

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22442Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-442

REZIRA
(Hydrocodone Bitartrate and
Pseudoephedrine Hydrochloride)
Oral Solution

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Cypress Pharmaceuticals, Inc.
135 Industrial Blvd.,
Madison, MS 39110

Indication:

(b) (4) relief of cough and (b) (4) relief of nasal congestion due to common cold.

Presentation: Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride. The commercial drug product is packaged in a 16 fl. oz. white HDPE bottle and the professional sample is packaged in a (b) (4)

EER Status:	Recommendations:	Acceptable
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	DMETS-	Acceptable
	Biopharm-	N/A
	Microbiology -	Satisfactory
	Pharm/toxicology -	Satisfactory

Original Submission: 07-November-2008

Re-submissions: 08-December-2010

Post-Approval CMC Agreements: None

Background:

This is a resubmission of the NDA (6 months) that was originally submitted in 2008. NDA in electronic format with electronic labeling provided in SPL format. There is a Quality Overall Summary. This NDA is filed as a 505(b) 2 application.

This NDA is submitted by the applicant after the FDA issued a guidance called Marketed Unapproved Drugs Compliance Policy Guide, which describes plans for enforcement in this area: "The FDA is telling manufacturers to either obtain approval for an unapproved drug or remove it from the market. Even if the drug has been marketed for many years with no known safety problems, companies will still need to comply. The absence of evidence of a safety problem does not mean a product is truly safe."

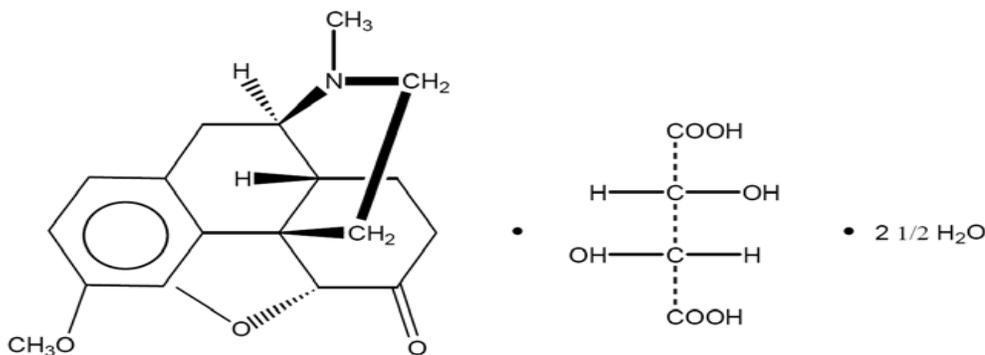
Drug Substance:

There are two drug substances for this NDA: hydrocodone bitartrate and chlorpheniramine maleate.

- **Hydrocodone bitartrate** USP is manufactured by (b) (4) and referenced to DMF (b) (4) which was last reviewed on Dec 14, 2010 and found adequate. The drug product manufacturer release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities, assay, related substances (specified and unspecified), residual solvents, and microbial limits. Hydrocodone bitartrate drug substance is packaged in (b) (4). The retest date is (b) (4) months from the manufacturing date.

Chemical name, structure, molecular weight and molecular formula are provided below.

Chemical Name: Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 α)-, [(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)



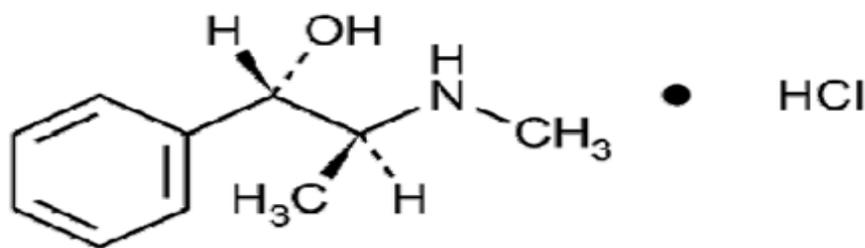
Molecular Formula: C₁₈H₂₁NO₃·C₄H₆O₆·2½H₂O

Molecular Weight: 494.490

- **Pseudoephedrine hydrochloride** is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed on Aug. 03, 2010, and found adequate. The drug product manufacturer release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), organic volatile impurities, residual solvents, heavy metals and microbial limits. Pseudoephedrine hydrochloride drug substance is packaged in (b) (4). The retest date is (b) (4) months from the manufacturing date.

Chemical name, structure, molecular weight and molecular formula are provided below.

Chemical Name: α -[1-(methylamino) ethyl]-[S-(R*,R*)] hydrochloride; (+)-Pseudoephedrine hydrochloride; Benzenemethanol and D-pseudoephedrine hydrochloride



Molecular Formula: C₁₀H₁₅NO·HCl

Molecular Weight: 201.69

Conclusion: The drug substances are satisfactory.

Drug Product:

The drug product REZIRA is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for (b) (4) relief of cough and (b) (4) relief of nasal congestion due to common cold.

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride. In addition to the two active pharmaceutical

ingredients, REZIRA contains excipients commonly used in oral solution products (e.g. water, citric acid, sodium citrate, sodium saccharin, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). Specifications for the drug product include appearance, density, viscosity, pH, volume, identification, assay, impurity, antimicrobial, total molds and yeasts count, packaging and (b) (4)

Manufacturing process involves (b) (4)

The product is manufactured by (b) (4)

The stability data provided in the application support a shelf life of 24 months for the drug product.

CMC issues that are still pending: None

Conclusion: The drug product is satisfactory.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Prasad Peri, Ph.D.
Chief, Branch VIII
DPA III/ONDQA

2 pages of draft labeling has been withheld in full as B(4)
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/

PRASAD PERI
05/18/2011
Recommend Approval

NDA 22-442

**REZIRA
(Hydrocodone Bitartrate and
Pseudoephedrine Hydrochloride)
Oral Solution**

Cypress Pharmaceuticals, Inc.

**Xiaobin Shen, Ph.D.
for
Division of Pulmonary, Allergy and Rheumatology Drug
Products**

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Chemistry Review Data Sheet

1. NDA 22-442
2. REVIEW #: 4
3. REVIEW DATE: 12-Apr-2011
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original

Amendment 0001

Amendment 0002

Amendment 0003

Amendment 0004

Amendment 0005

Amendment 0006

Amendment 0007

Amendment 0008

Amendment 0009

Amendment 0010

Document Date

07-Nov-2008

01-Dec-2008

26-Jan-2009

28-Jan-2009

29-Jan-2009

04-Mar-2009

08-Apr-2009

19-May-2009

10-Jul-2009

10-Dec-2009

09-Apr-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment 0011 (Safety information)

Amendment 0012 (Pediatric study plan)

Amendment 0013 (Response to labeling comments)

Amendment 0014 (Response to pediatric study plan comments)

Document Date

20-Apr-2010

06-May-2010

17-May-2010

19-May-2010

Chemistry Review Data Sheet

Amendment 0015 (Response to state intention to respond to the Agency's Complete Response letter)	15-Sep-2010
Amendment 0016 (Resubmission)	08-Dec-2010
Amendment 0017 (Response to clinical information request)	08-Feb-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Cypress Pharmaceuticals, Inc.

Address: 135 Industrial Blvd., Madison, MS 39110

Representative: Robert L. Lewis II

Telephone: 1-800-856-4393 ext. 120

Facsimile: 601-853-1567

Regulatory Agent Contact Information:

Address: Beckloff Associates, Inc.
Commerce Plaza II, Suite 300
7400 West 110th Street,
Overland Park, KS 66210

Representative: William (Trey) Putnam

Telephone: 913-451-3955

Facsimile: 913-451-3846

All communications regarding this NDA are requested to be sent to the regulatory agent.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: REZIRA Oral Solution (proposed);
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate/Pseudoephedrine Hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

Chemistry Review Data Sheet

The application is filed based on previously approved NDA and existing OTC monographs listed below:

Hydrocodone Bitartrate — Hycodan[®] Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.

Pseudoephedrine Hydrochloride — OTC monograph.

10. PHARMACOL. CATEGORY:

Hydrocodone bitartrate is an antitussive (cough suppressing); and pseudoephedrine hydrochloride is a nasal decongestant.

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 5 mg Hydrocodone Bitartrate / 60 mg Pseudoephedrine Hydrochloride per 5 mL.

