CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-474

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: August 12, 2010

To: NDA 22-474

From: Terrance Ocheltree, Ph.D., R. Ph.
Division Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-474 Ella (ulipristal acetate) tablets.

I have assessed the ONDQA review of NDA 22-474 by Bogdan Kurtyka. The initial review was finalized on June 25, 2010 with a recommendation for a Complete Response (not Approval) due to unresolved labeling issues. On August 12, 2010 the sponsor submitted updated labeling resolving the CMC related labeling issues. Therefore, the CMC reviewer changed the CMC recommendation to "Approval". The Office of Compliance has recommended "Acceptable" for the proposed manufacturing and testing sites, as shown in EES. Sufficient information has been provided to assure identity, strength, purity and quality.

No post marketing commitments are proposed in either of the ONDQA.

NDA 22-474 is for a non-coated oral tablet indicated for emergency contraception after unprotected intercourse. Each tablet contains 30 mg of ulipristal (as ulipristal acetate). The proposed commercial packaging is a single tablet in a blister foil inside of a carton. A 36 months expiry period has been granted when the product is stored at 15-25°C (59-77°F).

I concur with the approval recommendation from a CMC perspective without any post marketing commitments.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22474	ORIG-1	LABORATOIRE HRA PHARMA	Ella , Ulipristal Acetate

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/s/

TERRANCE W OCHELTREE
08/13/2010

Memorandum	Department of Health and Human Serviced Food and Drug Administration Center for Drug Evaluation and Research
Date:	12-AUG-2010
To:	NDA 22-474 CMC Review #1
From:	Bogdan Kurtyka, Ph.D.
Through:	Moo-Jhong Rhee, Ph.D. Chief, Branch IV ONDQA Division II
CC:	Donna Christner, Ph.D.
Subject:	**Final recommendation for NDA 22-474**

Previous CMC Review #1 dated 25-JUN-2010 noted following labeling issues with a recommendation of "Non Approval" action.

- Established name and route of administration are missing from section #11 (Description) of the package insert
- Strength of dosage form not listed in section #16 (How Supplied/Storage and Handling) of the package insert

The sponsor submitted the updated labeling on 12-AUG-2010 and addressed above issues satisfactorily.
Therefore, from a CMC perspective, NDA 22-474 is now recommended for "Approval".

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NDA-22474	ORIG-1	LABORATOIRE HRA PHARMA	Ella , Ulipristal Acetate

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/s/

BOGDAN KURTYKA
08/12/2010

MOO JHONG RHEE
08/12/2010
Chief, Branch IV

NDA 22-474

Ella (ulipristal acetate) tablets 30mg

Laboratoire HRA Pharma

Bogdan Kurtyka, Ph.D.
Review Chemist

Office of New Drug Quality Assessment
Division II, Branch IV

CMC REVIEW OF NDA 22-474
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

CMC Review Data Sheet

1. NDA 22-474

2. REVIEW #: 1

3. REVIEW DATE: 25-JUN-2010

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	14-OCT-2009
Amendment – Manufacturing sites update	27-OCT-2009
Amendment – Response to the IR Letter	07-MAY-2010
Amendment – Labeling Update	11-MAY-2010

7. NAME & ADDRESS OF SPONSOR:

Name:	Laboratoire HRA Pharma
Address:	15, Rue Beranger F-75003 Paris France
US Agent:	Target Health 261 Madison Ave. New York, NY 10021
Telephone:	212-681-2100
Fax:	212-681-2105

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ella
b) Non-Proprietary Name: Ulipristal acetate tablets
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Selective progesterone receptor modulator for emergency contraceptive use

11. DOSAGE FORM: Tablet, film coated CODE: 500

12. STRENGTH/POTENCY: 30 mg

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

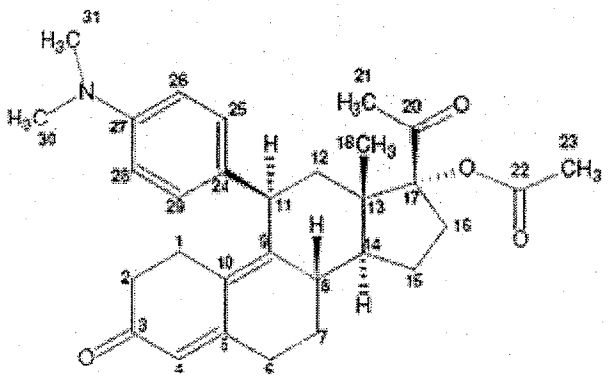
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__√__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 19-Norpregna-4,9-diene-3,20-dione, 17-(acetyloxy)-11-[4-(dimethylamino)phenyl]-, (11β)-;
USAN Name: Ulipristal acetate
CAS Number: CAS-126784-99-4
Structural Formula:



