NDA 22-410
Suboxone ®
(buprenorphine and naloxone)
sublingual film 2 mg/0.5 mg and 8 mg/2 mg

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

Applicant: Reckitt Benckiser Pharmaceuticals Inc.

Indication: Suboxone is indicated for maintenance treatment of opioid dependence.

Presentation: The drug product is two different film formulations: 2 mg/0.5 mg and 4 mg/2 mg (buprenorphine/naloxone). The drug product is supplied in individual child-resistant polyester/foil laminated pouches available in a lower strength (2mg/0.5 mg/film) and a higher strength (8 mg/2 mg/film). Each strength will be available in 30 pouches per carton.

EER Status: Recommendations: acceptable
Consults:
- EA – Categorical exclusion provided
- CDRH- N/A
- Statistics – N/A
- Methods Validation – Not recommended
- DMEPA- Completed
- Biopharm– N/A
- Microbiology – N/A
- Pharm/toxicology – N/A

Original Submission: 20-October-2008
Re-submissions: N/A
Post-Approval CMC PMC/PMR: None.

Background:
This NDA is submitted under 505b2. The drug product, Suboxone ®, a soluble film designed for sublingual delivery, is a combination of buprenorphine and naloxone indicated for maintenance treatment of opioid dependence. Naloxone is an opioid receptor antagonist. Suboxone is an alternative to the currently marketed Suboxone® (buprenorphine/naloxone) sublingual tablet (NDA 20-733).
Drug Substances:

There are two drug substances for this NDA:

- **Buprenorphine hydrochloride** is manufactured by the applicant. The information on the chemistry, manufacturing, and controls (CMC) for buprenorphine hydrochloride drug substance is referred to Type II Drug Master File (DMF) 12412. DMF 12412 was reviewed and found satisfactory. The specifications for Buprenorphine HCl Drug Substance include Physical Description (visual), Identification (NIR, UV, Chlorides), pH (aqueous suspension), Water (Karl Fischer), Residue on Ignition, Specific Optical Rotation, Residual Solvents by GC, Assay (HPLC, titration), Residual Chloride determination, Purity (HPLC) and Particle Size Distribution. Each known impurity and any individual unspecified impurity can not exceed and their total no more than The specifications for Buprenorphine HCl comply and exceed those required by USP. A re-test period is established at the time of manufacture and the expiration date is extended in six monthly units up to a shelf life of subject to the material meeting the specification criteria.

  **Buprenorphine hydrochloride**

  Laboratory Code: RX6029M.HCl

  C_{29}H_{43}NO_4 HCl

  MW: 467.6 (base) 504.1 (salt)

  CAS Registry number: 53152-21-9

  (2S)-2-[17-Cyclopentylmethyl-4,5a-epoxy-3-hydroxy-6-methoxy-6a,14-ethano-14a-morphinan-7a-y1]-3,3-dimethylbutan-2-ol hydrochloride

- **Naloxone hydrochloride dihydrate**

There are two suppliers of naloxone hydrochloride dihydrate drug substance; the first supplier is CMC information is referred to their DMF DMF was reviewed and found satisfactory. The second supplier is CMC information is referred to their DMF DMF was reviewed and found satisfactory. The Reckitt Benckiser’s naloxone HCl dihydrate purchasing specifications have been agreed with both suppliers. These specifications, which comply and exceed those required by both USP and Ph Eur, include Physical Description (visual), Identification (IR, TLC, Chloride), Acidity or alkalinity (titrimetric), Water content (Karl Fischer), Residue on Ignition, Specific Optical Rotation, Residual Solvents by GC, Assay (HPLC, titration), Ion
Chloride determination, Appearance of solution (visual), Loss on drying (gravimetric), and Purity (HPLC). Known impurities each NMT and Other impurities, including Ph Eur impurities each NMT and the total (known and unknown related substances) can not exceed .

The supporting shelf-life support storage re-test period naloxone hydrochloride dihydrate.

**Chemical Name, Structural Formula, Molecular Formula, Molecular Weight**

Naloxone hydrochloride dihydrate

\[
\text{C}_{19}\text{H}_{23}\text{NO}_4\cdot\text{HCl}\cdot2\text{H}_2\text{O}
\]

MW: 399.9

CAS RN: 465-65-6 Naloxone, 357-08-4 Naloxone hydrochloride anhydrous 51481-60-8 Naloxone hydrochloride dihydrate

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

**Conclusion:** The drug substances are satisfactory

**Drug Product:**

The manufacture process comprises

The drug product is manufactured in two different film formulations: 2 mg/0.5 mg and 4 mg/2 mg (buprenorphine/naloxone). Both dosage strengths have the same width and length, 0.875” x 0.5”, but differ in weight, 40 mg for the lower strength and 50 mg for the higher. Although both formulations share the same excipients, their composition is different. Those differences in formulation, obtained during product development, assure that each formulation has the desired properties (flexibility, disintegration and pharmacokinetic properties).

Drug product specifications include Appearance (visual), Identification (HPLC), Assay (buprenorphine and naloxone each by HPLC), Dissolution (currently Q = in 7 minutes for buprenorphine and Q = in 7 minutes for naloxone), Moisture content uniformity (NMT), Microbial limits
(USP<905>), and Purity (HPLC). Purity requirements for Buprenorphine Related Substances include any Individual Unidentified Impurity NMT, and their total can not exceed Purity requirements for Naloxone Related Substance include , and for each NMT Any Individual Unidentified Impurity NMT and the total of impurities can not exceed Based on the provided stability data, 12 months of expiry dating is granted for the drug product

**Conclusion:** The drug product is satisfactory.

**Overall Conclusion:**
From a CMC perspective, the application is recommended for approval.

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

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.
<table>
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<th>Drug Name / Subject</th>
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<tr>
<td>NDA 22410</td>
<td>ORIG 1</td>
<td>RECKITT BENCKISER PHARMACEUTICA LS INC</td>
<td>SUBOXONE (BUPRENORPHINE/NALOXONE ) sublingual film</td>
</tr>
</tbody>
</table>

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
08/21/2009
NDA 22-410

Suboxone
(buprenorphine and naloxone)
Sublingual Film
2 mg/0.5 mg and 8 mg/2 mg

Reckitt Benckiser Pharmaceuticals Inc.