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

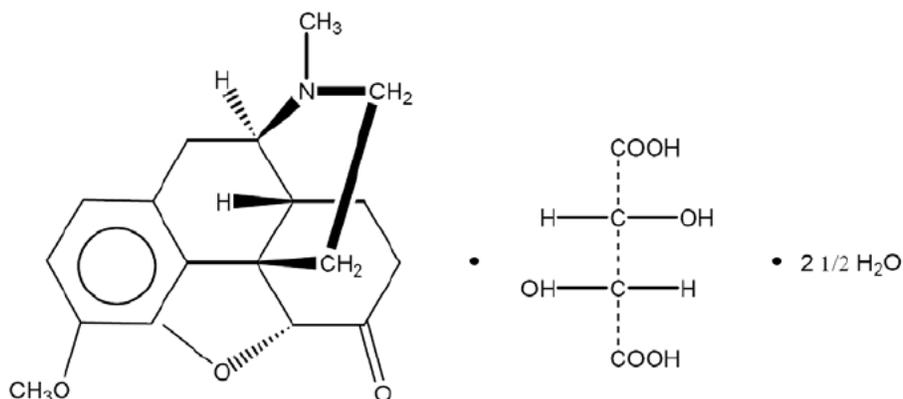
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

There are two active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

Chemistry Review Data Sheet

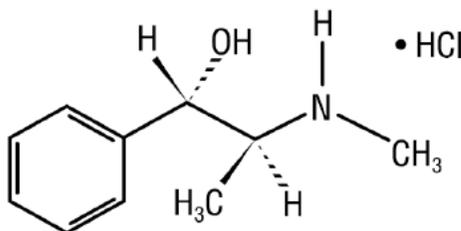


Molecular Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

Molecular Weight: 494.490

Pseudoephedrine Hydrochloride:

[S-(R*,R*)]- α -[1-(methylamino)ethyl]-benzenemethanol hydrochloride



Molecular Formula: $C_{10}H_{15}NO \cdot HCl$

Molecular Weight: 201.69

Comment: The applicant provided chemical name is incorrect: α -[1-(methylamino)ethyl]-[S-(R*,R*)] hydrochloride.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Hydrocodone bitartrate drug substance	3	Adequate	14-Dec-2010	The DMF is deemed adequate in support of an oral solution
(b) (4)	II	(b) (4)	Pseudoephedrine	3	Adequate	03-Aug-2010	The DMF is deemed adequate

Chemistry Review Data Sheet

						in support of an oral solution
(b) (4)	III		4			
	III		4			
	IV		1	Adequate	26-Mar-2010	The review deemed it adequate in support of an oral solution
	III		4			
	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	102177	Oral solution, 5 mg Hydrocodone Bitartrate, 4 mg Chlorpheniramine Maleate, and 60 mg Pseudoephedrine Hydrochloride per 5 mL

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

Biometrics	NA	NA	NA
EES	Adequate	23-Mar-2010	NA
Pharm/Tox	Adequate	23-Mar-2010	Grace Lee
Biopharm	NA	NA	NA
LNC	NA	NA	NA
Methods Validation	Validation is not required by FDA Lab	30-Jun-2009	Xiaobin Shen
DMEPA/OSE	NA	NA	NA
EA	Acceptable	30-Jun-2009	Xiaobin Shen
Microbiology	Acceptable	30-Jun-2009	James McVey

The Chemistry Review for NDA 22-442

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, an approval action is recommended for this NDA.

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

NA.

II. Summary of Chemistry Assessments

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

The drug product REZIRA solution is a clear, colorless to light-yellow solution with a grape odor. It is indicated for (b) (4) relief of cough and (b) (4) relief of nasal congestion due to common cold.

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride. In addition to the two active pharmaceutical ingredients, REZIRA contains excipients commonly used in oral solution products (water, citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial REZIRA is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in (b) (4)

The process used to manufacture the commercial product (b) (4)

The product is manufactured by (b) (4)

Microbial limit testing is performed by (b) (4) Testing of raw materials is performed by (b) (4) cGMP status of all facilities are acceptable.

Up to 24 month stability data are provided. The data support the claimed 24 month expiry. The solution color at (b) (4) month reached the stability specification upper limit of (b) (4) Specified impurities (b) (4) have not been detected or remain below reporting limits in the drug product at the 24 month time point when stored at 25°C/60% RH. They will continue to be tested. The unspecified impurity at RRT (b) (4) has increased to about (b) (4) but still within the (b) (4) limit.

Chemistry Assessment Section

There are two drug substances for this NDA: hydrocodone bitartrate, and pseudoephedrine hydrochloride.

1- Hydrocodone bitartrate (INN & USAN) was approved by FDA and marketed as Hycodan[®] Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4) which was last reviewed on 14-Dec-2010 by Dr. Maria Manzoni and found adequate. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, assay, related substances (specified and unspecified), residual solvents, and microbial limits. Hydrocodone bitartrate drug substance is packaged in (b) (4). The retest date is (b) (4) months from the manufacturing date.

2- Pseudoephedrine hydrochloride is an OTC monograph item. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is a white to almost white crystalline powder that is freely soluble in water. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was last reviewed by Dr. Gil Jong Kang on 03-Aug-2010 and deemed adequate. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, assay, related substances (specified and unspecified), (b) (4). Pseudoephedrine hydrochloride drug substance is packaged in (b) (4). The retest date is (b) (4) months from the manufacturing date.

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

The drug product REZIRA is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains (b) (4). Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride.

Dosing for adults (b) (4) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

The manufacturer proposed a two year expiry with 20 C to 25 C storage condition, the firm provided 24 month real time stability data to support the two year expiry and it is found acceptable.

C. Basis for Approvability or Not-Approval Recommendation

The drug product is filed as a 505b(2) application. From the perspective of chemistry, manufacturing and control, this drug product is recommended for approval.

Chemistry Assessment Section

REZIRA oral solution consists of two active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan[®] Syrup since 1988. The other active pseudoephedrine hydrochloride is an OTC monograph article. Both drug substances have adequate controls (specifications) and stability characteristics.

The drug product excipients are all of USP/NF grade. All excipients in the drug product formulation are present at levels below the highest in US approved drug products. The container closure systems are typical for oral solutions and provided adequate information in the NDA. The drug product is very stable and the provided stability data support 24 month expiry.

EES status are acceptable for all manufacturing facilities.

The labeling and package insert are acceptable from CMC perspective.

III. Administrative

A. Reviewer's Signature

Chemist: Xiaobin Shen, Ph.D. *{Signed electronically in DARRTS}*

B. Endorsement Block

ChemistName/Date:

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

C. CC Block

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

/s/

XIAOBIN SHEN

04/12/2011

The NDA is recommended for approval from CMC perspective.

PRASAD PERI

04/12/2011

I concur

NDA 22-442

**REZIRA
(Hydrocodone Bitartrate and
Pseudoephedrine Hydrochloride)
Oral Solution**

Cypress Pharmaceuticals, Inc.

Xiaobin Shen, Ph.D.

**Division of Pulmonary, Allergy and Rheumatology Drug
Products**

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I.3 Additional (Minor) Revisions	14
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Chemistry Review Data Sheet

1. NDA 22-442
2. REVIEW #: 3
3. REVIEW DATE: 21-Apr-2010
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	11/07/2008
Amendment 0001	12/01/2008
Amendment 0002	01/26/2009
Amendment 0003	01/28/2009
Amendment 0004	01/29/2009
Amendment 0005	03/04/2009
Amendment 0006	04/08/2009
Amendment 0007	05/19/2009
Amendment 0008	07/10/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0009	12/10/2009
Amendment 0010	04/09/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Cypress Pharmaceuticals, Inc.

Chemistry Review Data Sheet

Address: 135 Industrial Blvd., Madison, MS 39110

Representative: Robert L. Lewis II

Telephone: 1-800-856-4393 ext. 120

Facsimile: 601-853-1567

Regulatory Agent Contact Information:

Address: Beckloff Associates, Inc.
Commerce Plaza II, Suite 300
7400 West 110th Street,
Overland Park, KS 66210

Representative: William (Trey) Putnam

Telephone: 913-451-3955

Facsimile: 913-451-3846

All communications regarding this NDA are requested to be sent to the regulatory agent.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: REZIRA Oral Solution (proposed);
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate/Pseudoephedrine Hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

The application is filed based on previously approved NDA and existing OTC monographs listed below:

Hydrocodone Bitartrate — Hycodan[®] Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.

Pseudoephedrine Hydrochloride — OTC monograph.