Molecular Formula: $C_{30}H_{37}NO_4$
Molecular Weight: 475.619

17. RELATED/SUPPORTING DOCUMENTS:

CMC Review Data Sheet

A. DMFs:

DMF #	TYPE	(b) (4)	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		1	Adequate	15-JAN-2010	
	III		4	N/A	N/A	
	III		4	N/A	N/A	
	III		4	N/A	N/A	
	III		4	N/A	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10-MAY-2010	Bogdan Kurtyka
Pharm/Tox	N/A		
Biopharm	Acceptable after the dissolution acceptance criterion is revised	07-DEC-2009	Tapash Ghosh
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	Revisions recommended	18-MAR-2010	Walter Fava
EA	Categorical exclusion granted (see review)	04/15/2008	Bogdan Kurtyka
Microbiology	N/A		

The CMC Review for NDA 22-474

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. An overall "Acceptable" site recommendation has been made from the Office of Compliance.

However, issues on labels/labeling have not been resolved. Therefore, from a CMC perspective, this NDA is not recommended for "Approval" in its present form.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The proposed drug substance, ulipristal acetate, is a new molecular entity. The sponsor references (b) (4) for details on the description, characterization, manufacture, packaging, specification for the quality control testing, and stability data of ulipristal acetate. A letter of authorization to cross reference to the DMF is provided in the application. The (b) (4) has been reviewed and found ADEQUATE to support this application.

(2) Drug Product

The drug product is a non-coated tablet indicated for emergency contraception for up to 120 hours and it contains 30 mg of ulipristal acetate. The drug product is manufactured (b) (4) considered to be critical operations, and they are deemed well controlled with acceptable operating ranges.

The sponsor proposed two manufacturing sites; Leon Farma in Spain and (b) (4) Osny Pharma in France. Because of significant manufacturing equipment differences

between these two sites, bioequivalence studies were conducted and data demonstrated that they are bioequivalent.

The drug product specification includes; identification, assay, and content uniformity of the active ingredient, dissolution, disintegration, impurities, mean mass, and microbial purity tests and their analytical methods and acceptance criteria are deemed satisfactory for assuring the identity, strength, purity, and quality.

The container closure system is a single tablet blister in a carton box. Each tablet is packaged in a blister (b) (4)

The sponsor provided the results of 24 months long-term stability studies and there were no significant changes observed in the stability lots. The sponsor has proposed an 36-month expiration dating period under the controlled room conditions, and it is granted.

B. Description of How the Drug Product is Intended to be Used

The drug product should be taken orally, a single ulipristal acetate tablet, up to 120 hours (5 days) after the unprotected intercourse.

C. Basis for Approvability or Not-Approval Recommendation

Adequate controls for raw materials are in place; manufacturing processes are robust and adequately controlled; and the specifications are adequate for ensuring the identity, strength, quality, and purity of the drug substance and the drug product. Adequate container/closure system is in place to protect the drug product during the storage. Sufficient stability data are provided to allow 36-month of the expiration dating period. An overall "Acceptable" recommendation is made from the Office of Compliance.

However, labeling issues are still pending as of this review. Therefore, this NDA is not recommended for "Approval" from a CMC perspective.

III. Administrative

A. Reviewer's Signature: *(See appended electronic signature page)*
Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV/Division II/ONDQA

B. Endorsement Block: *(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV/Division II/ONDQA

C. CC Block: entered electronically in DARRTS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

BOGDAN KURTYKA
06/25/2010

MOO JHONG RHEE
06/25/2010
Chief, Branch IV

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	22-474
Applicant:	HRA Pharma
Stamp Date:	15-Oct-2009
PDUFA Date:	13-Aug-2010 (15-Apr-2010 if Priority)
Trademark:	Ella
Established Name:	Ulipristal acetate
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Emergency contraception up to 120 hours
PAL:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	☐
Comments for 74-Day Letter	X	☐

Summary and Critical Issues:

A. Summary

Ulipristal acetate is a New Molecular Entity (NME). Full information is provided in the referenced DMF.

The drug product is a white to off-white, round, 9 mm diameter tablet engraved on both faces with "ella". The dosage is 30 mg of ulipristal acetate. Each tablet is packaged individually in a colorless transparent (b) (4) /aluminum foil blister stored in a carton box.

The drug product is indicated for emergency contraception up to 120 hours (5 days) after unprotected intercourse.

B. Critical issues for review

The drug substance DMF will require review. Some packaging DMFs may also require review.

The PharmTox reviewer should be consulted to determine if the impurities have been adequately qualified.

It appears that the diasteriomers are not routinely measured in the drug substance. More information may be provided in the DMF. The reviewer should note this during the review of both the DMF and the NDA to see if the DMF holder and the NDA sponsor have adequately addressed this issue.