Xavier Ys ern, PhD
ONDQA/ DPA I/ Branch II

Clinical Review Division: DAARP (HFD-170)
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Chemistry Assessment See CMC Review # 1

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2. REVIEW #: 2
3. REVIEW DATE: 20-Aug-2009
4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

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<tr>
<th>Previous Documents</th>
<th>Document Date</th>
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6. SUBMISSION(S) BEING REVIEWED:

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<th>Submission(s) Reviewed</th>
<th>Document Date</th>
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<tbody>
<tr>
<td>Original</td>
<td>20-Oct-2008</td>
</tr>
<tr>
<td>Amendments:</td>
<td></td>
</tr>
<tr>
<td>0002</td>
<td>30-Oct-2008 (Proposed proprietary name Suboxone)</td>
</tr>
<tr>
<td>0005</td>
<td>08-Dec-2008 (Environmental Assessment)</td>
</tr>
<tr>
<td>0009</td>
<td>03-Mar-2009 (Updated stability data)</td>
</tr>
<tr>
<td>0014</td>
<td>28-Apr-2009 (Change of secondary packaging facility)</td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

Name: Reckitt Benckiser Pharmaceuticals Inc.
Address: 10710 Midlothian Turnpike, Suite 430
         Richmond, VA23235
Representative: Deborah C. Moffitt
                Manager, Regulatory Affairs Operations
Telephone: 804 423-6970

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Suboxone
b) Non-Proprietary Name (USAN): (buprenorphine and naloxone) sublingual film (established name)
c) Code Name/# (ONDC only): --
d) Chem. Type/Submission Priority: 
   · Chem. Type: 4
   · Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of opiod dependence

11. DOSAGE FORM: Sublingual film

12. STRENGTH/POTENCY: 2 mg/0.5 mg and 8 mg/2 mg (buprenorphine/naloxone)

13. ROUTE OF ADMINISTRATION: Sublingual route
CHEMISTRY REVIEW

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

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

**Naloxone hydrochloride dihydrate**

\[ C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O \]

MW: 399.9

357-08-4 Naloxone hydrochloride anhydrous
51481-60-8 Naloxone hydrochloride dihydrate

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

**Buprenorphine hydrochloride**

Laboratory Code: RX6029M.HCl

\[ C_{29}H_{41}NO_4 \cdot HCl \]

MW: 467.6 (base) 504.1 (salt)

CAS Registry number: 53152-21-9

(2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-
dimethylbutan-2-ol hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

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<th>DMF #</th>
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<td>Type II</td>
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<tr>
<td>12412</td>
<td>Reckitt Benckiser Healthcare (UK) Ltd.</td>
<td>Buprenorphine HCl</td>
<td>(b)</td>
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<td>05-Feb-2009</td>
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</tr>
</tbody>
</table>

1 Action codes for DMF Table:
1 – DMF Reviewed.
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:

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<tr>
<th>Document</th>
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<th>Description</th>
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<tr>
<td>NDA</td>
<td>20-732</td>
<td>Subutex (Buprenorphine) Tablets 2 mg and 8 mg</td>
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<tr>
<td>NDA</td>
<td>20-733</td>
<td>Suboxone (Buprenorphine and Naloxone) sublingual tablet 2/0.5 mg and 8/2 mg</td>
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18. STATUS:

<table>
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<th>CONSULTS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
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<td>Biometrics</td>
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<td>EES</td>
<td>Acceptable recommendation</td>
<td>20-Aug-2009</td>
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<td>Pharm/Tox</td>
<td>--</td>
<td></td>
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<td>Biopharm</td>
<td>--</td>
<td></td>
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<tr>
<td>Labeling</td>
<td>OSE does not object the use of the tradename Suboxone. The drug product should be referred as “Suboxone (Buprenorphine and Naloxone) sublingual film” throughout all labels and labeling documentation.</td>
<td>08-Aug-2009</td>
<td>Multidisciplinary</td>
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<td>Methods Validation</td>
<td>Revalidation by Agency laboratories is not recommended</td>
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<td>EA</td>
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<td>Microbiology</td>
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CHEMISTRY REVIEW

The Chemistry Review for NDA 22410

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for approval.

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, Suboxone 

The drug product, Suboxone 

The drug product, Suboxone 

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Buprenorphine hydrochloride

Buprenorphine hydrochloride, chemical name (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride, has the molecular formula C_{29}H_{41}NO_{4}·HCl and a molecular weight of 504.10 g/mol. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol and practically insoluble in cyclohexane.

Buprenorphine, the active component of buprenorphine hydrochloride, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine is a thebaine (paramorphine an opiate alkaloid) derivative with powerful analgesia approximately twenty-five to forty times as potent as morphine. Buprenorphine also has very high binding affinity for the µ receptor such that opioid receptor antagonists (e.g. naloxone) only partially reverse its effects.

Buprenorphine hydrochloride is manufactured by the applicant at their facility, “Fine Chemical Plant” (Reckitt Benckiser Healthcare Limited), located in Hull, United Kingdom. The information on the chemistry, manufacturing, and controls (CMC) for buprenorphine hydrochloride drug substance is referred to Reckitt Benckiser Healthcare (UK) Limited’ Type II Drug Master File (DMF) 12412.

The specifications for Buprenorphine HCl Drug Substance include Physical Description (visual), Identification (NIR, UV, Chlorides), pH (aqueous suspension), Water (Karl Fischer), Residue on Ignition (b) (4), Specific Optical Rotation (aqueous suspension) (b) (4), Residual Solvents (b) (4) by GC, Assay (HPLC, titration), Ion Chloride determination, Purity (HPLC) and Particle Size Distribution. Each known impurity can not exceed (b) (4) and their total no more than (b) (4) Reckitt Benkiser’s specifications for Buprenorphine HCl comply and exceed those required by USP.
CHEMISTRY REVIEW

Bulk drug substance is stored in a re-test data is applied at the time of manufacture and the expiration date is extended in six monthly units up to a shelf life of subject to the material meeting the specification criteria.

Naloxone hydrochloride dihydrate

Naloxone hydrochloride dihydrate, chemical name 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate, has the molecular formula C₁₉H₂₁NO₄·HCl·2H₂O and a molecular weight of 399.87 g/mol. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol; practically insoluble in toluene and ether.

Naloxone, the active component of naloxone hydrochloride dihydrate, is a potent antagonist at mu-opioid receptors and produces opioid withdrawal effects in individuals physically dependent on full opioids. Naloxone is included in the Suboxone formulation to deter users from diverting its use to intravenous injection by producing opioid antagonist effects of short duration in subjects dependent on full opioid agonists.

There are two suppliers of naloxone hydrochloride dihydrate drug substance, and naloxone hydrochloride dihydrate is manufactured in their facility. The pertinent CMC information is referred to their proprietary Type II DMF. Naloxone hydrochloride dihydrate is manufactured at their facility in The CMC information is referred to their proprietary Type II DMF.

The Reckitt Benckiser’s naloxone HCl dihydrate purchasing specifications have been agreed with both (main drug substance supplier) and (alternate supplier). These specifications, which comply and exceed those required by both USP and Ph Eur, include Physical Description (visual), Identification (IR, TLC, Chloride), Acidity or alkalinity (titrimetric), Water content (Karl Fischer), Residue on Ignition, Optical Rotation, Residual Solvents by GC, Assay (HPLC, titration), Ion Chloride determination, Appearance of solution (visual), Loss on drying (gravimetric), and Purity (HPLC). Known impurities Naloxone hydrochloride dihydrate is supplied by in containers and in containers by The supporting shelf-life given by the suppliers exceed the storage period before re-test applied by Reckitt Benckiser.

