

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204242Orig1s000

CHEMISTRY REVIEW(S)

NDA 204242

**Zubsolv™ Tablets
(Buprenorphine and Naloxone SL Tablets)**

Orexo AB

**Julia C. Pinto, Ph.D.
Office of New Drug Quality Assessment, Division III**

Division of Anesthesia, Analgesia and Addiction Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	8
III. Administrative	8
A. Reviewer’s Signature	8
B. Endorsement Block	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	9
S DRUG SUBSTANCE [Buprenorphine and Naloxone SL Tablets, Orexo AB]	9
P DRUG PRODUCT [Buprenorphine and Naloxone SL Tablets, Orexo AB]	33
A APPENDICES	57
R REGIONAL INFORMATION	60
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1	
A. Labeling & Package Insert	61
B. Environmental Assessment Or Claim Of Categorical Exclusion	61
III. List Of Deficiencies/Comments Communicated	61

Chemistry Review Data Sheet

1. NDA 204242
2. REVIEW #: 1
3. REVIEW DATE: December 10, 2012
4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	September 5, 2012
Amendment	February 26, 2013
Amendment	April 16, 2013
Amendment	April 19, 2013

6. SUBMISSIONS BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	May 30, 2013
Amendment	June 7, 2013
Amendment	June 21, 2013

7. NAME AND ADDRESS OF APPLICANT:

Name: DJA Global Pharmaceuticals, Inc. on Behalf of Orexo AB
Drug Development and Global Regulatory Consulting

Address: 115 Commons Court
Chadds Ford, PA 19317

8. Product Drug Code and Name:

- a) Proprietary Name: Zubsolv™ Tablets
- b) Non-Proprietary Name (USAN): Buprenorphine and Naloxone SL Tablets
- c) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: Type 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:
Maintenance treatment of opioid dependence

11. DOSAGE FORM: Sublingual Tablets

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 5.7mg/1.4mg and 1.4mg/0.36mg buprenorphine/naloxone

13. ROUTE OF ADMINISTRATION: Oral

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:

I: Buprenorphine HCl:

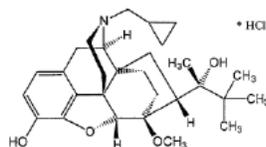
INN Name: Buprenorphine Hydrochloride

USAN name: Buprenorphine Hydrochloride

IUPAC name: (2S)-2-[-(-)-(5R,6R,7R,14S)-9 α -cyclopropylmethyl-4,5-epoxy-6,14-ethanomorphinan-7-yl]-3-hydroxy-6-methoxy-3,3-dimethylbutan-2-ol hydrochloride

Molecular formula: C₂₉H₄₁NO₄ · HCl

Relative molecular weight: 504.1



II: Naloxone HCl

INN Name: Naloxone Hydrochloride

USAN name: Naloxone Hydrochloride

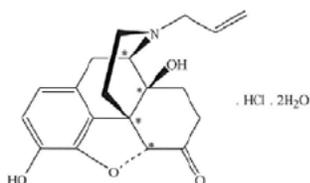
Compendial Names (USP and EP): Naloxone Hydrochloride

Chemical name: 4,5 α -Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride

Molecular formula: C₁₉H₂₁NO₄ · HCl · 2H₂O

Relative molecular weight: 399.9

Chemistry Review Data Sheet



17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code ¹	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	April 2013	J. Pinto/B.Bolan
	II			3	Adequate	March 2013	M. Pineiro-Sanchez
	III			4			

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110637	OX219: Buprenorphine and Naloxone SL Tablets

18. Status

Chemistry Review Data Sheet

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Adequate	June 25 2013	Office of Compliance
Pharm/Tox	Adequate	Rev #1	Beth Bolan, Ph.D.
Biopharm	Adequate	March 2013	A.Khairuzzaman, Ph.D.
LNC	NA		
Methods Validation	NA		
DMETS/DDMAC	NA		
EA	Categorical exclusion satisfactory	April 2013	Julia Pinto, Ph.D.