10. PHARMACOL. CATEGORY:

Hydrocodone bitartrate is an antitussive (cough suppressing); and pseudoephedrine hydrochloride is a nasal decongestant.

Chemistry Review Data Sheet

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 5 mg Hydrocodone Bitartrate / 60 mg Pseudoephedrine Hydrochloride per 5 mL.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product Form Completed

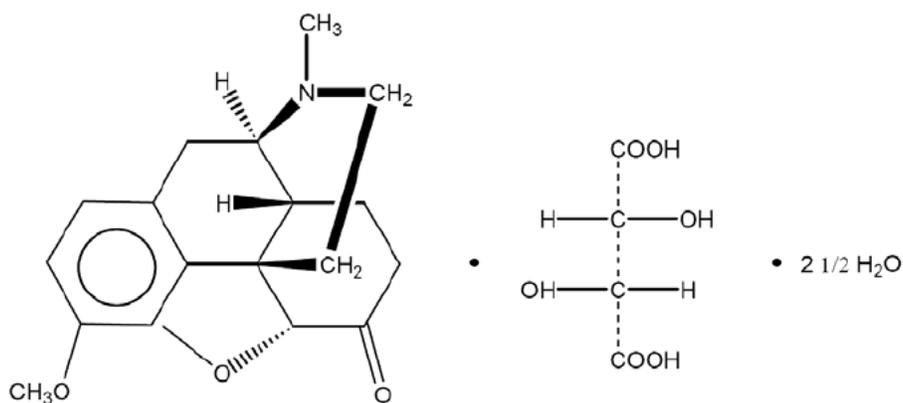
Not a SPOTS product

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

There are two active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)



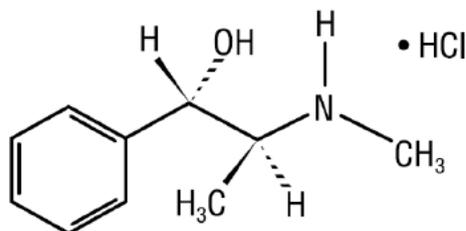
Molecular Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

Molecular Weight: 494.490

Chemistry Review Data Sheet

Pseudoephedrine Hydrochloride:

[S-(R*,R*)]- α -[1-(methylamino)ethyl]-benzenemethanol hydrochloride



Molecular Formula: C₁₀H₁₅NO·HCl

Molecular Weight: 201.69

Comment: The applicant provided chemical name is incorrect: α -[1-(methylamino)ethyl]-[S-(R*,R*)] hydrochloride.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Hydrocodone bitartrate drug substance	3	Adequate	19-Feb-2010	The DMF is deemed adequate in support of an oral solution
	II	(b) (4)	Pseudoephedrine hydrochloride drug substance	3	Adequate	15-Oct-2009	The DMF is deemed adequate in support of an oral solution
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
	IV	(b) (4)	(b) (4)	1	Adequate	26-Mar-2010	The review deemed it adequate in support of an oral solution
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			

Chemistry Review Data Sheet

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	102177	Oral solution, 5 mg Hydrocodone Bitartrate, 4 mg Chlorpheniramine Maleate, and 60 mg Pseudoephedrine Hydrochloride per 5 mL

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	NA
EES	Adequate	23-Mar-2010	NA
Pharm/Tox	Adequate	23-Mar-2010	Grace Lee
Biopharm	NA	NA	NA
LNC	NA	NA	NA
Methods Validation	Validation is not required by FDA Lab	30-Jun-2009	Xiaobin Shen
DMEPA/OSE	NA	NA	NA
EA	Acceptable	30-Jun-2009	Xiaobin Shen
Microbiology	Acceptable	30-Jun-2009	James McVey

The Chemistry Review for NDA 22-442

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, an approval action is recommended for this NDA.

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

NA.

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

The drug product REZIRA solution is a clear, colorless to light-yellow solution with a grape odor. It is indicated for (b) (4) relief of cough and (b) (4) relief of nasal congestion due to common cold.

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The process used to manufacture the commercial product (b) (4)

The product is manufactured by (b) (4)
Microbial limit testing is performed by (b) (4) Testing of raw materials is performed by (b) (4) cGMP status of all facilities are acceptable.

Specified impurities (b) (4) have not been detected or remain below reporting limits in the drug product at the 21 month time point when stored at 25 °C/60% RH. For this reason, the applicant removed these impurities from the specifications of the commercial batches. Instead, the applicant proposes to continue testing the registration batches for these impurities throughout the remainder of the 48 month stability program. If they detect the impurities during the extended stability at the proposed limits during the stability study, Cypress will evaluate the data and discuss plans with the Agency. The Agency does not agree with this approach and

Chemistry Assessment Section

will send a comment to request the applicant to handle the change of specifications in a post-approval supplement.

Additionally, impurity (b) (4) was not detected in 6 month accelerated and 18 month 25 °C/60% RH stability data. It is removed from the commercial specifications. This is acceptable as (b) (4) is a drug substance process impurity and does not require to be reported in the drug product.

There are two drug substances for this NDA: hydrocodone bitartrate, and pseudoephedrine hydrochloride.

1- Hydrocodone bitartrate (INN & USAN) was approved by FDA and marketed as Hycodan[®] Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4) which was last reviewed on 19-Feb-2010 by Dr. Maria Manzoni and found adequate. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities, assay, related substances (specified and unspecified), residual solvents, and microbial limits. Hydrocodone bitartrate drug substance is packaged in (b) (4). The retest date is (b) (4) months from the manufacturing date.

2- Pseudoephedrine hydrochloride is an OTC monograph item. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is a white to almost white crystalline powder that is freely soluble in water. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was last reviewed by Dr. Bahar Zarabi on 15-Oct-2009 and deemed adequate. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), organic volatile impurities, residual solvents, heavy metals and microbial limits. Pseudoephedrine hydrochloride drug substance is packaged in (b) (4). The retest date is (b) (4) months from the manufacturing date.

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

The drug product REZIRA is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains (b) (4). Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride.

Chemistry Assessment Section

Dosing for adults [REDACTED] (b) (4) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. [REDACTED] (b) (4)

[REDACTED] (b) (4) The manufacturer proposed a two year expiry with 20 C to 25 C storage condition, the firm provided 12 month real time stability data to support the two year expiry and it is found acceptable.

C. Basis for Approvability or Not-Approval Recommendation

The drug product is filed as a 505b(2) application. From the perspective of chemistry, manufacturing and control, this drug product is recommended for approval.

REZIRA oral solution consists of two active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan[®] Syrup since 1988. The other active pseudoephedrine hydrochloride is an OTC monograph article. Both drug substances have adequate controls (specifications) and stability characteristics.

The drug product excipients are all of USP/NF grade. The container closure systems are typical for oral solutions and provided adequate information in the NDA. The drug product is very stable and the provided stability data support 24 month expiry.

EES status are acceptable for all manufacturing facilities.

The labeling and package insert are acceptable from CMC perspective.

III. Administrative**A. Reviewer's Signature**

Chemist: Xiaobin Shen, Ph.D. {Signed electronically in DARRTS}

B. Endorsement Block

ChemistName/Date:

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

C. CC Block

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA ^(b) ₍₄₎ (HYDROCODONE BITARTRATE AND PSEU

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

/s/

XIAOBIN SHEN

04/21/2010

The NDA is recommended for approval. There are comments to be communicated to the applicant in the action letter.

PRASAD PERI

04/21/2010

I concur

NDA 22-442

REZIRA
(Hydrocodone Bitartrate and
Pseudoephedrine Hydrochloride)
Oral Solution

Cypress Pharmaceuticals, Inc.

Xiaobin Shen, Ph.D.
Division of Pulmonary and Allergy Drug Products

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Chemistry Review Data Sheet

1. NDA 22-442
2. REVIEW #: 2
3. REVIEW DATE: 28-Aug-2009
4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	11/07/2008
Amendment 0001	12/01/2008
Amendment 0002	01/26/2009
Amendment 0003	01/28/2009
Amendment 0004	01/29/2009
Amendment 0005	03/04/2009
Amendment 0006	04/08/2009
Amendment 0007	05/18/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0008	07/10/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Cypress Pharmaceuticals, Inc.