Drug Product

Suboxone is a pale orange soluble film strip imprinted with a logo identifying the product and strength in white ink designed to provide immediate release of buprenorphine and naloxone in a 4:1 w/w ratio sublingually.

In addition to the active components buprenorphine and naloxone, the film contains polyethylene oxide hydroxypropyl methylcellulose, maltitol ( ), aceosulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow # 6 (colorant) and white ink (print ink). All excipients, with the exception of lime flavor, FD&C yellow # 6 and white ink, meet compendial requirements. The lime flavor, Lime Flavor is the same used in approved Suboxone Tablets (NDA 20-733), complies with food additives as per 21 CFR §172.510. FD&C Yellow # 6 is a FDA certified colorant permitted for food use as per 21 CFR §74.706, also
employed in Suboxone Tablets. The ink is an edible grade supplied by and all components are compendial.

The drug product is manufactured in two different film formulations: 2 mg/0.5 mg and 4 mg/2 mg (buprenorphine/naloxone), referred as lower and higher strengths respectively. Both dosage strengths have the same width and length, 0.875” x 0.5”, but differ in weight, 40 mg for the lower strength and 50 mg for the higher. Although both formulations share the same excipients, their composition is different. Those differences in formulation, obtained during product development, assure that each formulation has the desired properties (flexibility, disintegration and pharmacokinetic properties).

The manufacture process comprises

Drug product specifications include Appearance (visual), Identification (HPLC), Assay (buprenorphine and naloxone each by HPLC), Dissolution (currently Q = in 7 minutes for buprenorphine and Q = in 7 minutes for naloxone), Moisture content uniformity (NMT ), Microbial limits (USP<905>), and Purity (HPLC). Purity requirements for Buprenorphine Related Substances include any Individual Unidentified Impurity NMT and their total can not exceed Purity requirements for Naloxone Related Substance include and for each NMT Any Individual Unidentified Impurity NMT and the total of impurities can not exceed

Both buprenorphine and naloxone are susceptible to radical oxidative degradation processes. The degradation products forming in Suboxone appear consistent with those observed in the sublingual tablets, although there is some difference in their relative rates of formation. Based on the provided stability data, a 12 months expiration dating is granted.

The drug product is supplied in individual child-resistant polyester/foil laminated pouches available in a lower strength (buprenorphine/naloxone 2 mg/0.5 mg/strip) 30 pouches per carton (NDC 12496-1402-3), and a higher strength (buprenorphine/naloxone 8 mg/2 mg/strip; content expressed in terms of free base) 30 pouches per carton (NDC 12496-1408-3). The product is recommended to be stored at room temperature, “Store at 25 °C (77 °F), excursions permitted to 15 - 30 °C (59 - 86 °F) [see USP Controlled Room Temperature]”, and advised to store it out of sight and reach of children.

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

Suboxone is indicated for maintenance treatment of opioid dependence. The drug product is designed to deliver buprenorphine by the sublingual route; it is an alternative to the currently marketed Suboxone® sublingual tablet (NDA20-733).
C. Basis for Approvability or Not-Approval Recommendation

The pending issue, an acceptable recommendation for the overall cGMP status of the manufacturing, testing and packaging facilities by the Office of Compliance, has been satisfactorily resolved (EER summary report, dated 20-Aug-2009, is attached).

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance DMF and DMF for Naloxone Hydrochloride Dihydrate, and DMF 12412 for Buprenorphine Hydrochloride) and drug product manufactured, tested and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments.

From the CMC standpoint NDA 22-410 is recommended for approval.

III. Administrative

A. Reviewer’s Signature
Xavier Ysern, PhD Review Chemist/ ONDQA/ DPA I/ Branch II

B. Endorsement Block
Ali Al-Hakim, PhD Branch Chief/ ONDQA/ DPA I/ Branch II

C. CC Block
Matthew Sullivan Project Manager/ OND/ ODE II/ DAARP
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<td>SUBOXONE (BUPRENORPHINE/NALOXONE)</td>
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<td>RECKITT BENCKISER PHARMACEUTICALS INC</td>
<td>SUBOXONE (BUPRENORPHINE/NALOXONE)</td>
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/s/
XAVIER J YSERN
08/20/2009

ALI H AL HAKIM
08/20/2009
NDA 22-410

Suboxone *
(buprenorphine and naloxone) sublingual film
2 mg/0.5 mg and 8 mg/2 mg

Reckitt Benckiser Pharmaceuticals Inc.

Xavier Ysere, PhD
Office of New Drug Quality Assurance

Division of Analgesia, Anesthesia, and Rheumatology Products (HFD-170)

* The originally proposed tradename is used throughout the review. The proposed tradename is not acceptable.
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Attachments .........................................................................................................................................................130
Chemistry Review Data Sheet

1. NDA: 22-410
2. REVIEW #: 1
3. REVIEW DATE: 06-Jul-2009
4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
<th>Previous Documents</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
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</tbody>
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6. SUBMISSION(S) BEING REVIEWED:

<table>
<thead>
<tr>
<th>Submission(s) Reviewed</th>
<th>Document Date</th>
</tr>
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<tbody>
<tr>
<td>Original</td>
<td>20-Oct-2008</td>
</tr>
<tr>
<td>Amendments:</td>
<td></td>
</tr>
<tr>
<td>0002</td>
<td>30-Oct-2008 (Proposed proprietary name Suboxone)</td>
</tr>
<tr>
<td>0005</td>
<td>08-Dec-2008 (Environmental Assessment)</td>
</tr>
<tr>
<td>0009</td>
<td>03-Mar-2009 (Updated stability data)</td>
</tr>
<tr>
<td>0014</td>
<td>28-Apr-2009 (Change of secondary packaging facility)</td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

| Name:                         | Reckitt Benckiser Pharmaceuticals Inc. |
| Address:                      | 10710 Midlothian Turnpike, Suite 430   |
| Richmond, VA 23235            |                                           |
| Representative:               | Deborah C. Moffitt                      |
| Manager, Regulatory Affairs Operations |                                   |
| Telephone:                    | 804 423-6970                           |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Suboxone (proposed by the applicant)
b) Non-Proprietary Name (USAN): (buprenorphine and naloxone) sublingual film (established name)
c) Code Name/# (ONDC only): --
d) Chem. Type/Submission Priority:  
   · Chem. Type: 4
   · Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of opioid dependence

11. DOSAGE FORM: Sublingual film

12. STRENGTH/POTENCY: 2 mg/0.5 mg and 8 mg/2 mg (buprenorphine/naloxone)

13. ROUTE OF ADMINISTRATION: Sublingual (b) (4) route
CHEMISTRY REVIEW

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

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

**Naloxone hydrochloride dihydrate**

\[\text{C}_{19}\text{H}_{21}\text{NO}_4\cdot\text{HCl}\cdot2\text{H}_2\text{O}\]