Executive Summary Section

The Chemistry Review for NDA 204242**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, has been provided in this NDA submission for the two drug substances. However two deficiencies had been identified during the first review, concerning the analytical methods for determination of Assay of Naloxone HCL in the drug product and the determination of the related substances in the drug product. These deficiencies have been satisfactorily addressed. The Sponsor has agreed to a PMC to revise and validate the organic impurities analytical method. Further, the Office of Compliance has made overall recommendation of adequate for all facilities related to this application. Therefore, from a quality perspective, this NDA is recommended for approval with the PMC stated in the next section.

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

Revise and validate the analytical method for organic impurities in the Naloxone API of the drug product accordingly to reflect an accuracy of (b) (4) RSD and intermediate precision of (b) (4) RSD.

II. Summary of Chemistry Assessment**A. Description of Drug Substance and Drug Product:**

There are two drug substances in the drug product. The first, buprenorphine HCL, is referenced to DMF (b) (4) and has been reviewed as Adequate (Rev 1, J. Pinto/B. Bolan, April 2013). Buprenorphine will be (b) (4) and has a retest period of (b) (4). The Second drug substance, Naloxone HCl dihydrate, is referenced to DMF (b) (4) also reviewed as adequate by M. Pineiro-Sanchez, Chem Review #5, March 2013). A retest period for Naloxone HCl dehydrate is (b) (4) when stored at 25°C/60% RH. The drug substances are (b) (4) and a (b) (4) particle size is controlled according to USP <429>.

The drug product is a sublingual tablet in two strengths 1.4mg/0.36mg and 5.7mg/1.4mg. The (b) (4)

(b) (4) The inactive ingredients include mannitol, citric acid, sodium citrate (b) (4), microcrystalline cellulose, croscarmellose sodium, sucralose, menthol, silicon dioxide (b) (4) and sodium stearyl fumarate. The RLD for this drug product is

Executive Summary Section

Suboxone® , also a sublingual tablet with the same APIs in the same 4:1 ratio. The tablets are packaged in blister packages in sheets of 10 with 3 sheets to one carton. The requested expiry of 18 months for the low strength is supported by real time data. The requested expiry of (b) (4) months for the higher strength is not. Therefore an expiry of 18 months is recommended for both tablet strengths. The Office of Compliance has made an adequate recommendation for all the facilities.

A request for a biowaiver for the lower strength tablet was reviewed and granted by the ONDQA Biopharm reviewer (Akm Khairuzzaman Ph.D.).

The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 18 months is supported.

B. Description of How the drug is intended to be used:

Zubsolv™ is a Sublingual tablet that delivers a combination of buprenorphine and naloxone for maintenance treatment of opioid dependence. Zubsolv™ sublingual tablets, are easily placed under the tongue, and are rapidly disintegrating tablets with (b) (4). They are available in two strengths used for dose titration: a high strength of 5.7 mg of buprenorphine /1.4 mg naloxone and a low strength of 1.4 mg buprenorphine/ 0.36 mg naloxone. Both tablets are white and are differentiated by shape and debossing on one side of the tablet. The high strength is a round flat-faced radius-edged tablet 7 mm in diameter debossed with 5.7, representing 5.7 mg buprenorphine. The low strength is a triangular shaped (base 7.2 mm, height 6.9 mm) flat-faced, radius-edged tablet debossed with 1.4, representing 1.4 mg buprenorphine.

C. Basis for Approvability Recommendation

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission. All previously identified deficiencies have been adequately addressed and the Office of Compliance has recommended all facilities related to this application as Satisfactory.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemistry Reviewer: Julia Pinto, Ph.D.

Pharmaceutical Assessment Leader: Julia Pinto, Ph.D.

Project Manager: Matthew Sullivan, R.Ph.

Branch Chief: Prasad Peri, Ph.D.

55 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JULIA C PINTO
06/28/2013

PRASAD PERI
06/29/2013
I concur.

