CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-401 / S-014

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Division of Anesthetic, Critical Care, and Addiction Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 18-401

Name of Drug: Buprenex Injectable

Sponsor: Reckitt & Benckiser

Material Reviewed

Submission Date(s): November 16, 2001 (S-014/BL)

Receipt Date(s): November 26, 2001

Background and Summary Description: A submission in response to our approvable letter dated February 15, 2001, for supplement S-014. Changes were done to the "Drug Interactions" and the "Carcinogenesis, Mutagenesis and Impairment of Fertility" subsections of the PRECAUTIONS section. Cartons and containers were also sent in this response (update the new company name).

This submission was compared to the label from S-014, dated January 17, 2001. The cartons/containers were compared to S-010, approved on April 29, 1994.

Status Report

Reviews Completed: Sara E. Shepherd, RPM, December 10, 2001, revised 2/5/02

Reviews Pending: none

RPM Review

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label

BOX WARNING: Not applicable

DESCRIPTION: No changes noted

CLINICAL PHARMACOLOGY: No changes noted

INDICATIONS AND USAGE: No changes noted

CONTRAINDICATIONS: No changes noted

WARNINGS: No changes noted

PRECAUTIONS:
In the subsection 'Drug Interactions", a the following information was added as requested in the February 15, 2001, AE letter.

> CYP3A4 Inhibitors: Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of buprenorphine. Thus patients coadministered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritanovir) while receiving Buprenex should be carefully monitored and dosage adjustment made if warranted.
>
> CYP3A4 Inducers: Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and as such may cause increased clearance of buprenorphine. Caution is advised when administering Buprenex to patients receiving these medications and if necessary dose adjustments should be considered.

The following changes were made to the subsection "Carcinogenesis, Mutagenesis and Impairment of Fertility" as requested in the February 15, 2001 AE letter.

> *Carcinogenesis*: Carcinogenicity studies were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet at doses of 0.6, 5.5, and 56 mg/kg/day for 27 months in rats. These doses were approximately equivalent to 5.7, 52 and 534 times the recommended human dose (1.2 mg) on a mg/m^2 body surface area basis. Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred, according to the trend test ~~un~~adjusted for survival. Pair-wise comparison of the high dose against control failed to show statistical significance. In the mouse study, buprenorphine was administered in the diet at doses of 8, 50, and 100 mg/kg/day for 86 weeks. The high dose was approximately equivalent to 477 times the recommended human dose (1.2 mg) on a mg/m^2 basis. Buprenorphine was not carcinogenic in mice.

ADVERSE REACTIONS: No changes noted

DRUG ABUSE AND DEPENDENCE: No changes noted

OVERDOSAGE: No changes noted

DOSAGE AND ADMINISTRATION: No changes noted

HOW SUPPLIED: No changes noted

Carton/Container Label

The labels were updated to include "Rx only" and the new name "Reckitt Benckiser." The cartons/containers were compared to S-010, approved on April 29, 1994. These changes are acceptable.

RECOMMENDATIONS

The changes, requested in the February 15, 2001 AE letter, were incorporated into the package insert. This supplement should be approved.

Sara E. Shepherd, Regulatory Project Manager 2/5/02

Parinda Jani, Acting, Chief Project Management Staff 2/11/02

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

/s/

Sara Shepherd
2/11/02 10:34:17 AM
CSO

Parinda Jani
2/11/02 10:51:39 AM
CSO

Division of Anesthetic, Critical Care, and Addiction Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 18-401

Name of Drug: Buprenex Injectable

Sponsor: Reckitt & Colman

Material Reviewed

Submission Date(s): January 17, 2001 (S-014)

Receipt Date(s): January 19, 2001

Background and Summary Description: A submission in response to our letter dated July 12, 2000, requesting the label to be updated to furnish adequate information for the safe and effective use of the drug:

- Revise the preclinical sections to include the human multiples of doses used in animal studies on the basis of body surface area, or preferably, AUC in plasma, if toxicokinetic data are available. The current label gives multiples without identifying the dosing units upon which these multiples are based.

This submission was compared to the label approved on June 25, 1993 (supplement S-011).