MW: 399.9

CAS RN: 465-65-6 Naloxone. 357-08-4 Naloxone hydrochloride anhydrous 51481-60-8 Naloxone hydrochloride dihydrate

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

**Buprenorphine hydrochloride**

Laboratory Code: RX6029M.HCl

\[\text{C}_{29}\text{H}_{41}\text{NO}_4\cdot\text{HCl}\]

MW: 467.6 (base) 504.1 (salt)

CAS Registry number: 53152-21-9

(2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<th>Status</th>
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<td>12412</td>
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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")

Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
**B. Other Documents:**

<table>
<thead>
<tr>
<th>Document</th>
<th>Application #</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA</td>
<td>20-732</td>
<td>Subutex (Buprenorphine) Tablets 2 mg and 8 mg</td>
</tr>
<tr>
<td>NDA</td>
<td>20-733</td>
<td>Suboxone (Buprenorphine and Naloxone) sublingual tablet 2/0.5 mg and 8/2 mg</td>
</tr>
</tbody>
</table>

18. STATUS:

<table>
<thead>
<tr>
<th>CONSULTS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
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<tr>
<td>Biometrics</td>
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<tr>
<td>EES</td>
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<td>Pharm/Tox</td>
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<td>Labeling</td>
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<td>Methods Validation</td>
<td>Revalidation by Agency laboratories is not recommended</td>
<td></td>
<td>Part of this review</td>
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<tr>
<td>EA</td>
<td>Acceptable</td>
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<tr>
<td>Microbiology</td>
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</tbody>
</table>
CHEMISTRY REVIEW

The Chemistry Review for NDA 22410

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for approval pending an acceptable recommendation for the overall cGMP status of the manufacturing, testing and packaging facilities by the Office of Compliance.

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, Suboxone, a soluble film designed for sublingual delivery, is a combination of buprenorphine and naloxone indicated for maintenance treatment of opioid dependence. Buprenorphine is a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. Naloxone is an opioid receptor antagonist. Suboxone is an alternative to the currently marketed Suboxone® (buprenorphine/naloxone) sublingual tablet (NDA20-733).

- Drug Substance(s)

**Buprenorphine hydrochloride**

Buprenorphine hydrochloride, chemical name (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-y]-3,3-dimethylbutan-2-ol hydrochloride, has the molecular formula C_{29}H_{41}NO_{4}·HCl and a molecular weight of 504.10 g/mol. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol and practically insoluble in cyclohexane.

Buprenorphine, the active component of buprenorphine hydrochloride, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine is a thebaine (paramorphine an opiate alkaloid) derivative with powerful analgesia approximately twenty-five to forty times as potent as morphine. Buprenorphine also has very high binding affinity for the μ receptor such that opioid receptor antagonists (e.g. naloxone) only partially reverse its effects.

Buprenorphine hydrochloride is manufactured by the applicant at their facility, “Fine Chemical Plant” (Reckitt Benckiser Healthcare Limited), located in Hull, United Kingdom. The information on the chemistry, manufacturing, and controls (CMC) for buprenorphine hydrochloride drug substance is referred to Reckitt Benckiser Healthcare (UK) Limited’ Type II Drug Master File (DMF) 12412.

The specifications for Buprenorphine HCl Drug Substance include Physical Description (visual), Identification (NIR, UV, Chlorides), pH (aqueous suspension), Water (Karl Fischer), Residue on Ignition (b) (4), Specific Optical Rotation (aqueous suspension), Residual Solvents (b) (4) by GC, Assay (HPLC, titration), Ion Chloride determination, Purity (HPLC) and Particle Size Distribution. Each known impurity (b) (4) and their total no more than (b) (4) and any individual unspecified impurity can not exceed (b) (4) Reckitt Benkiser’s specifications for Buprenorphine HCl comply and exceed those required by USP.
CHEMISTRY REVIEW

Bulk drug substance is stored in . A re-test data is applied at the time of manufacture and the expiration date is extended in six monthly units up to a shelf life of subject to the material meeting the specification criteria.

Naloxone hydrochloride dihydrate

Naloxone hydrochloride dihydrate, chemical name 17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate, has the molecular formula C₁₉H₂₁NO₄·HCl·2H₂O and a molecular weight of 399.87 g/mol. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol; practically insoluble in toluene and ether.

Naloxone, the active component of naloxone hydrochloride dihydrate, is a potent antagonist at mu-opioid receptors and produces opioid withdrawal effects in individuals physically dependent on full opioids. Naloxone is included in the Suboxone formulation to deter users from diverting its use to intravenous injection by producing opioid antagonist effects of short duration in subjects dependent on full opioid agonists.

There are two suppliers of naloxone hydrochloride dihydrate drug substance, naloxone hydrochloride dihydrate is manufactured in their facility. The pertinent CMC information is referred to their proprietary Type II DMF. The CMC information is referred to their proprietary Type II DMF.

The Reckitt Benckiser’s naloxone HCl dihydrate purchasing specifications have been agreed with both (main drug substance supplier) and (alternate supplier). These specifications, which comply and exceed those required by both USP and Ph Eur, include Physical Description (visual), Identification ( ), Acidity or alkalinity (titrimetric), Water content (Karl Fischer), Residue on Ignition ( ), Optical Rotation ( ), Residual Solvents (HPLC, titration), Ion Chloride determination, Appearance of solution (visual), Loss on drying ( ), and Assay (HPLC, titration). Purity (HPLC). Known impurities (b) (4) . Other impurities, including Ph Eur impurities (b) (4) each NMT (b) (4) and the total (known and unknown related substances) can not exceed (b) (4) %.

Naloxone hydrochloride dihydrate is supplied by in containers and in containers by . The supporting shelf-life given by the suppliers exceed the storage period before re-test applied by Reckitt Benckiser.

Drug Product

Suboxone is a pale orange soluble film strip imprinted with a logo identifying the product and strength in white ink designed to provide immediate release of buprenorphine and naloxone in a 4:1 w/w ratio sublingually.

In addition to the active components buprenorphine and naloxone, the film contains polyethylene oxide (b) (4), hydroxypropyl methylcellulose (b) (4), maltitol (b) (4), aspartame potassium (b) (4), lime flavor (b) (4), citric acid (b) (4), sodium citrate (b) (4), FD&C yellow # 6 (colorant) and white ink (print ink). All excipients, with the exception of lime flavor, FD&C yellow # 6 and white ink, meet compendial requirements. The lime flavor, Lime Flavor is the same used in approved Suboxone Tablets (NDA 20-733), complies with food additives as per 21 CFR §172.510. FD&C Yellow # 6 is a FDA certified colorant permitted for food use as per 21 CFR §74.706, also
CHEMISTRY REVIEW

employed in Suboxone Tablets. The ink is an edible grade supplied by and all components are compendial.