Executive Summary Section

Address: 135 Industrial Blvd., Madison, MS 39110

Representative: Robert L. Lewis II

Telephone: 1-800-856-4393 ext. 120

Facsimile: 601-853-1567

Regulatory Agent Contact Information:

Address: Beckloff Associates, Inc.
Commerce Plaza II, Suite 300
7400 West 110th Street,
Overland Park, KS 66210

Representative: William (Trey) Putnam

Telephone: 913-451-3955

Facsimile: 913-451-3846

All communications regarding this NDA are requested to be sent to the regulatory agent.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rezira
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate/Pseudoephedrine Hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

The application is filed based on previously approved NDA and existing OTC monographs listed below:

Hydrocodone Bitartrate — Hycodan[®] Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.

Pseudoephedrine Hydrochloride — OTC monograph.

10. PHARMACOL. CATEGORY:

Hydrocodone bitartrate is antitussive (cough suppressing); Pseudoephedrine hydrochloride a decongestant.

Executive Summary Section

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 5 mg Hydrocodone Bitartrate / 60 mg Pseudoephedrine Hydrochloride per 5 mL.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product Form Completed

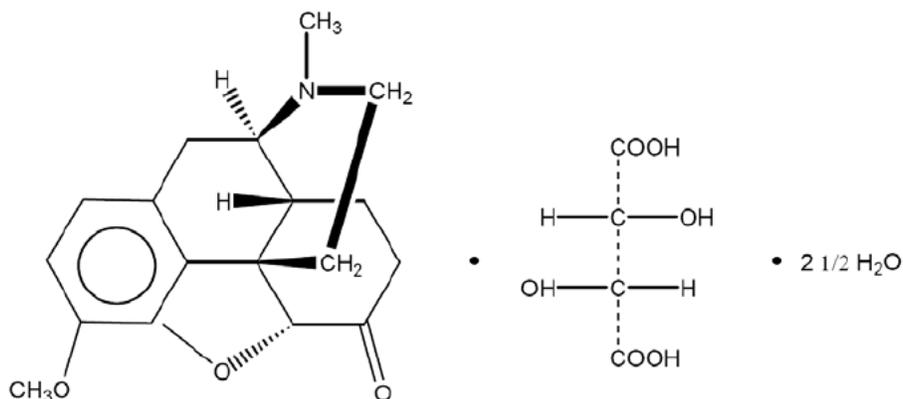
Not a SPOTS product

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

There are two active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

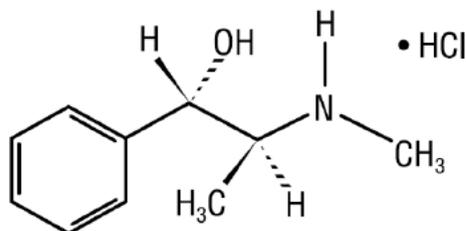
4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)



Molecular Formula: C₁₈H₂₁NO₃·C₄H₆O₆·2½H₂O

Molecular Weight: 494.490

Executive Summary Section

Pseudoephedrine Hydrochloride:[S-(R*,R*)]- α -[1-(methylamino)ethyl]-benzenemethanol hydrochlorideMolecular Formula: C₁₀H₁₅NO·HCl

Molecular Weight: 201.69

Comment: The applicant provided chemical name is incorrect: α -[1-(methylamino)ethyl]-[S-(R*,R*)] hydrochloride.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Hydrocodone bitartrate drug substance	3	Adequate	04-07-2009	The review in support of an oral solution identified deficiencies, which was corrected and then deemed adequate.
(b) (4)	II	(b) (4)	Pseudoephedrine hydrochloride drug substance	3	Adequate	08-13-2008	Based on this and the previous reviews, the DMF is deemed adequate in support of an oral solution
(b) (4)	III	(b) (4)	(b) (4)	NA	NA	NA	NA
(b) (4)	III	(b) (4)	(b) (4)	NA	NA	NA	NA
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	08-14-2008	The review deemed it

Executive Summary Section

		(b) (4)					adequate in support of an oral solution
(b) (4)	III		(b) (4)	NA	NA	NA	NA
	III			NA	NA	NA	NA

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	102177	IND review summary indicated CMC related items are considered and evaluated in this NDA review.

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	NA
EES	Acceptable	6/30/2009	NA
Pharm/Tox	Adequate	5/22/2009	Marcus Delatte
Biopharm	NA	NA	NA
LNC	Pending	6/30/2009	NA
Methods Validation	Validation is not required by FDA Lab	6/30/2009	Xiaobin Shen
OPDRA	NA	NA	NA
EA	Acceptable	3/30/2009	Xiaobin Shen
Microbiology	Acceptable	3/30/2009	James McVey

The Chemistry Review for NDA 22-442

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable pending adequate responses to the outstanding issues summarized at end of this review.

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

None.

II. Summary of Chemistry Assessments

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

The drug product REZIRA is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for (b) (4) relief of cough and (b) (4) relief of nasal congestion due to common cold.

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride. In addition to the two active pharmaceutical ingredients, REZIRA contains excipients commonly used in oral solution products (e.g. water, citric acid, sodium citrate, sodium saccharin, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial REZIRA is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in (b) (4)

The process used to manufacture the commercial product (b) (4) is equivalent to that used for the product used in the clinical studies (b) (4)

There are two drug substances for this NDA: hydrocodone bitartrate and pseudoephedrine hydrochloride.

1- Hydrocodone bitartrate (INN & USAN) was approved by FDA and marketed as Hycodan[®] Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4) which was last reviewed in April, 2009 by Dr. Maria Manzoni and found adequate. The DMF's EES status is acceptable. The drug product manufacturer release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities,

Executive Summary Section

assay, related substances (specified and unspecified), residual solvents, and microbial limits.

2- Pseudoephedrine hydrochloride is also OTC monograph item. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is a white to almost white crystalline powder that is freely soluble in water. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed by Guoping Sun, Ph.D. in Feb. 2008 and deemed adequate. Arthur Shaw, Ph.D. reviewed it last in Aug. 2008 after the DMF was resubmitted in CTD-Q format and also deemed it adequate. The holder's EES status is acceptable. The drug product manufacturer release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), organic volatile impurities, (b) (4).

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

The drug product REZIRA is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains (b) (4). Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride.

Dosing for adults (b) (4) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. (b) (4)
(b) (4) The manufacturer proposed a two year expiry with 20 C to 25 C storage condition, the firm provided 12 month real time stability data to support the two year expiry and it is found acceptable.

C. Basis for Approvability or Not-Approval Recommendation

From the perspective of chemistry, manufacturing and control, this drug product is approvable pending satisfactory responses to the outstanding CMC deficiencies.

REZIRA oral solution consists of two active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan[®] Syrup since 1988. The other active pseudoephedrine hydrochloride is an OTC monograph article.

There are CMC requests related to both drug substances and the drug product which need to be addressed by the DMF holders or the sponsors (see section III of the review summary). EES evaluations are acceptable for all facilities.

The product's trade name has been changed to REZIRA and deemed acceptable.

The labeling and package insert are acceptable from CMC perspective with minor comments.

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

Chemist: Xiaobin Shen, Ph.D. *{Signed electronically in DFS}*

B. Endorsement Block

ChemistName/Date: Xiaobin Shen/28-Aug-2009

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

C. CC Block

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22442	ORIG 1	CYPRESS PHARMACEUTICA L INC	REZIRA ^(b) ₍₄₎ (HYDROCODONE BITARTRATE AND PSEU

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/s/

XIAOBIN SHEN

08/31/2009

This NDA is approvable pending satisfactory responses to CMC deficiencies related to analytical methods and specifications.

ALI H AL HAKIM

08/31/2009

NDA 22-442

REZIRA
(Hydrocodone Bitartrate and
Pseudoephedrine Hydrochloride)
Oral Solution

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Cypress Pharmaceuticals, Inc.
135 Industrial Blvd.,
Madison, MS 39110

Indication:

(b) (4) relief of cough and (b) (4) relief of nasal congestion due to common cold.

Presentation: Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride. The commercial drug product is packaged in a 16 fl. oz. white HDPE bottle and the professional sample is packaged in (b) (4).

EER Status:	Recommendations:	Acceptable
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	DEMETS-	Pending
	Biopharm-	N/A
	Microbiology -	Satisfactory
	Pharm/toxicology -	Satisfactory

Original Submission: 07-November-2008

Re-submissions: N/A

Post-Approval CMC Agreements: None

Background:

This is a standard (10 months) NDA in electronic format with electronic labeling provided in SPL format. There is a Quality Overall Summary. This NDA is filed as a 505(b) 2 application.