Status Report

Reviews Completed: Sara E. Shepherd, RPM, January 30, 2001

Reviews Pending: none

RPM Review

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label

BOX WARNING: Not applicable

DESCRIPTION: No changes noted

CLINICAL PHARMACOLOGY: No changes noted

INDICATIONS AND USAGE: No changes noted

CONTRAINDICATIONS: No changes noted

WARNINGS: No changes noted

PRECAUTIONS:
In the subsection 'Drug Interactions", a second paragraph was added:

[ ]

NOTE: Suresh Doddapaneni, Clinical Pharmacologist Team Leader, stated that the following information should replace the above paragraph:

CYP3A4 Inhibitors: Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of buprenorphine. Thus patients coadministered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritanovir) while receiving Buprenex should be carefully monitored and dosage adjustment made if warranted.

CYP3A4 Inducers: Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and as such may cause increased clearance of buprenorphine. Caution is advised when administering Buprenex to patients receiving these medications and if necessary dose adjustments should be considered.

The following changes were made to the subsection "Carcinogenesis, Mutagenesis and Impairment of Fertility:"

Carcinogenesis, Mutagenesis and Impairment of Fertility:

[ ]

Carcinogenesis: Carcinogenicity studies were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet at doses of 0.6, 5.5, and 56 mg/kg/day for 27 months in rats. These doses were approximately equivalent to 5.7, 52 and 534 times the recommended human dose (1.2 mg) on a mg/m^2 body surface area basis. Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred, according to the trend test ~~un~~adjusted for survival. Pair-wise comparison of the high dose against control failed to show statistical significance. In the mouse study, buprenorphine was administered in the diet at doses of 8, 50, and 100 mg/kg/day for 86 weeks. The high dose was approximately equivalent to 477 times the recommended human dose (1.2 mg) on a mg/m^2 basis. Buprenorphine was not carcinogenic in mice.

Mutagenesis: Buprenorphine was studied in a series of tests. Results were negative in Chinese hamster bone marrow and spematogonia cells, and negative in mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive in frame shift mutation at high dose (5 mg/plate) in a third study.

Impairment of Fertility: Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg (approximately 763 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) or up to 5 mg/kg I.M. or S.C. (approximately 48 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis).

NOTE: T. Papoian, Supervisory Pharmacologist changed the word "unadjusted" to "adjusted" in the Carcinogenesis section.

The first paragraph in subsection "Pregnancy: Pregnancy Category C" was re-written to read as follows:

> **Pregnancy: Pregnancy Category C**
> *Teratogenic effects:* Buprenorphine was not teratogenic in rats or rabbits after I.M. or S.C. doses up to 5 mg/kg/day (approximately 48 and 95 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), I.V. doses up to 0.8 mg/kg/day (approximately 8 and 15 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), or oral doses up to 160 mg/kg/day in rats (approximately 1525 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) and 25 mg/kg/day in rabbits (approximately 475 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis). Significant increases in skeletal abnormalities (e.g. extra thoracic vertebra or thoracolumbar ribs) were noted in rats after S.C. administration of 1 mg/kg/day and up (approximately 9.5 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) and in rabbits after I.M. administration of 5 mg/kg/day (approximately 95 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), but these increases were not statistically significant. Increases in skeletal abnormalities after oral administration were not observed in rats, and increases in rabbits (1-25 mg.kg/day) were not statistically significant.

The paragraph in subsection "Nursing Mothers" was re-written to read as follows:

> **Nursing Mothers:** An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices. Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in nursing mothers treated with Buprenex.

ADVERSE REACTIONS: No changes noted

DRUG ABUSE AND DEPENDENCE: No changes noted

OVERDOSAGE: No changes noted

DOSAGE AND ADMINISTRATION: No changes noted

HOW SUPPLIED:
The following changes were made:

Manufactured by:
~~Reckitt & Colman Products~~, Reckitt Benckiser
Hull, England, HU8 7DS
England

Distributed by:
~~Reckitt & Colman Products~~, Reckitt Benckiser Pharmaceuticals Inc.
Richmond, VA 23235

~~REVISED JULY 1998~~ REVISED JANUARY 2001
~~149146~~

RECOMMENDATIONS

The comments from the Clinical Pharmacologist and the Pharmacologist will be sent to the sponsor.

The changes were concurred by T. Papoian, (2-5-01), S. Doddpaneni (2-8-01) and C. Schumaker (1-30-01).

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Sara E. Shepherd, Regulatory Project Manager

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Cathie Schumaker/Supervisory Comment/Concurrence

/s/

Sara Shepherd
2/15/01 01:34:56 PM
CSO

Cathie Schumaker
2/16/01 08:45:10 AM
CSO