The drug product is manufactured in two different film formulations: 2 mg/0.5 mg and 4 mg/2 mg (buprenorphine/naloxone), referred as lower and higher strengths respectively. Both dosage strengths have the same width and length, 0.875” x 0.5”, but differ in weight, 40 mg for the lower strength and 50 mg for the higher. Although both formulations share the same excipients, their composition is different. Those differences in formulation, obtained during product development, assure that each formulation has the desired properties (flexibility, disintegration and pharmacokinetic properties).

The manufacture process comprises

Drug product specifications include Appearance (visual), Identification (HPLC), Assay (buprenorphine and naloxone each by HPLC), Dissolution (currently Q = in 7 minutes for buprenorphine and Q = in 7 minutes for naloxone), Moisture content uniformity (NMT Microbial limits (USP<905>), and Purity (HPLC). Purity requirements for Buprenorphine Related Substances include any Individual Unidentified Impurity NMT and their total can not exceed Purity requirements for Naloxone Related Substance include Any Individual Unidentified Impurity NMT and the total of impurities can not exceed

Both buprenorphine and naloxone are susceptible to radical oxidative degradation processes. The degradation products forming in Suboxone appear consistent with those observed in the sublingual tablets, although there is some difference in their relative rates of formation. Based on the provided stability data, a 12 months expiration dating is granted.

The drug product is supplied in individual child-resistant polyester/foil laminated pouches available in a lower strength (buprenorphine/naloxone 2 mg/0.5 mg/strip) 30 pouches per carton (NDC 12496-1402-3), and a higher strength (buprenorphine/naloxone 8 mg/2 mg/strip; content expressed in terms of free base) 30 pouches per carton (NDC 12496-1408-3). The product is recommended to be stored at room temperature, “Store at 25 °C (77 °F), excursions permitted to 15 - 30 °C (59 - 86 °F) [see USP Controlled Room Temperature]”, and advised to store it out of sight and reach of children.

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

Suboxone is indicated for maintenance treatment of opioid dependence. The drug product is designed to deliver buprenorphine by the sublingual route; it is an alternative to the currently marketed Suboxone® sublingual tablet (NDA20-733).
C. Basis for Approvability or Not-Approval Recommendation

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DMF and DMF 12412 for Noloxone Hydrochloride Dihydrate, and DMF 12412 for Buprenorphine Hydrochloride) and drug product manufactured, tested and packaged in accordance with the procedures and recommendation given in the original submission and pertinent amendments. NDA 22-410 is recommended for approval from the standpoint of chemistry, manufacturing and controls (CMC) pending an acceptable recommendation for the overall cGMP status of the manufacturing, testing and packaging facilities by the Office of Compliance.

III. Administrative

A. Reviewer’s Signature  Xavier Ysern, PhD  Review Chemist/ ONDQA/ DPA I/ Branch II
B. Endorsement Block  Ali Al-Hakim, PhD  Branch Chief/ ONDQA/ DPA I/ Branch II
C. CC Block  Matthew Sullivan  Project Manager/ OND/ ODE II/ DAARP

123 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/
---------------------
Xavier Ysern
7/6/2009 06:00:56 PM
CHEMIST

Ali Al-Hakim
7/7/2009 11:16:05 AM
CHEMIST
Initial Quality Assurance (IQA)

NDA 22-410

Sponsor: Reckitt Benckiser Pharmaceuticals Inc.
Proposed trade name: Suboxone
Non-proprietary name: Buprenorphine and naloxone soluble film (proposed).
Indication: Treatment of opioid dependence.

This NDA is a 505(b)(1) application but relies partially on the information previously submitted to their other two NDAs, Subutex (Buprenorphine) Tablets 2 and 8 mg (NDA 20-732) and Suboxone (Buprenorphine and Naloxone) Sublingual Tablets 2 mg/0.5 mg and 8 mg/2 mg.

Key Dates

- Letter date: 20-Oct-2008
- Stamp date: 21-Oct-2008
- Filing meeting date: 03-Dec-2008
- Filing decision: 20-Dec-2008 (Day 60)
- Mid cycle date: 21-Mar-2009 (end of Month 5)
- W/U: 21-Jun-2009 (end Month 8)
- 1ry and 2ry reviews due: 21-Jun-2009
- PDUFA Date: 21-Aug-2009

Drug Substance

The drug product, Suboxone® (buprenorphine and naloxone soluble film), contains two active components, buprenorphine (formulated into the drug product as buprenorphine hydrochloride) and naloxone (formulated into the drug product as naloxone hydrochloride dihydrate).

- Buprenorphine hydrochloride

Buprnorphine, a semisynthetic opioid, is a thebaine derivative with powerful analgesia approximately twenty-five to forty times as potent as morphine. Its analgesic effect is due to partial agonist activity at µ-opioid receptors. Buprenorphine is also a κ-opioid receptor antagonist.

Buprenorphine hydrochloride is manufactured by the applicant at their’s facility, “Fine Chemical Plant” (Reckitt Benckiser Healthcare Limited), located in Hull, United Kingdom. The information on the quality, chemistry, and manufacturing (CMC) for buprenorphine hydrochloride drug substance is referred to Reckitt Benckiser Healthcare (UK) Limited’ Type II Drug Master File (DMF) 12412. Buprenorphine hydrochloride is sparingly soluble in water, freely soluble in methanol, soluble in ethanol and practically insoluble in cyclohexane. Its chemical name, structure, empirical formula and molecular weight are given below.

Laboratory Code: RX6029M-HCl

C_{30}H_{41}NO_{4}·HCl
MW: 467.6 (base) 504.1 (salt)
CAS Registry number (CAS RN): 53152-21-9

\[ \text{(2S)}-2\{17\text{-Cyclopropylmethyl-4,5a-epoxy-3-hydroxy-6-methoxy-6a,14-ethano-14a-morphinan-7a-yl]-3,3-dimethylbutan-2-ol hydrochloride} \]

\[ \text{(2S)}-2\{(-)-(5R,6R,7R,14S)-9a-cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylbutan-2-ol hydrochloride} \]
The specifications for Buprenorphine HCl Drug Substance are shown in Table S-1 (details on the analytical procedures and corresponding validation are referred to DMF 12412).

<table>
<thead>
<tr>
<th>Test</th>
<th>Acceptance criteria</th>
<th>Test Method Reference</th>
</tr>
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<tbody>
<tr>
<td>Physical description</td>
<td>White to off-white powder, free from visible contamination</td>
<td>65541 - TM EU</td>
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<tr>
<td>Identification</td>
<td>Shall be positive</td>
<td>65542 - TM EU, 23455 - TM EU, 23456 - TM EU</td>
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<td>Water by Karl Fischer</td>
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<td>23460 - TM EU, 23462 - TM EU, 23461 - TM EU</td>
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<td>Specific optical rotation</td>
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<td>Total:</td>
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<td>Assay by HPLC</td>
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<td>Particle size (b)</td>
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</table>

\(a\) Chemical Structures shown in Table S-2.

