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***APPLICATION NUMBER:***

**022410Orig1s000**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

**Addendum to the Primary Clinical Pharmacology Review Dated June 23, 2009**

| | | | |
|---|---|---|---|
| *NDA* | 22-410 | *Submission Date(s)* | Oct 21, 2008 |
| *Brand Name* | | Suboxone (b) (4) | |
| *Generic Name* | | Buprenorphine (bup) and Naloxone (nal) | |
| *Reviewer* | | Sheetal Agarwal, Ph.D. | |
| *Team Leader* | | Suresh Doddapaneni, Ph.D. | |
| *OCP Division* | | Division of Clinical Pharmacology-2 | |
| *OND Division* | | Division of Anesthesia, Analgesia, and Rheumatology | |
| *Sponsor* | | Reckitt Benckiser Pharmaceuticals Inc. | |
| *Submission Type; Code* | | 505 (b) (1) | S |
| *Formulation; Strength(s)* | | Sublingual film strips; 2 mg bup/0.5 nal and 8 mg bup/2 mg nal | |
| *Indication* | | Maintenance treatment of opioid dependence | |
| *Proposed Dosing Regimen* | | Recommended target dose for maintenance is 16 mg bup/4 mg nal per day | |

This addendum addresses the two following specific issues that were not captured in the primary Clinical Pharmacology review authored by this reviewer dated June 23, 2009; (1) Division of Scientific Investigations (DSI) inspection results of pivotal BA/BE Study 20-273-SA and (2) Implications on the bioavailability of the sublingual film strips if the strips were to be placed on the floor of the mouth (b) (4) These two issues are discussed below:

(1) <u>DSI Inspection report of study 20-273-SA:</u>
At the time of signing off the primary review for NDA 22-410, report of the DSI inspection of Study 20-273-SA was pending. Subsequently, DSI finalized their report on June 29, 2009 (see review by Dr. Sean Kassim, Ph.D. dated 6/29/2009 for details).

The conclusions from DSI report were:

1. Accuracy of the reported naloxone concentrations for subjects 407 (period 2) and 443 (all periods) has not been assured due to unresolved chromatographic interference in at least half the reportable naloxone values in each period. The naloxone data for these periods should be omitted and bioequivalence should be re-evaluated.
2. The Clinical portion and the remaining analytical data from 20-273-SA are acceptable for review.

This reviewer reanalyzed the data as suggested by DSI omitting the naloxone concentrations for subjects 407 and 443. The reanalysis showed no significant differences between the original and reanalyzed data (see table below) and

consequently the conclusions made in the primary review dated June 23, 2009 regarding the outcome of this study stand.

BE analysis results for Study 20-273-SA (8/2 mg Suboxone strips vs. tablets)

| Buprenorphine | 90% CI lower limit (original) | 90% CI upper limit (original) | 90% CI lower limit (after reanalysis) | 90% CI upper limit (after reanalysis) |
|---|---|---|---|---|
| Cmax | 116.98 | 139.77 | 117.09 | 140.53 |
| AUClast | 111.34 | 129.61 | 111.96 | 130.59 |
| AUCinf | 111.18 | 128.34 | 111.7 | 129.14 |
| Naloxone | | | | |
| Cmax | 127.32 | 155.75 | 127.84 | 156.93 |
| AUClast | 119.35 | 141.15 | 119.43 | 141.55 |
| AUCinf | 111.02 | 134.25 | 111.19 | 134.82 |

(2) (b) (4)

Although, not sought for approval, sponsor tested the buccal mode of administration as well in several of the PK studies. Although not reviewed in detail, a quick overview of the studies showed that the strips administered by buccal route were either bioequivalent (for example 2 mg, 4 mg, and 8 mg doses) or the bioavailability differences were minor (12 mg dose). Buccal and sublingual routes are considered to be two distinct routes of administration and the observation that these two routes of administration yielded similar bioavailability indicates lends further comfort that any bioavailability differences resulting from the potentially different ways in which the sublingual strips may have been used in the NDA database may not be clinically significant.

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---|---|---|---|
| NDA 22410 | ORIG 1 | RECKITT BENCKISER PHARMACEUTICALS INC | BUPRENORPHINE/NALOXONE 2MG/8MG FILM STRP |

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/s/

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SHEETAL S AGARWAL
07/28/2009

SURESH DODDAPANENI
07/28/2009

# CLINICAL PHARMACOLOGY REVIEW

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