NDA 204242

**Zubsolv™ Tablets
(Buprenorphine and Naloxone SL Tablets)**

Orexo AB

**Julia C. Pinto, Ph.D.
Office of New Drug Quality Assessment, Division III**

Division of Anesthesia, Analgesia and Addiction Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	8
III. Administrative	8
A. Reviewer's Signature	8
B. Endorsement Block	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	9
S DRUG SUBSTANCE [Buprenorphine and Naloxone SL Tablets, Orexo AB]	9
P DRUG PRODUCT [Buprenorphine and Naloxone SL Tablets, Orexo AB]	35
A APPENDICES	75
R REGIONAL INFORMATION	78
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1	
A. Labeling & Package Insert	79
B. Environmental Assessment Or Claim Of Categorical Exclusion	80
III. List Of Deficiencies/Comments Communicated	81

Chemistry Review Data Sheet

1. NDA 204242
2. REVIEW #: 1
3. REVIEW DATE: December 10, 2012
4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NONE

6. SUBMISSIONS BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

September 5, 2012

Amendment

February 26, 2013

Amendment

April 8, 2013

Amendment

April 16, 2013

Amendment

April 19, 2013

7. NAME AND ADDRESS OF APPLICANT:

Name: DJA Global Pharmaceuticals, Inc. on Behalf of Orexo AB
Drug Development and Global Regulatory Consulting

Address: 115 Commons Court
Chadds Ford, PA 19317

8. Product Drug Code and Name:

a) Proprietary Name: Zubsolv™ Tablets

b) Non-Proprietary Name (USAN): Buprenorphine and Naloxone SL Tablets

c) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:

Maintenance treatment of opioid dependence

11. DOSAGE FORM: Sublingual Tablets

12. STRENGTH/POTENCY: 5.7mg/1.4mg and 1.4mg/0.36mg buprenorphine/naloxone

Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Oral

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:

I: Buprenorphine HCl:

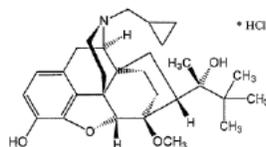
INN Name: Buprenorphine Hydrochloride

USAN name: Buprenorphine Hydrochloride

IUPAC name: (2S)-2-[-(-)-(5R,6R,7R,14S)-9 α -cyclopropylmethyl-4,5-epoxy-6,14-ethanomorphinan-7-yl]-3-hydroxy-6-methoxy-3,3-dimethylbutan-2-ol hydrochloride

Molecular formula: C₂₉H₄₁NO₄ · HCl

Relative molecular weight: 504.1



II: Naloxone HCl

INN Name: Naloxone Hydrochloride

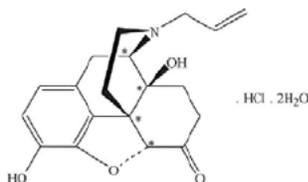
USAN name: Naloxone Hydrochloride

Compendial Names (USP and EP): Naloxone Hydrochloride

Chemical name: 4,5 α -Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride

Molecular formula: C₁₉H₂₁NO₄ · HCl · 2H₂O

Relative molecular weight: 399.9



Chemistry Review Data Sheet

17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code ¹	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	April 2013	J. Pinto/B.Bolan
	II		3	Adequate	March 2013	M. Pineiro-Sanchez	
	III		4				

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110637	OX219: Buprenorphine and Naloxone SL Tablets

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

EES	Pending		Office of Compliance
Pharm/Tox	Adequate	Rev #1	Beth Bolan, Ph.D.
Biopharm	Adequate	March 2013	A.Khairuzzaman, Ph.D.
LNC	NA		
Methods Validation	NA		
DMETS/DDMAC	NA		
EA	Categorical exclusion satisfactory	April 2013	Julia Pinto, Ph.D.

Executive Summary Section

The Chemistry Review for NDA 204242**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, has been provided in this NDA submission for the two drug substances. A few deficiencies have been observed concerning the inconsistency in specifications used to control the release and stability of the drug product. Further the analytical method for determination of Assay of Naloxone HCL in the drug product has not been satisfactorily validated. Further, the Office of Compliance has not yet made an overall recommendation. Therefore, from a quality perspective, this NDA is recommended for approval pending resolution of the deficiencies listed at the end of this review and a satisfactory overall recommendation from the Office of Compliance

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

No Post Approval commitments are required.

II. Summary of Chemistry Assessment**A. Description of Drug Substance and Drug Product:**

There are two drug substances in the drug product. The first, buprenorphine HCL, is referenced to DMF (b) (4) and has been reviewed as Adequate (Rev 1, J. Pinto/B. Bolan, April 2013). (b) (4)

. The Second drug substance, Naloxone HCl dihydrate, is referenced to DMF (b) (4) also reviewed as adequate by M. Pineiro-Sanchez, Chem Review #5, March 2013). A retest period for Naloxone HCl dehydrate is (b) (4) when stored at 25°C/60% RH. The drug substances are (b) (4) and a (b) (4) particle size is controlled according to USP <429>.

