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RESEARCH**

*APPLICATION NUMBER:*

**020687Orig1s020**

**PHARMACOLOGY REVIEW(S)**

## PHARMACOLOGY REVIEW OF NDA EFFICACY SUPPLEMENT

NDA: 20687 S-020

Drug: Mifeprex (mifepristone) Tablets

Sponsor: Danco Laboratories, LLC

Submission date: 5/20/2015

Division: (b) (6)

Reviewer: (b) (6)

Secondary Reviewer: (b) (6)

Date: February 26, 2016

Currently, Mifeprex (mifepristone) is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 49 days of gestation. In this efficacy supplement, the applicant proposes to extend the days of gestation to 70 days.

Also, this supplement proposes changes in the dosing regimen of both Mifeprex and the prostaglandin misoprostol. The approved dosing regimen consists of 600 mg Mifeprex on day 1 followed two days later with 400 ug misoprostol orally.

The proposed dosing protocol to be used during the first 70 days of gestation consists of 200 mg oral Mifeprex on day 1 followed by 800 ug buccal misoprostol on day 2 or day 3.

The proposed dose of Mifeprex at 200 mg is lower than the approved dose. The proposed 800 ug misoprostol dose is twice the approved dose, but has extensive clinical use.

No preclinical data were submitted. My comments are on labeling revisions. I have changed the format to conform to the Pregnancy and Lactation Labeling Rule.

Pharm/tox labeling

Section 5.8 Pregnancy

.8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

In animal reproduction studies, increased fetal losses were observed in mice, rats, and rabbits and skull deformities were observed in rabbits with administration of mifepristone at doses lower than the human exposure level based on body surface area.

## Animal Data

In teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure based on body surface area), because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from inhibition of progesterone action.

## 8.2 Lactation

Only clinical data will be labeled in this section. Following a literature search, there appears to be no animal data on mifepristone in mothers milk.

## 12 Clinical Pharmacology

### 12.1 Mechanism of Action

The statement: Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity was moved from section 12.1 to section 12.2.

### 12.2 Pharmacodynamics

No changes from approved label

## 13 Nonclinical Toxicology

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

No changes from approved label.

#### Mutagenesis

No changes from approved label

Impairment of Fertility

In rats, administration of 0.3 mg/kg mifepristone per day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effects on reproductive performance were observed.

Conclusion: The supplement is approvable from a Pharm/tox standpoint.

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/s/  
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03/04/2016

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I concur