\(b\) With reference to the solvent-free anhydrous material.

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**Table S-2. Chemical Structures of Buprenorphine and Known Impurities**

RX6029M (Buprenorphine)
The specifications for Buprenorphine HCl meet compendial requirements, and are stricter than those required by USP. A comparison of the Reckitt Benckiser Healthcare (UK) Ltd. (Reckitt) specifications and USP monograph for buprenorphine hydrochloride (buprenorphine) is presented in Table S-3.

<table>
<thead>
<tr>
<th>Table S-3. Buprenorphine HCl Drug Substance Specifications Comparison</th>
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<tbody>
<tr>
<td><strong>Reckitt Benckiser Specification</strong></td>
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<td><strong>Physical description</strong></td>
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<td>Identification:</td>
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<td>· IR</td>
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<tr>
<td>pH</td>
</tr>
<tr>
<td>Water by Karl Fischer</td>
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<tr>
<td>Residue on Ignition</td>
</tr>
<tr>
<td>Specific Optical Rotation</td>
</tr>
<tr>
<td>Related substances (HPLC)</td>
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<td>Any individual unspecified impurity:</td>
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<tr>
<td>Total:</td>
</tr>
<tr>
<td>Assay: Titrimetric</td>
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<tr>
<td>Additional In-House Tests</td>
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<tr>
<td>Appearance</td>
</tr>
<tr>
<td>Shall be clear, colorless and essentially free from particles</td>
</tr>
<tr>
<td>Assay by HPLC (anhydrous)</td>
</tr>
<tr>
<td>Particle Size</td>
</tr>
</tbody>
</table>

* = with reference to the solvent-free anhydrous material.

- Buprenorphine hydrochloride drug substance manufactured by Reckitt Benckiser Healthcare (UK) Ltd. according to the procedures and control given in DMF 12421 is used in the manufacture of the drug products of approved Subutex (buprenorphine) tablets (NDA 20-732 and Suboxone (buprenorphine and naloxone) sublingual tablets.
- DMF 12412 has been reviewed and deemed acceptable (2002).
- The last update to DMF 12412 is the 2008 update (Report No. RC080087) and no significant changes are reported. Therefore, buprenorphine HCl drug substance manufactured and controlled as described in DMF 12412 is acceptable for use in the manufacture of the drug product Suboxone® (buprenorphine and naloxone soluble film).
- Naloxone hydrochloride dihydrate

Naloxone is a potent antagonist at the µ-opioid and κ-opioid receptors and produces opioid withdrawal effects in opioid dependent subjects. Naloxone is poorly bioavailable by the sublingual route but has an increased bioavailability when administered by injection. Naloxone was added to Suboxone in an effort to dissuade patients from grinding up the Suboxone tablet and using it as part of a combination of opiates that the user would inject into their body.

Naloxone is manufactured by a number of opioid manufacturers including the supplier of naloxone hydrochloride dihydrate drug substance, and the alternate supplier The information on the quality, chemistry, and manufacturing (CMC) for naloxone hydrochloride dihydrate drug substance is referred to Type II DMFs and .

Naloxone hydrochloride dehydrate, a white or almost white crystalline powder, is freely soluble in water, soluble in alcohol and practically insoluble in toluene. Its chemical name, structure, empirical formula and molecular weight are given below.

\[\text{C}_{19}\text{H}_{21}\text{NO}_4 \cdot \text{HCl} \cdot 2\text{H}_2\text{O}\]

MW: 399.9

357-08-4 Naloxone hydrochloride anhydrous
51481-60-8 Naloxone hydrochloride dihydrate

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

Drug substance supplied by is manufactured at their plant, according to their confidential Type II DMF supplied drug substance is manufactured at their plant, where naloxone hydrochloride dihydrate is manufactured by Reckitt Benckiser’s purchasing specifications comply fully with both but with a more stringent, ICH3 compliant, specification for the levels of impurities. In particular, a synthesis impurity in naloxone has an associated structural alert and has been shown to be weakly clastogenic. As a consequence it is controlled to a limit of a level accepted by the Agency, and below the guideline limit for genotoxic impurities.

The Reckitt Benckiser’s naloxone HCl dihydrate purchasing specifications, shown in Table S-4, have been agreed with both (main drug substance supplier) and (alternate supplier).

- Naloxone HCl dihydrate manufactured by according to the procedures and control given in DMF is used in the manufacture of the approved drug Suboxone (buprenorphine and naloxone) sublingual tablets.
- DMF has been reviewed and deemed acceptable (2002).
- The last update to DMF is the 2008 update and no significant changes are reported. Therefore, naloxone HCl dihydrate manufactured and controlled as described in DMF is acceptable for use in the manufacture of the drug product Suboxone (buprenorphine and naloxone soluble film).
- DMF, Naloxone HCl dihydrate manufactured by at their site, is currently under review. According to the DMF holder, no significant degradation of the drug substance was detected after storage at 25 °C / 60 % relative humidity (RH) for 36 months and 40 °C / 75 % RH for 6 months.
Table S-4. Specification for Naloxone HCl Dihydrate

<table>
<thead>
<tr>
<th>Test</th>
<th>Recliff / Benckiser Acceptance Criteria</th>
<th>Ph Eur Acceptance Criteria</th>
<th>USP Acceptance Criteria</th>
<th>Tyco/Mallinckrodt DMF Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Description</td>
<td>White or almost white powder or (b) (4)</td>
<td>A white or almost white, crystalline powder, hygroscopic, freely soluble in water, soluble in alcohol, practically insoluble in toluene</td>
<td>-</td>
<td>White to off-white powder</td>
</tr>
<tr>
<td>Identification (A/C or B/C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Naloxone (IR)</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Matches standard</td>
</tr>
<tr>
<td>B Naloxone (TLC)</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
<td>Matches standard</td>
</tr>
<tr>
<td>C Chloride</td>
<td>Positive</td>
<td>Positive</td>
<td>-</td>
<td>White precipitate</td>
</tr>
<tr>
<td>Specific rotation ¤</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Loss on drying</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noroxymorphone HCl and other impurities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride content ¤</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Appearance of solution</td>
<td>Complies with Ph Eur test</td>
<td>(b) (4)</td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Acidity or alkalinity</td>
<td>Complies with Ph Eur test</td>
<td>Conforms</td>
<td></td>
<td></td>
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<tr>
<td>Related substances</td>
<td></td>
<td>(b) (4)</td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Any other impurity (including impurities)</td>
<td></td>
<td>(b) (4)</td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Related substances (each)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unknown related substances</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Assay ¤</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USP</td>
<td>98.0 to 100.5%</td>
<td>98.0 to 100.5%</td>
<td>98.0 to 100.5%</td>
<td>98.0 to 100.5%</td>
</tr>
<tr>
<td>Ph Eur</td>
<td>98.0 to 102.0%</td>
<td>98.0 to 102.0%</td>
<td>98.0 to 102.0%</td>
<td>98.0 to 102.0%</td>
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<tr>
<td>HPLC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>98.0 to 102.0%</td>
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<tr>
<td>Identification UV</td>
<td>(b) (4)</td>
<td>-</td>
<td>-</td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Melting range ¤</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(b) (4)</td>
</tr>
</tbody>
</table>

The chemical structures of the naloxone related substances are shown in Figure P-2.
Drug Product

Suboxone (buprenorphine/naloxone) soluble film is a pale orange film strip, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine hydrochloride and naloxone hydrochloride dihydrate at a ratio of 4:1 (ratio as free basis), and is available in two strengths: Suboxone (8 mg buprenorphine/2 mg naloxone), and Suboxone (2 mg buprenorphine/0.5 mg naloxone).