This NDA is submitted by the applicant after the FDA issued a guidance called Marketed Unapproved Drugs Compliance Policy Guide, which describes plans for enforcement in this area: "The FDA is telling manufacturers to either obtain approval for an unapproved drug or remove it from the market. Even if the drug has been marketed for many years with no known safety problems, companies will still need to comply. The absence of evidence of a safety problem does not mean a product is truly safe."

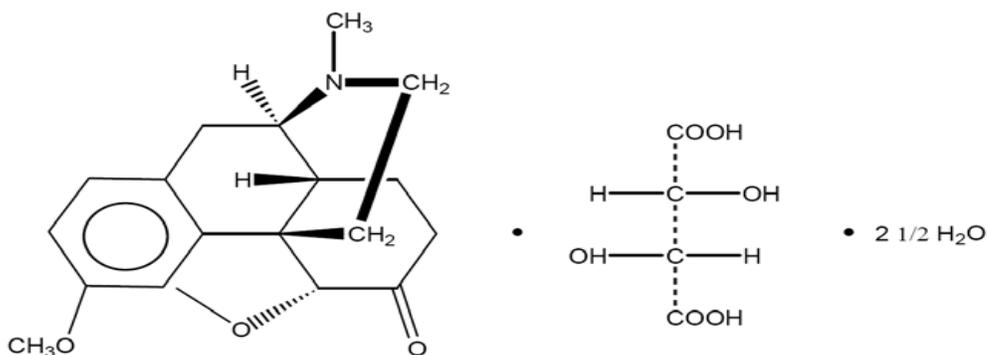
Drug Substance:

There are two drug substances for this NDA: hydrocodone bitartrate and chlorpheniramine maleate.

- **Hydrocodone bitartrate** USP is manufactured by (b) (4) and referenced to DMF (b) (4) which was last reviewed on April 7, 2009 and found adequate. The drug product manufacturer release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities, assay, related substances (specified and unspecified), (b) (4).

Chemical name, structure, molecular weight and molecular formula are provided below.

Chemical Name: Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 α)-, [R*(R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)



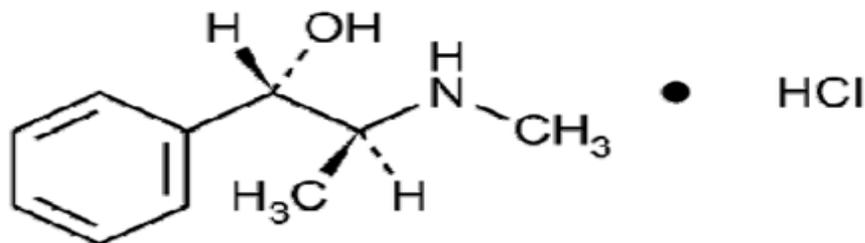
Molecular Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

Molecular Weight: 494.490

- **Pseudoephedrine hydrochloride** is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed and found adequate. The drug product manufacturer release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), organic volatile impurities, (b) (4).

Chemical name, structure, molecular weight and molecular formula are provided below.

Chemical Name: α -[1-(methylamino) ethyl]-[S-(R*,R*)] hydrochloride; (+)-Pseudoephedrine hydrochloride; Benzenemethanol and D-pseudoephedrine hydrochloride



Molecular Formula: C₁₀H₁₅NO·HCl

Molecular Weight: 201.69

Conclusion: The drug substances are satisfactory.

Drug Product:

The drug product REZIRA is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for (b) (4) relief of cough and (b) (4) relief of nasal congestion due to common cold.

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride. In addition to the two active pharmaceutical ingredients, REZIRA contains excipients commonly used in oral solution products (e.g. water, citric acid, sodium citrate, sodium saccharin, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). Specifications for the drug product include appearance, density, viscosity, pH,

volume, identification, assay, impurity, antimicrobial, total molds and yeasts count, packaging and (b) (4)

Manufacturing process involves (b) (4)

The stability data provided in the application support expiry dating of 24 months for the drug product.

CMC issues that are still pending

There are several outstanding CMC issues that are still pending for this NDA.

The issues are related to

- Reducing the total impurity level of the drug product
- Analytical test methods
- Labeling issues

Conclusion: The drug product is not satisfactory.

Overall Conclusion:

From a CMC perspective, the application is approvable pending satisfactory responses to the CMC deficiencies.

Ali Al-Hakim, Ph.D.
Branch Chief,
DPA I/ONDQA

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22442	----- ORIG 1	----- CYPRESS PHARMACEUTICA L INC	----- REZIRA ^(b) ₍₄₎ (HYDROCODONE BITARTRATE AND PSEU

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

/s/

ALI H AL HAKIM
07/30/2009

NDA 22-442

REZIRA
(Hydrocodone Bitartrate and
Pseudoephedrine Hydrochloride)
Oral Solution

Cypress Pharmaceuticals, Inc.

Xiaobin Shen, Ph.D.
Division of Pulmonary and Allergy Drug Products

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CHEMISTRY REVIEW



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Chemistry Review Data Sheet

1. NDA 22-442
2. REVIEW #: 1
3. REVIEW DATE: 09-Jul-2009
4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment 0001

Amendment 0002

Amendment 0003

Amendment 0004

Amendment 0005

Amendment 0006

Amendment 0007

Document Date

11/07/2008

12/01/2008

01/26/2009

01/28/2009

01/29/2009

03/04/2009

04/08/2009

05/18/2009

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Cypress Pharmaceuticals, Inc.
Address: 135 Industrial Blvd., Madison, MS 39110
Representative: Robert L. Lewis II
Telephone: 1-800-856-4393 ext. 120
Facsimile: 601-853-1567

Regulatory Agent Contact Information:

Address: Beckloff Associates, Inc.
Commerce Plaza II, Suite 300
7400 West 110th Street,
Overland Park, KS 66210
Representative: William (Trey) Putnam
Telephone: 913-451-3955
Facsimile: 913-451-3846

All communications regarding this NDA are requested to be sent to the regulatory agent.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Rezira
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate/Pseudoephedrine Hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

The application is filed based on previously approved NDA and existing OTC monographs listed below:

Hydrocodone Bitartrate — Hycodan[®] Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.

Pseudoephedrine Hydrochloride — OTC monograph.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY:

Hydrocodone bitartrate is antitussive (cough suppressing); Pseudoephedrine hydrochloride a decongestant.

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 5 mg Hydrocodone Bitartrate / 60 mg Pseudoephedrine Hydrochloride per 5 mL.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

 SPOTS product Form Completed

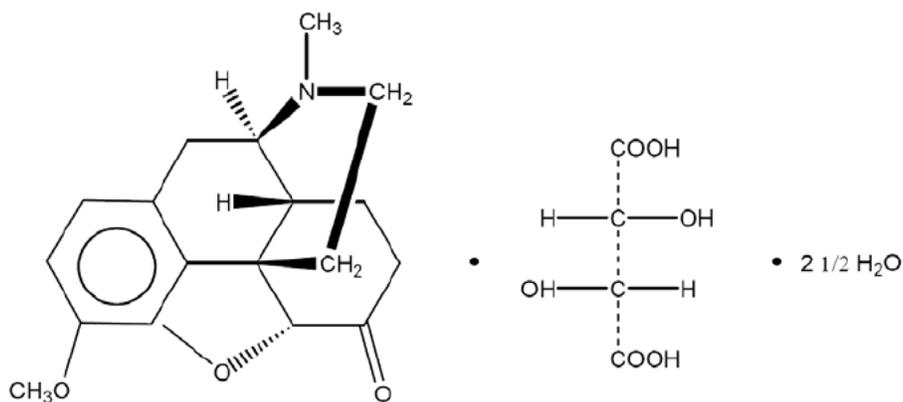
 X Not a SPOTS product

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

There are two active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

4,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)



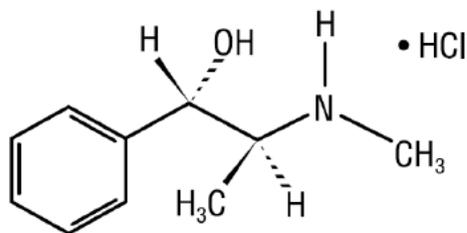
Chemistry Review Data Sheet

Molecular Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

Molecular Weight: 494.490

Pseudoephedrine Hydrochloride:

[S-(R*,R*)]- α -[1-(methylamino)ethyl]-benzenemethanol hydrochloride



Molecular Formula: $C_{10}H_{15}NO \cdot HCl$

Molecular Weight: 201.69

Comment: The applicant provided chemical name is incorrect: α -[1-(methylamino)ethyl]-[S-(R*,R*)] hydrochloride.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Hydrocodone bitartrate drug substance	3	Adequate	04-07-2009	The review in support of an oral solution identified deficiencies, which was corrected and then deemed adequate.
(b) (4)	II	(b) (4)	Pseudoephedrine hydrochloride drug substance	3	Adequate	08-13-2008	Based on this and the previous reviews, the DMF is deemed adequate in support of an oral solution
(b) (4)	III	(b) (4)	(b) (4)	NA	NA	NA	NA

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	NA	NA	NA	NA
	IV		3	Adequate	08-14-2008	The review deemed it adequate in support of an oral solution
	III		NA	NA	NA	NA
	III		NA	NA	NA	NA

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	102177	IND review summary indicated CMC related items are considered and evaluated in this NDA review.

