CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022410Orig1s000

CHEMISTRY REVIEW(S)

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 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 (b) (4), Specific Optical Rotation (b) (4) Residual Solvents (b) (4) by GC), Assay (HPLC, titration), Ion Chloride determination, Purity (HPLC) and Particle Size Distribution. Each known impurity (b) (4)) and any individual unspecified impurity can not exceed (b) (4) and their total no more than (b) (4) The specifications for Buprenorphine HCl comply and exceed those required by USP. A (b) (4) 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 (b) (4) subject to the material meeting the specification criteria.

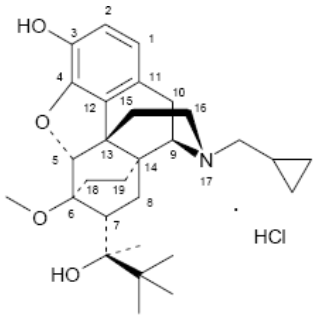
Buprenorphine hydrochloride

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



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

- **Naloxone hydrochloride dihydrate**

There are two suppliers of naloxone hydrochloride dihydrate drug substance; the first supplier is (b) (4) CMC information is referred to their DMF (b) (4). DMF (b) (4) was reviewed and found satisfactory.The second supplier is (b) (4) CMC information is referred to their DMF (b) (4). DMF (b) (4) 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 (b) (4) Optical Rotation (b) (4), Residual Solvents (b) (4) by GC), Assay (HPLC, titration), Ion

Chloride determination, Appearance of solution (visual), Loss on drying (gravimetric), and Purity (HPLC). Known impurities [redacted] each NMT [redacted] NMT [redacted] and [redacted] NMT [redacted] Other impurities, including Ph Eur impurities [redacted] each NMT [redacted] and the total (known and unknown related substances) can not exceed [redacted].

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

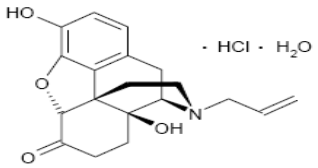
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGH

Naloxone hydrochloride dihydrate

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

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 [redacted]

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 [redacted] by HPLC), Dissolution (currently Q = [redacted] in 7 minutes for buprenorphine and Q = [redacted] in 7 minutes for naloxone), Moisture content uniformity (NMT [redacted]), Microbial limits

(USP<905>), and Purity (HPLC). Purity requirements for Buprenorphine Related Substances include (b) (4) any Individual Unidentified Impurity NMT (b) (4) and their total can not exceed (b) (4) Purity requirements for Naloxone Related Substance include (b) (4) , and for (b) (4) each NMT (b) (4) Any Individual Unidentified Impurity NMT (b) (4) and the total of impurities can not exceed (b) (4)
Based on the provided stability data, 12 months of expiry dating is granted for the drug product (b) (4)

Conclusion: The drug product is satisfactory.

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

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Branch Chief,
DPA I/ONDQA

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