The product is designed to deliver buprenorphine and naloxone by the sublingual route; it is an alternative to the currently marketed Suboxone® sublingual tablet (NDA 20-733), providing a shorter and improved oral residence time. Naloxone is included to deter diversion and misuse by injection and is not clinically available when Suboxone is taken as intended.

Table P-1. Quantitative Formula for Suboxone (b) (4)

<table>
<thead>
<tr>
<th>Component</th>
<th>Quality reference</th>
<th>Function</th>
<th>mg/strip</th>
<th>% (w/w)</th>
<th>mg/strip</th>
<th>% (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine HCl</td>
<td>In-House (b)</td>
<td>Active</td>
<td>8.64</td>
<td>17.28</td>
<td>2.16</td>
<td>5.40</td>
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<tr>
<td>Naloxone HCl Dihydrate</td>
<td>In-House (b)</td>
<td>Active</td>
<td>2.44</td>
<td>4.88</td>
<td>0.61</td>
<td>1.53</td>
</tr>
<tr>
<td>Acesulfame Potassium</td>
<td>NF</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Citric Acid,</td>
<td>USP</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Polyethylene Oxide</td>
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<tr>
<td>Polyethylene Oxide</td>
<td>NF</td>
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<tr>
<td>Sodium Citrate</td>
<td>USP</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lime Flavor</td>
<td>In-House (b)</td>
<td>Flavorant</td>
<td></td>
<td>Trace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FD&amp;C Yellow No. 6</td>
<td>In-House (b)</td>
<td>Colorant</td>
<td></td>
<td>Trace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Ink</td>
<td>In-House (b)</td>
<td>Print ink</td>
<td></td>
<td>Trace</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total                                           Trace   Trace   Trace   Trace

<table>
<thead>
<tr>
<th>8 mg / 2 mg a</th>
<th>2 mg / 0.5 mg a</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.0</td>
<td>100.0</td>
</tr>
<tr>
<td>100.0</td>
<td>40.0</td>
</tr>
<tr>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

a “low strength” 2 mg/0.5 mg, dimensions 0.875” x 0.5” [mass per area: 89.1 mg/sq. inches]

b “high strength” 8 mg/2 mg, dimensions 0.875” x 0.5” [mass per area: 114.3 mg/sq. inches]

In-House specifications comply with USP/Ph. Eur. and include additional controls

Used as a processing aid and removed during the manufacturing process

All excipients, except the flavoring agent Lime Flavor and the colorant FD&C Yellow # 6, meet compendial requirements. However, the flavoring and the colorant agents are both used in the formulation of approved Suboxone® tablets (NDA 20-733) and considered acceptable.

Suboxone® film was developed to improve and shorten the oral residence time of the currently marketed Suboxone sublingual tablets using soluble film technology. Compared to the tablets, the film formulation provides the following advantages:

- Reduced oral residence time (tablet disintegration time up to 10 minutes versus 3 minutes for the film)
- Availability in a unit dose format (pouch)
- Decreased product shipping damage (sublingual tablets are inherently more friable than regular tablets, but film strips would not suffer such damage)
- Improved child resistant packaging at the unit dose level
The flow chart, Figure P-1, summarizes the manufacturing process and in-process controls for the Suboxone (buprenorphine/naloxone) soluble film.

Figure P-1. Overview of the Manufacturing Process for Suboxone

The manufacturing process phases:

-

-
Suboxone specifications are listed in Table P-2; the chemical structures of buprenorphine and naloxone known impurities are shown in Tables P-3 and P-4 respectively.

<table>
<thead>
<tr>
<th>Table P-2. Suboxone Specifications</th>
<th>2 mg/0.5 mg Acceptance Criteria</th>
<th>8 mg/2 mg Acceptance Criteria</th>
<th>Analytical Procedure Reference</th>
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<tbody>
<tr>
<td>Appearance</td>
<td></td>
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<td>Visual (SOP AN21) SAM013</td>
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<tr>
<td>Identification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Procedure</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Assay:</td>
<td>Buprenorphine</td>
<td>SAM013 and SAM012</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related Substances:</td>
<td>(b) (4)</td>
<td></td>
<td></td>
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<tr>
<td>Buprenorphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual Unidentified Impurity</td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Naloxone Related</td>
<td>(b) (4)</td>
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<td></td>
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<tr>
<td>Moisture Content</td>
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<td></td>
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<tr>
<td>Uniformity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution:</td>
<td>Buprenorphine</td>
<td>SAM013</td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td></td>
<td>and SAM013</td>
<td></td>
</tr>
<tr>
<td>Individual Unidentified Impurity</td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>(b) (4)</td>
<td></td>
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<tr>
<td>Microbial Limits:</td>
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<tr>
<td>E. coli</td>
<td>(b) (4)</td>
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<td>Salmonella</td>
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<tr>
<td>Enterobacteria</td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = One batch to be analyzed initially, every six months and at the end of shelf life in stability studies.

* = Results reported to 2 decimal places and acceptance criteria limit applied.
Table P-4. Naloxone Known Related Substances

Specification tests are claimed to be validated and fulfill their intended purpose. A justification of the specifications is provided by the applicant.

Four batches of each Suboxone (buprenorphine and naloxone soluble film) dosage strength are being examined as part of the stability program. The stability batches are at least of the proposed commercial scale with one batch of each strength at the full commercial scale; all batches have been manufactured by the commercial process and all are packed in the proposed commercial primary packaging materials. The first batch of each dosage strength was packed by a process, whereas the later, pivotal batches were all using a machine intended for commercial packing.

Nine (9) months stability data are provided for the first batch of each dosage strength, which lack dissolution data because a validated method was not in place. For the pivotal batches 6 month stability data at 25 °C/60 % RH, 30 °C/65 % RH, and 40 °C/75 % RH are provided.

