, 04-Dec-2009
8. SUPPLEMENT PROVIDES FOR:		
The reduction of total mortality and the risk of major cardiovascular events in adult patients with an increased risk of cardiovascular disease.		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Lipid lowering agent	Rx	
12. DOSAGE FORM	13. POTENCY	
Oral	5mg, 10mg, 20mg, 40mg	
14. CHEMICAL NAME AND STRUCTURE		
See Chemistry Review #1		

15. COMMENTS

1. The applicant has requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR, part 25, §25.31 (b) for rosuvastatin calcium. This supplement meets the requirements of a categorical exclusion under 21 CFR §25.31 (b) because the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (refer to next page for expected introduction concentration (EIC). To the best of the applicant's knowledge, no extraordinary circumstances exist relative to this action. The applicant's request for a categorical exclusion is granted.

2. There are no CMC labeling changes for CRESTOR® *(rosuvastatin calcium) Tablets, Film Coated for Oral Use* in sections 3 DOSAGE FORMS AND STRENGTHS, 11 DESCRIPTION, and 16 HOW SUPPLIED/STORAGE AND HANDLING.

3. From a CMC standpoint, this supplement can be approved.

16. CONCLUSION AND RECOMMENDATION

The applicant's request for a categorical exclusion from preparing an environmental assessment is granted. There are no CMC labeling changes. From a CMC standpoint, this supplement can be approved.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
JANICE T. BROWN	See attached electronic signature sheet	09-Dec-2009

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

APPLICANT'S EXPECTED INTRODUCTION CONCENTRATION (EIC)

The EIC was calculated using the procedure outlined in the Food and Drug Administration's (FDA) guidance and an evaluation of the projected sales and production volumes for the years 2009 through 2013 (5-year projection). According to the applicant the EIC calculation, as described below, assumes that:

- All drug products produced in a year are used and enter the publicly owned treatment works (POTWs) system;
- Drug product usage occurs throughout the USA in proportion to the population and amount of waste water generated, and;
- There is no metabolism. However, the EIC calculation can consider the extent of metabolism of the active moiety to less pharmacologically active or inactive compounds, if that information is available.

The following EIC is based on all AstraZeneca LP drug products containing rosuvastatin. The calculation includes the largest projected production forecast for direct use, per year, in the US market for the years 2009 to 2013 inclusive. Based on these assumptions, the maximum quantity of rosuvastatin is estimated to be produced in year 2013. The EIC calculation is based on a worst-case scenario, i.e. no metabolism or degradation is taken into account.

EIC Aquatic (ppb) = A · B · C · D

(b) (4)

Based on the 5-year sales estimates through to 2013, and using the highest quantity of the active moiety expected to be produced for direct use in any of the next five years, the EIC for rosuvastatin, was calculated to be(b) (4) µg/liter (ppb).

EXPECTED ENVIRONMENTAL CONCENTRATION (EEC)

The Expected Environmental Concentration (EEC) of the active moieties is calculated by dividing the EIC with a dilution factor of 10, which is the dilution factor for POTWs available from the U.S. Environmental Protection Agency.

EEC = EIC/10 = (b) (4) µg/L

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICALS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

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

/s/

JANICE T BROWN
01/08/2010

JAMES D VIDRA
01/08/2010