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	NA
EES	Acceptable	6/30/2009	NA
Pharm/Tox	Adequate	5/22/2009	Marcus Delatte
Biopharm	NA	NA	NA
LNC	Pending	6/30/2009	NA
Methods Validation	Validation is not required by FDA	6/30/2009	Xiaobin Shen



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	Lab		
OPDRA	NA	NA	NA
EA	Acceptable	3/30/2009	Xiaobin Shen
Microbiology	Acceptable	3/30/2009	James McVey

The Chemistry Review for NDA 22-442

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable pending adequate responses to support the outstanding issues summarized at end of this review.

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

II. Summary of Chemistry Assessments

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

The drug product REZIRA is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for (b) (4) relief of cough and (b) (4) relief of nasal congestion due to common cold.

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride. In addition to the two active pharmaceutical ingredients, REZIRA contains excipients commonly used in oral solution products (e.g. water, citric acid, sodium citrate, sodium saccharin, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial REZIRA is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in (b) (4)

The process used to manufacture the commercial product (b) (4)

There are two drug substances for this NDA: hydrocodone bitartrate and pseudoephedrine hydrochloride.

1- Hydrocodone bitartrate (INN & USAN) was approved by FDA and marketed as Hycodan[®] Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4) which was last reviewed in April, 2009 by Dr. Maria Manzoni and found adequate. The DMF's EES status is acceptable. The drug product manufacturer release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on

Executive Summary Section

drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities, assay, related substances (specified and unspecified), residual solvents, and microbial limits.

2- Pseudoephedrine hydrochloride is also OTC monograph item. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is a white to almost white crystalline powder that is freely soluble in water. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed by Guoping Sun, Ph.D. in Feb. 2008 and deemed adequate. Arthur Shaw, Ph.D. reviewed it last in Aug. 2008 after the DMF was resubmitted in CTD-Q format and also deemed it adequate. The holder's EES status is acceptable. The drug product manufacturer release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), organic volatile impurities, residual solvents, heavy metals and microbial limits.

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

The drug product REZIRA is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains (b) (4). Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate and 60 mg of pseudoephedrine hydrochloride.

Dosing for adults (b) (4) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

(b) (4) The manufacturer proposed a two year expiry with 20 C to 25 C storage condition, the firm provided 12 month real time stability data to support the two year expiry and it is found acceptable.

C. Basis for Approvability or Not-Approval Recommendation

From the perspective of chemistry, manufacturing and control, this drug product is approvable pending satisfactory responses to the CMC deficiencies listed in Section III of the review summary.

REZIRA oral solution consists of two active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan[®] Syrup since 1988. The other active pseudoephedrine hydrochloride is an OTC monograph article.

There are CMC requests related to both drug substances and the drug product which need to be addressed by the DMF holders or the sponsors (see section III of the review summary). EES evaluations are acceptable for all facilities.

The product's trade name has been changed to REZIRA and deemed acceptable.

Executive Summary Section

The labeling and package insert are acceptable from CMC perspective with minor comments.

III. Administrative**A. Reviewer's Signature**

Chemist: Xiaobin Shen, Ph.D. *{Signed electronically in DFS}*

B. Endorsement Block

ChemistName/Date: Xiaobin Shen/09-Jul-2009

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

C. CC Block

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

/s/

Xiaobin Shen
7/13/2009 09:40:18 AM
PHARMACIST

Ali Al-Hakim
7/13/2009 10:43:39 AM
CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 8, 2009

TO: NDA 22439 and NDA 22442 ([REDACTED] (b) (4)
[REDACTED] (b) (4)

THROUGH: Ali Al-Hakim, Ph.D., Chief, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

Xiaobin Shen, Ph.D., Quality Reviewer, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

Sheldon Markofsky Ph.D., Quality Reviewer, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

FROM: Philantha Bowen, M.P.H., RN, Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

SUBJECT: **CMC Inquiry: Leachables in hydrocodone containing NDA products**

The following CMC inquiry was received, via e-mail correspondence, on February 10, 2009, from Dr. William Putnam of Beckloff Associates, consultant for Cypress Pharmaceuticals:

We are in the process of preparing our responses to the comments presented in the filing letters for the hydrocodone containing NDA products (NDA 022439, [REDACTED] (b) (4) and NDA 022442). One of the questions involves provision of information related to the leachables in our drug products. I know that you, Dr. Prasad Peri, and Cypress Pharmaceutical, Inc. (Janet DeLeon and Rob Lewis) have had a couple of communications related to this topic and the information required to fulfill this requirement during the IND phase of this product. Based on that information we have prepared the following response.

Would it be possible for you to check with the chemistry reviewer to determine if this response would be sufficient to fulfill the response?

- 7. An assessment of leachables in the drug product was not provided in the NDA. Submit the results of your evaluation of extractables and leachables from the container closure system and how you concluded that they do not exist and are not necessary for routine monitoring. We strongly recommend that you use appropriate analytical methods that are capable of monitoring and separating these compounds from other degradants and impurities in the drug product. Leachables specifications should be proposed when the data in your drug product have reached an asymptote.*

Response

Cypress requested clarification to a similar earlier request in an e-mail to Lt. Philantha Bowen, Senior Regulatory Management Officer, FDA on February 18, 2008. Lt. Bowen responded on February 29, 2008 with the following comment: "...All the stability time points should be pulled and tested as per the stability protocol for impurities (using a validated stability indicating method). Any unknown impurity found above the ICH Q3B(R) identification and qualification threshold needs to be identified and acted on per the guidance. If these impurities are detected and not related to the drug substance or excipients, and are identified of extraneous source (possibly container closure system), they are termed leachables...". Therefore, Cypress' validated test method for identification and quantitation of impurities will be used to detect any possible leachables as requested. This validated test method is used at product release and at each stability time point to evaluate the drug product for impurities arising from the drug substance, excipients, and extraneous sources such as the container closure system. Of note, through 6 months of ICH accelerated (40 ± 2 °C/ $75 \pm 5\%$ relative humidity) and room temperature (25 ± 2 °C/ $60 \pm 5\%$ relative humidity) no impurities arising from extraneous sources have been found to be above the ICH identification threshold.

CMC reviewed the response and communicated via e-mail on February 13, 2009, that the sponsor's response was acceptable. Eunice Chung, Regulatory Project Manager, left a voice message for Dr. Putman on February 18, 2009, informing him of the acceptability of Cypress' response from the CMC standpoint.

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

/s/

Philantha M Bowen
4/8/2009 11:35:17 AM
CSO

OND Division of Pulmonary and Allergy Products

NDA: 22-442

Applicant: Cypress Pharmaceuticals, Inc.

Letter Date: Nov 6, 2008

Stamp Date: Nov 7, 2008

PDUFA Date: 7-Sep-2009

Proposed Proprietary Name: Rezira^(b)₍₄₎ Oral Solution

Established Name: Hydrocodone bitartrate, Pseudoephedrine Hydrochloride

Dosage form and strength: Oral Solution, 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride each in 5 mL.

Route of Administration: Oral

Indications: Indicated for the ^(b)₍₄₎ relief of cough, the ^(b)₍₄₎ relief of nasal congestion due to common cold.

Dose: Adults ^(b)₍₄₎ (5 mL) every 4 to 6 hours, not to exceed 4 doses (20 mL) in 24 hours. ^(b)₍₄₎

PAL: Prasad Peri, Ph.D. Branch 2/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Primary reviewer: Xiaobin Shen, Ph.D.