The sponsor has submitted two different drug product manufacturing sites which are linked by comparative dissolution and a Bioequivalence study. In addition, the container closure system (blister film) was changed during development from (b) (4) *manufacturing site to a clear transparent film used at the second manufacturing site. Extensive stability data has been provided in both container closure systems to qualify these changes. A 36 month expiration dating period is requested based on the stability package.*

C. Comments for 74-Day Letter

We have the following preliminary labeling comments:

- *The NDC numbers should be updated on both the container closure and the PI*
- *Manufacturer and distributor information should be included on the PI*
- *Watson is listed on the container labels, but not on the PI. Please clarify and update the labels accordingly.*

D. Recommendation:

This NDA is fileable from a CMC perspective. A single reviewer, Bogdan Kurtyka, Ph.D., has been assigned. There is one comment for the 74-day letter.

Donna F. Christner, Ph.D.

NDA Number: 22-474 **Type: 1S** **Established/Proper Name: ulipristal acetate**

Applicant: HRA Pharma **Letter Date: 14-Oct-2009** **Stamp Date: 15-Oct-2009**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**		X	N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested as per 21 CFR 25.31(b)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Cross reference to (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross reference to (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross reference to (b) (4)
15.	Does the section contain controls for the DS?	X		Cross reference to (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross reference to (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	10-Sep-2009	Will require review
	III			21-Jul-2009	No review found citing relevant sections. May require review.
	III			29-Jul-2009	No review found citing relevant sections. May require review.
	III			29-Jul-2009	Last review 26-Jul-2005. Updated since then. May require review.
	III			06-Jul-2009	Reviewed 30-Nov-1999. May require review. (See ONDC Policies on Bottles and Blisters*)

**Policy on the Revi ducts (Bottles), 26-Apr-2001*
Policy on the Revie nd Hard Gelatin Capsules, 29-May-2002

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		Manufacturer not listed. SPL provided. NDC numbers need to be updated
33.	Have the immediate container and carton labels been provided?	X		Manufacturer listed as Watson. This should be confirmed. NDC number needs to be updated.

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.		X	N/A
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		See Section C of cover sheet

Donna F. Christner, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Date

REVIEW NOTES

Clinical studies for this NDA were performed under IND 49,381. The sponsor has provided a list of milestone meetings that occurred during development.

Date of Meeting	Type of Meeting	Meeting Objective	Meeting Minutes
30 Sept 1996	End of Phase 1 meeting	To discuss Phase 1 trail results, and toxicological and trial design requirements for Phase 2 and Phase 3 trials.	• Memorandum of Meeting Minutes (Nr 1)
28 April 1998	Pre-Phase 2/3 meeting	To discuss the proposed Phase 2/3 protocol and clinical development plans.	• Memorandum of Meeting Minutes (Nr 2)
25 July 2006	Type A. Post-SPA*	To reach agreement with the Agency on: • the primary efficacy analysis for the phase 3 studies: Protocol 2914-004 (HRA2914-513) and Protocol 2914-005 (HRA2914-509) • the secondary objectives and corresponding analyses for both studies (HRA2914-513 and HRA2914-509) • the definition of study success in Protocol 2914-005 (HRA2914-509) • the pooled-analysis of the two studies (HRA2914-513 and HRA2914-509)	• Memorandum of Meeting Minutes (Nr 3)
N/A	Type C	The objective of this Meeting was to request clarification from the Agency regarding the Quality data requirements for Module 3 of the CTD to support approval of two manufacturing facilities for ulipristal acetate 30 mg tablets in the NDA submission.	• Meeting Request Denial (10 Sept 2008) • Response from FDA (24 Oct 2008)
12 Dec 2008	Type B. Pre-NDA	The objective of the meeting was to discuss the format and contents of the NDA file to support an NDA submission for ulipristal acetate in emergency contraception.	• Memorandum of Meeting Minutes (Nr 4) • Memorandum of Meeting Minutes - Revised (Nr 5)
N/A	Type C	The objective of the meeting was to discuss the format and contents of the NDA file to support an NDA submission for ulipristal acetate in emergency contraception.	• Meeting Request Denial (26 June 2009) • Response from FDA (19 Aug 2009)

* A Special Protocol Assessment request was submitted on July 10, 2006. This Type A meeting was held at the Sponsor's request to discuss the Agency's response.

General CMC advice was given in the 1996 and 1998 meetings.

A CMC meeting was requested in September 2008 and was denied. Written answers were provided for the questions, which dealt with changes in manufacturing and the container closure system. It was recommended that the manufacturing changes were too great to be linked by CMC alone, and that a BE study should be performed. In addition, additional information beyond the planned studies was recommended to support the container closure changes. The letter is included in the NDA submission, but the review in DARRTS dated 16-Oct-2008 should be consulted for the reasoning behind the decisions made.

In the meeting held on 12-Dec-2008, it was emphasized that the BE study should be conducted prior to and submitted in the original NDA submission. The sponsor accepted the recommendation and provides the detail in the submission.

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NDA-22474	ORIG-1	LABORATOIRE HRA PHARMA	Ella , Ulipristal Acetate

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/s/

DONNA F CHRISTNER
12/03/2009

MOO JHONG RHEE
12/04/2009
Chief, Branch III