CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022410Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-410**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**February 4, 2009**
PRODUCT:	**Suboxone** (b) (4) **(buprenorphine and naloxone)**
INTENDED CLINICAL POPULATION:	**Treatment of opioid dependence**
APPLICANT:	**Reckitt Benckiser Pharmaceuticals, Inc.**
DOCUMENTS REVIEWED:	**All nonclinical information in the above submission**
REVIEW DIVISION:	**Division of Analgesia, Anesthesia and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Elizabeth A. Bolan, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Matthew Sullivan**

Date of review submission to Division File System (DFS): May 22, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This NDA can be approved from a nonclinical pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies

There are no recommendations for nonclinical studies.

C. Recommendations on labeling

The table below contains the draft labeling submitted by the Applicant, the proposed changes and the rationale for the proposed changes. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red or strikeout font.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Pregnancy Category C.	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** Pregnancy Category C.	no changes to this section.
(b) (4)		
Teratogenic effects: Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated	***Teratogenic effects:*** Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated	

exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphacele was observed in two rabbit fetuses from the same litter in the mid dose group; no findings were observed in fetuses from the high dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day. In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at intravenous (IV) doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). ***Non-teratogenic effects:*** Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). (b) (4) fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after subcutaneous doses of 0.1	exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphacele was observed in two rabbit fetuses from the same litter in the mid dose group; no findings were observed in fetuses from the high dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day. In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at intravenous (IV) doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). ***Non-teratogenic effects:*** Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). (b) (4) fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after subcutaneous doses of 0.1	

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