Time goals:

Initial Quality Assessment in DFS: by 15-Dec-2008

Chemistry filing memo in DFS: by 6-Jan-2009 (after filing meeting)

Filing decision "Day 60": 6-Jan-2009

Filing Date "Day 74": 20-Jan-2009

Chemistry Review (DR/IR) letter: by 8-Apr-2009

Mid-cycle meeting "Month 5": 31-Mar-2009

Final Chemistry Review "Month 8" in DFS: by 31-Jul-2009

Wrap-Up Meeting (end of mo 8): June 29, 2009

Primary Review (1 wk after WU): July 31, 2009

Secondary Review (6 wks before Action): ~ Jul 25th, 2009

Labeling Tcon (5 wks before Action): Jul 30, 2009

CDTL Memo (4 wks before Action): Aug 7, 2009

PDUFA: 7-Sept-2009

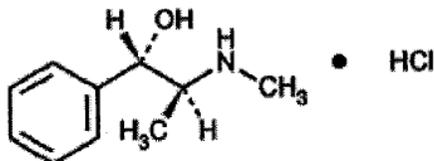
Related Documents

INDs pertaining to this are: ^(b)₍₄₎

NDA's pertaining to this are: None

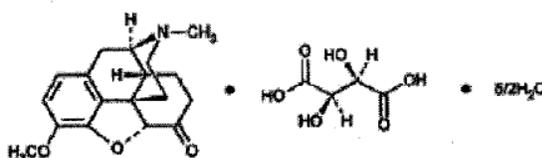
USAN/INN/JAN	Pseudoephedrine Hydrochloride USP
Chemical Name	Benzenemethanol, a-(1-(methylamino)eth)YL-, (S-(R* ,R*)J , hydrochloride
CAS #	345-78-8
Molecular formula	C ₁₀ H ₁₄ NO ₄ HCl
Molecular weight	201.69

Structure



USAN/INN/JAN	Hydrocodone Bitartrate USP
Chemical Name	Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5a)-, (R-(R*,R*))-2,3-dihydroxybutanedioate.(1 : 1), hydrate (2:5); also known as 4,5a - Epoxy-3-methoxy-17-methylmorphinan-6-one (1 : 1) hydrate (2:5)
CAS #	143-71-5 (anhydrous) 34195-34-1 (Hydrocodone Bitartrate)
Molecular formula	C ₁₈ H ₂₁ N ₀₃ . C ₄ H ₆ O ₆ . 2 1/2 H ₂ O
Molecular weight	494.490

Structure



CONSULTS/ CMC RELATED REVIEWS	COMMENT
Clinical Pharm (BA/BE) - Dissolution	No Applicable
CDRH	Not Applicable
EA	To be assessed by Primary Reviewer
EES	The drug substance site (b) (4) has an acceptable status however, it is not clear who does the stability testing of the drug substance. The drug product manufacturing sites are entered into EES on Sept. 5, 2007. No contact names and phone numbers are provided. They have been requested.
DMETS/DDMAC	Consensus is pending.
Methods Validation	Not necessary
Microbiology	Consult for antimicrobial assessment to be requested.
Pharm/Tox	Depends to stability data for leachables and impurities.
Biometrics	To be decided by the reviewer

Summary:

- This is a standard (10 months) NDA in electronic format with electronic labeling provided in SPL format. There is a Quality Overall Summary. This NDA is filed as a 505(b) 2 application. This is a new combination containing two ingredients one of which (pseudoephedrine hydrochloride) is listed in the OTC monograph part 341. Hydrocodone Bitartrate is a generally recognized antitussive, with efficacy established in DESI Notice #5213, dated June 1, 1982. Note that relevant NDAs for this application and that of Hycodan and Hycomine. The NDA is based on a PK bioavailability and food

effect study in a very few number (15-18) of patients. The two drug substances are specified as USP grade.

- This NDA is submitted by the applicant after the FDA issued a guidance called Marketed Unapproved Drugs Compliance Policy Guide, which describes plans for enforcement in this area: "The FDA is telling manufacturers to either obtain approval for an unapproved drug or remove it from the market. Even if the drug has been marketed for many years with no known safety problems, companies will still need to comply. The absence of evidence of a safety problem does not mean a product is truly safe."

Drug Substances

- The two drug substances are stated as USP grades and the proposed tests and certificates of analysis and specifications do support the compliance to the monograph.
- Hydrocodone bitartrate dihydrate is a white or slightly yellow-white color powder. It is fairly soluble in water and but not soluble in ether and chloroform and pH of a 2% Aqueous solution is about 3.6. Hydrocodone is manufactured by (b) (4). The drug substance is referenced in a DMF (b) (4) which was It was found adequate for a solid oral dosage form in a review completed on April 19, 2007 by Rosario D'Costa, Ph.D. Special attention should be given to impurities in hydrocodone since several impurities have the potential to be genotoxic (b) (4). (b) (4) The sponsor states that they have not yet identified (b) (4) in their drug product. The agency (pharmacologist/toxicologists) has been alerting the manufacturers of hydrocodone of the potential genotoxic impurities and that they should limit the levels of these impurities to less than (b) (4). For the current indication the maximum daily dose of hydrocodone is 20 mg/day for Adults (b) (4).
- Pseudoephedrine hydrochloride USP is made by (b) (4). Information is presented in a DMF (b) (4). This DMF was reviewed for safety during the IND review by Dr. Art Shaw (date 8/14/2008) and previously for and NDA by Dr. Guoping Sun (date 2/26/2008). The GSL drug substance specification complies with the USP monograph for pseudoephedrine hydrochloride, ICH Q3C(R3) for residual solvents, and with the ICH Q3A(R2) qualification limit for related substances. The limits for total aerobic counts and total combined yeast and molds counts are those required by USP <1111>.
- The sponsor claims that the DMF holders have validated methods that are suitable for stability indication purposes and have documented stability data for the drug substance.

Drug Product

- Drug Product is an aqueous solution containing (b) (4) sucrose and (b) (4) sodium saccharine with a grape flavoring agent. It is a clear, colorless to light yellow liquid with a grape odor and free of any precipitates.
- The registration batches are (b) (4) size while the proposed commercial scale is stated to be (b) (4). All excipients are USP or NF grade with the exception of the grape flavor. Note that there was a discussion during the evaluation of safety during the IND safety review, and issues that need to be sorted out are stated below.

Table 2.3.P-1. Unit Composition of REZIRA (b) (4) Oral Solution						
Component	Reference to Quality Standards	Function	Unit Composition			
			% w/v	mg/mL	mg/15 mL	mg/480 mL
Hydrocodone Bitartrate	USP	Active ingredient	(b) (4)			
Pseudoephedrine Hydrochloride	USP	Active ingredient				
Citric Acid, Anhydrous	USP					
Sodium Citrate	USP					
Sodium Saccharin	USP					
Methylparaben	NF					
Propylparaben	NF					
Sucrose	NF					
Glycerin, (b) (4)	USP					
Propylene Glycol	USP					
Grape Flavor (b) (4)	In-house					
Water, Purified	USP					

NF = National Formulary.

Table 2.3.P-2. Container Closure for REZIRA (b) (4) Oral Solution		
Component	Professional Sample (15 mL)	Commercial Product (480 mL)
Container	(b) (4)	
Closure		
(b) (4)		

Table 2.3.P-3. Conformance to Inactive Ingredient Guide for Approved Drug Products			
Ingredient	REZIRA (b) (4) Oral Solution	IIG Levels	
	Quantity (w/v)	Highest Quantity Approved ^a	
Citric Acid, Anhydrous	(b) (4)	72.2%	
Sodium Citrate		32.5%	
Sodium Saccharin		5%	
Methylparaben		13%	
Propylparaben		20%	
Sucrose		82.1%	
Glycerin, (b) (4)		94%	
Propylene Glycol		92%	
Grape Flavor (b) (4)		1.0%	
Purified Water		(b) (4)	

^a = Highest quantity approved (%) in oral solution, oral syrup, or oral suspension.

- Drug product is manufactured at by (b) (4). The methods of manufacturing are relatively straight forward. (b) (4)
- (b) (4)
- Drug product specifications are listed on the following page along with the results for three batches.
- Stability data for three batches at accelerated and long term storage conditions are provided. For both the conditions, **only 3 months of data** are provided and the sponsor has proposed a 2 year shelf life in the application.
- The reviewer needs to evaluate the provided data and may propose a (b) (4) shelf life for the drug product based on the available data. Note that ICH Q1A only allows a 12 months extrapolation of stability data, if the data are robust.
- The sponsor mentions that no leachables are observed in the drug product.
- The reviewer needs to send a consult to the microbiology staff about the antimicrobial effectiveness testing.
- A consult is needed to evaluate the results of genotox results for (b) (4) as provided by the sponsor.