The drug product is a sublingual tablet in two strengths 1.4mg/0.36mg and 5.7mg/1.4mg. The (b) (4)

(b) (4)
The inactive ingredients include mannitol, citric acid, sodium citrate (b) (4), microcrystalline cellulose, croscarmellose sodium, sucralose, menthol, silicon dioxide (u) (4) and sodium stearyl fumarate. The RLD for this drug product is Suboxone® , also a sublingual tablet with the same APIs in the same 4:1 ratio. The tablets are packaged in blister packages in sheets of 10 with 3 sheets to one carton. The requested expiry of 18 months for the low strength is supported by real time data. The requested expiry of (b) (4) months for the higher strength is not. Therefore an expiry of 18 months is recommended for both tablet

Executive Summary Section

strengths. The Office of Compliance has not yet made an overall recommendation for the facilities.

A request for a biowaiver for the lower strength tablet was reviewed and granted by the ONDQA Biopharm reviewer (Akm Khairuzzaman Ph.D.).

The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 18 months is supported.

B. Description of How the drug is intended to be used:

Zubsolv™ is a Sublingual tablet that delivers a combination of buprenorphine and naloxone for maintenance treatment of opioid dependence. Zubsolv™ sublingual tablets, are easily placed under the tongue, and are rapidly disintegrating tablets with [REDACTED] (b) (4). They are available in two strengths used for dose titration: a high strength of 5.7 mg of buprenorphine /1.4 mg naloxone and a low strength of 1.4 mg buprenorphine/ 0.36 mg naloxone. Both tablets are white and are differentiated by shape and debossing on one side of the tablet. The high strength is a round flat-faced radius-edged tablet 7 mm in diameter debossed with 5.7, representing 5.7 mg buprenorphine. The low strength is a triangular shaped (base 7.2 mm, height 6.9 mm) flat-faced, radius-edged tablet debossed with 1.4, representing 1.4 mg buprenorphine.

C. Basis for Approvability Recommendation

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is not provided in this NDA submission. Approvability is pending satisfactory resolution to several deficiencies listed at the end of this review.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemistry Reviewer: Julia Pinto, Ph.D.
Pharmaceutical Assessment Leader: , Ph.D.
Project Manager: Matthew Sullivan, R.Ph.
Branch Chief: Prasad Peri, Ph.D.

75 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JULIA C PINTO
06/05/2013

PRASAD PERI
06/06/2013
I concur

Established/Proper Name:

NDA Number: 204242

NDA Number and Type: 5S

Buprenorphine and naloxone
1.4:0.36 mg and 5.7:1.4 mg
sublingual tablets

Applicant: Orexo AB

Letter Date: 09/06/2012

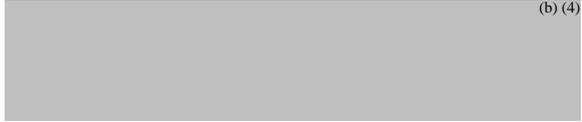
Stamp Date: 09/06/2012

The NDA is recommended for filing with respect to CMC. No filing comments to be communicated to the applicant.

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		IND 110637, pre-NDA 8/7/2012

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
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.			NA

7.	<p>Are the drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		 (b) (4)
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>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:</p> <ul style="list-style-type: none"> • 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		

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		Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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		(Master and Executed)
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		A biowaiver from BA/BE studies was requested for the lower strength
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		Principles of QbD and previous manufacturing experience in Edluar™ (US approved NDA 21-997) and Abstral® (US approved NDA 22-510). DoEs included for robustness of formulation and process scale up
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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	Solid oral dosage form

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		See below

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	(b) (4)	(b) (4)	7/6/2012	Drug substance
	2			11/23/2011	Drug Substance
	3			11/21/2011	Packaging components

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?			Based on sufficient body of data and pre-NDA agreements
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		
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}

Name of

CMC Lead: Danae Christodoulou 11/15/12
 Division III
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of

Branch Chief: Prasad Peri
 Division III
 Office of New Drug Quality Assessment

Date

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

/s/

DANAE D CHRISTODOULOU
11/15/2012
Filing Template - CMC

PRASAD PERI
11/15/2012