All the facilities involved in the manufacture, testing, packaging and labeling of both drug substance and drug product have been requested for inspection. Pertinent facilities are listed in Table P-5; establishment evaluation request (EER) is attached.
Table P-5. Establishment Information

<table>
<thead>
<tr>
<th>Drug Substance</th>
<th>Manufacturer Name and Address</th>
<th>Contact Name and Telephone #</th>
<th>FEI or CFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine Hydrochloride, Manufacturing, Packaging, Testing, and DMF Holder (DMF 12412)</td>
<td>Fine Chemical Plant Reckitt Benckiser Healthcare (UK) Limited Dunsmore Lane Hull, HU8 7DS UK</td>
<td>Dave Price Tel: 0044 (0)1482 582158 <a href="mailto:David.Price@ReckittBenckiser.com">David.Price@ReckittBenckiser.com</a></td>
<td>CFN 9610643 FEI 3002807985</td>
</tr>
</tbody>
</table>

Environmental Assessment

A categorical exclusion from preparing an environmental assessment under 21 CFR 25.31(a) is claimed. According to the applicant, approval of the NDA (20-410) and marketing of Suboxone® (buprenorphine and naloxone soluble film) in the United States is a class of action that will not increase the use of the active moieties. Suboxone® (buprenorphine and naloxone soluble film) is a new dosage form that substitutes directly for Suboxone® (buprenorphine HCl and naloxone HCl sublingual tablets), an approved product (NDA 20-733). Suboxone® will be used for the same indication, at the same dosage levels, and for the same duration of use as Suboxone® sublingual tablets (NDA 20-733). Suboxone® is a dosage form product line extension (new delivery system) that may be substituted directly for Suboxone® sublingual tablets (NDA 20-733). To the best knowledge of the applicant, no extraordinary circumstances exist.
IQA summary

Drug Substance

Buprenorphine hydrochloride

DMF

- Buprenorphine hydrochloride drug substance manufactured by Reckitt Benckiser Healthcare (UK) Ltd. according to the procedures and control given in DMF 12421 is used in the manufacture of the drug products of approved Subutex (buprenorphine) tablets (NDA 20-732) and Suboxone (buprenorphine and naloxone) sublingual tablets.
- DMF 12412 has been reviewed and deemed acceptable (2002).
- The last update to DMF 12412 is the 2008 update (Report No. RC080087) and no significant changes are reported.
- Therefore, **buprenorphine HCl drug substance manufactured and controlled as described in DMF 12412 is acceptable** for use in the manufacture of the drug product Suboxone® (buprenorphine and naloxone soluble film).

Naloxone hydrochloride dihydrate

Drug Product

- The drug product Suboxone® is an alternative to the currently marketed Suboxone® sublingual tablet (NDA 20-733).
- The description and composition of the drug product is adequately provided.
- Pharmaceutical development is described, and the rational for a soluble film dosage with short disintegration time (desired attribute of the drug product) is provided.
- Manufacturing facilities and their responsibilities are given. The manufacturing process is conventional.
- Adequacy of in-process control is a review issue.
- Executed batches provided.
- Besides the flavoring Lime Flavor, the colorant FD&C Yellow # 6, and White ink, all other excipients meet compendial requirements.
- Lime Flavor and FD&C Yellow # 6 are non compendial excipients are used in the formulation of approved Suboxone® sublingual tablet (NDA 20-733). The white ink is an edible grade supplied by; all ink components are compendial, and the level of the ink in the film strip is a trace amount.
The drug product specifications, although similar to those for Suboxone® sublingual tablet (NDA 20-733), differ—as expected—in the acceptance criteria for identification, dissolution and additional requirements for four additional known impurities not observed in the tablet counterpart.

The acceptability of the acceptance criteria for these four previously mentioned known impurities is a review issue.

Specification tests are claimed to be validated and fulfill their intended purpose. A justification of the specifications is provided by the applicant.

The proposed test methods are well known and widely used by the pharmaceutical industry. Consequently, revalidation of analytical methods by Agency laboratories is not recommended.

Soloxone film strips are packed individually into pouches. The acceptability of the material (pouch component) in contact with the film product should be evaluated.

Four batches of each Suboxone (buprenorphine and naloxone soluble film) dosage strength are being examined as part of the stability program. The stability batches are at least of the proposed commercial scale with one batch of each strength at the full commercial scale; all batches have been manufactured by the commercial process and all are packed in the proposed commercial primary packaging materials.

At least six (6) most of stability data is provided per batch.

Requested expiration date is , stored a room temperature. Acceptability of the proposed expiry dating is a review issue.

A categorical exclusion from preparing an environmental assessment under 21 CFR 25.31(a) is claimed, and the criteria is met.

Overall evaluation: There are no CMC standing issues that preclude the filing of NDA 22-410. This NDA relies partially on the information previously submitted to their other two NDAs, Subutex (Buprenorphine) Tablets 2 mg and 8 mg, (NDA 20-732) and Suboxone® (Buprenorphine and Naloxone) sublingual tablet (NDA 20-733). The main goal of the proposed product Suboxone which is to provide an alternative to Suboxone Tablets with a shorter oral residence time by the development of a soluble film dosage product, is accomplished by the applicant. Although there are not standing issues, minor requests to the applicant as the review progresses may be send to the applicant.

Xavier Ysern, PhD Review Chemist ONDQA/ DPA I/ Branch II
Init. Ali Al-Hakim, PhD Branch Chief ONDQA/ DPA I/ Branch II

Attached:
EER summary report dated 05-Dec-2008 (3 pages)...

Page 14
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 22410/000
Sponsor: RECKITT BENCKISER
Org Code: 170
Priority: 
Stamp Date: 21-OCT-2008
Brand Name: SUPRENORPHIN/NALOXONE 2MG/8MG
PDUFA Date: 21-AUG-2009
FILM STRIP
Action Goal: 
District Goal: 22-JUN-2009
Generic Name: SUPRENORPHON/NALONE 2MG/8MG
Dosage Form: FILM STRIPS
Strength: 2MG/5MG AND 2MG/0.5MG

FDA Contacts: X. YSERN Review Chemist 301-796-2410
D. CHRISTODOULOU Team Leader 301-796-1342

---Overall Recommendation:

Establishment: CFN: FEI: DFM No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: NEC OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 05-DEC-08

---

Establishment: CFN: FEI: DFM No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: NEC OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 05-DEC-08

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Establishment: CFN: FEI: DFM No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
**DRUG SUBSTANCE STABILITY TESTER**

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|                  | DRUG SUBSTANCE RELEASE TESTER  
|                  | DRUG SUBSTANCE STABILITY TESTER |

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|                  | FINISHED DOSAGE PACKAGER  
|                  | FINISHED DOSAGE STABILITY TESTER |

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Establishment :  CFN : 9610643  FEI : 3002807985
RECKITT BENCKISER PLC
CHAPMAN STREET & DANSON LANE
HULL, EAST YORKSHIRE, UK  HU8 7DS
DMF No:  12412  AADA:

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

Profile       :       CSN                         OAI Status:    NONE
Last Milestone:  SUBMITTED TO OC
Milestone Date:  05-DEC-08

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

/s/

Xavier Ysern 12/12/2008 02:25:42 PM CHEMIST

Ali Al-Hakim 12/12/2008 04:31:28 PM CHEMIST