CRITICAL ISSUES

- **Pharmaceutical development**
Formulation development has been reported and the selection of each excipient has been justified. The levels of monographed excipients are reported to be lower than the levels stated in the FDA's Inactive Ingredients Guide.
- **Dose Dumping.** Not applicable.
- **Microbial Testing:**
It is not clear if the sponsor has done a (b) (4). The reviewer should evaluate the possibility of consulting microbiology staff if this is an issue.

Overage in the formulation

No overages are proposed for drug substance.

- **Excipients from Animal Origin.** None proposed.
- **OVI in the drug Product.** Not applicable.
- **Manufacturing differences between pilot and commercial scales**
None proposed. The registration stability batches are (b) (4) and the proposed commercial batches are (b) (4).
- **GMP status of the drug substance/drug product manufacturing sites.**

Note that the (b) (4) (mfg of HCB) was found acceptable based on profile. (b) (4) and (b) (4) sites are sent to the DO for evaluation. (b) (4) (Drug product manufacturing site) was assigned for inspection.

- **Safety of imprinting inks**

Although the sponsor claims no leachables, there are several extractables that will need to be evaluated in this NDA. The sponsor has not proposed acceptance criteria for leachables.

- **Dissolution of the drug product**

Not applicable

- **Assay**

It appears that the Assay values for two of the three batches for Hydrocodone bitartrate, pseudoephedrine, propylparaben and methyl Paraben, appear rather on the lower side. This should be investigated in the analytical methods section by the reviewer.

- **Degradation products in the drug product:** The sponsor claims no degradation products in the stability data provided. No specification for Total Unspecified impurity exists. This needs to be specified in the specifications.

- **Sensitivity of product to moisture and light.** This is an aq. solution packaged in (b) (4) and HDPE bottles. There is a possibility of degradants. The sponsor claims the color of the product to be slightly yellow however, no explanation on why the color is provided.

- **Weight Loss:** None proposed.

- **Shelf life:** None proposed. Will need to be evaluated by reviewer.

- (b) (4) **Drug Product Stability Packaging Data and Protocol**

(b) (4) period is proposed yet no data are provided.

- **Comparability Protocol:** None proposed.

Stability: The stability data provided are on 3 months of accelerated and long term. A 2 year tentative expiration date is proposed with directions to store the product at 20 to 25 °C (68 to 77 °F). A statistical analysis with the 6 month data will be performed if the data show trending that is amenable to analysis.

- The first three consecutive commercial batches will be placed on stability.

Drug product specifications with batch results are provided in the table below.

(b) (4)



ONDQA PAL's Initial Quality Assessment
Prasad Peri, Ph.D., Division of Pre Marketing Assessment 1, Branch 2

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	II	(b) (4)	Hydrocodone Bitartrate	Reviewed by R. D. Costa Ph.D. on 19-APR-2007 and found adequate. No review required.
	II	(b) (4)	Pseudoephedrine HCl	Reviewed by G. Kang, Ph.D. on 30-Mar-2006 and found adequate.
	III	(b) (4)	(b) (4)	Review Needed. Direct food contact regulations needed for components.
	III	(b) (4)	(b) (4)	Review Needed. Direct food contact regulations needed for components.
	III	(b) (4)	(b) (4)	Adequate for Oral Solution in review dated 9/1/1999. Direct food contact regulations needed for components.
	III	(b) (4)	(b) (4)	Adequate for solid oral dosage forms. Complies with food contact regulations as listed in 21 CFR 177.1520 178.3297 and 181.5

Table 3.2.P.8.1-1. Stability Protocol for Registration Batches (480 mL and (b) (4))

Batch		Storage Condition	Test Intervals (Months)	Container Storage Position	Data Available (Months)
00998/P08020	16 fl oz (480 mL)	25 ± 2 °C/60 ± 5% RH (long-term)	0, 3, 6, 9, 12, 18, 24, 36, 48	Horizontal	0, 3
01028/P08022		40 ± 2 °C/75 ± 5% RH (accelerated)	0, 1, 2, 3, 6	Horizontal	0, 1, 2, 3
01058/P08024					
00998/P08021	(b) (4)	25 ± 2 °C/60 ± 5% RH (long-term)	0, 3, 6, 9, 12, 18, 24, 36, 48	Horizontal	0, 3
01028/P08023		40 ± 2 °C/75 ± 5% RH (accelerated)	0, 1, 2, 3, 6	Horizontal	0, 1, 2, 3
01058/P08025					

Table 2.3.P-4. Specifications for REZIRA-^(b)₍₄₎ Oral Solution			
Test	Acceptance Criterion		Analytical Procedure
	Release	Stability	
(b) (4)			

ONDQA PAL's Initial Quality Assessment
Prasad Peri, Ph.D., Division of Pre Marketing Assessment 1, Branch 2

Table 2.3.P-4. Specifications for REZIRA ^(b)₍₄₎ Oral Solution			
Test	Acceptance Criterion		Analytical Procedure
	Release	Stability	
(b) (4)			

• **CHEMISTRY NDA FILEABILITY CHECKLIST**

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		Applicant shows calculations of less than the specified amount listed in the regulations. Consult to be sent
7	Does the section contain controls for the drug substance?	X		Reference to DMFs and NDA
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?		X	3 months stability data provided. No shelf life proposed
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?		X	Described in the development report
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		Antimicrobial Effectiveness testing to be provided and evaluated
16	Is a production batch record provided	X		

Draft CMC Comments for 74 day Letter

- 1. Provide references to direct food additive regulations for all the packaging materials (b) (4) that are in contact with the formulation.**
- 2. We note that you have not provided us with an assessment of leachables in the drug product. Provide us results of your evaluation of extractables and leachables from the container closure system and how have you concluded that they do not exist and are not necessary for routine monitoring. We strongly encourage you to use appropriate analytical methods that are capable of monitoring and separate these compounds from other degradants and impurities in the drug product. Leachables specifications will be applied when the data in your drug product have reached an asymptote.**
- 3. We note that you have provided only 3 months long term and accelerated stability data for your drug product and have proposed a 24 months shelf life. Based on the stability data in your NDA, you could potentially get a shelf life equal to the available real time data. It is inappropriate to set final specification based on the available stability data. This is a potential review issue as you will need to generate stability data to be able to assess trends in attributes listed in your drug product specifications.**
- 4. Provide the CMC information (qualitative and quantitative composition, stability data etc.) of the comparison drug products: pseudoephedrine hydrochloride oral solution and chlorpheniramine maleate oral solution. If this information has already been provided, provide a reference to the section and page number in your NDA.**
- 5. Provide a quantitative and qualitative chemical composition of the grape flavor (b) (4). Alternately this information may be provided in an authorized Drug Master File (DMF).**
- 6. Provide results of your Antimicrobial Effectiveness testing for your drug product.**
- 7. Provide draft mock ups (100 % size) of the proposed carton, container labels.**

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

/s/

Prasad Peri
12/16/2008 02:16:19 PM
CHEMIST

Ali Al-Hakim
12/18/2008 09:39:51 AM
CHEMIST

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 22442/000
Priority: 570
Priority: 4S
Stamp Date: 10-NOV-2008
PDUFA Date: 10-SEP-2009
Action Goal:
District Goal: 12-JUL-2009

Sponsor: CYPRESS PHARM
 135 INDUSTRIAL BLVD
 MADISON, MS 39110
Brand Name: REZIRA^{(b)(4)} HYDROCODONE BITARTRATE AND PSEU
Estab. Name:
Generic Name: HYDROCODONE BITARTRATE, PSEUDOEPHEDRINE
Product Number; Dosage Form: Ingredient; Potency

FDA Contacts:	P. BOWEN	Project Manager	(HFD-570)	301-796-2466
	P. PERI	Review Chemist	(HFD-820)	301-796-1730
	A. AL HAKIM	Team Leader		301-796-1323

Overall Recommendation: ACCEPTABLE on 29-JUN-2009 by M. STOCK (HFD-320) 301-796-4753

Establishment: CFN: (b)(4) FEI: (b)(4)
 (b)(4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE PACKAGER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile: (b)(4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b)(4) FEI: (b)(4)
 (b)(4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS, **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-JUN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE
