

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s020

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

(b) (6) **CLINICAL PHARMACOLOGY REVIEW**

NDA Number	020687
Submission Dates	05/28/15, 08/13/15, 09/22/15 and 02/25/16
Brand Name	Mifeprex®
Generic Name	Mifepristone
Strength and Formulation	Immediate release tablet containing 200mg
Regimen	<ul style="list-style-type: none">· The proposed new regimen For pregnancies through 70 days gestation: 200 mg Mifeprex on Day 1, followed in 24-48 hours after Mifeprex dosing by 800 mcg buccal misoprostol· The currently approved regimen For pregnancies through 49 days gestation: 600 mg Mifeprex on Day 1, followed on Day 3 by 400 mcg oral misoprostol
Sponsor	Danco Laboratories LLC
Proposed Indication	Medical termination of intrauterine pregnancy
Submission Type	Efficacy supplement (S-20)
Clinical Pharmacology Reviewer	(b) (6)
Clinical Pharmacology	(b) (4)
(b) (6) Division	(b) (6)
(b) (6) Division	(b) (6)

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	2
1.1	Recommendation	2
1.2	Post-Marketing Commitment/Requirement.....	2
1.3	Summary of Clinical Pharmacology Findings	2
2	QUESTION-BASED REVIEW	3
2.1	General Attributes of the Drug	3
2.2	General Clinical Pharmacology.....	5
3	LABELING RECOMMENDATIONS.....	9
4	APPENDIX.....	11
4.1	Filing Review	11

1 EXECUTIVE SUMMARY

Mifeprex[®] (mifepristone) is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy (approval date, September 28, 2000). The currently approved dose of Mifeprex[®] is 600 mg (three tablets of a 200 mg tablet) in a single oral dose followed by 400 mcg oral misoprostol two days after ingesting Mifeprex[®]. On May 28, 2015, the Sponsor submitted an efficacy supplement to seek an approval of a new treatment regimen: 200 mg mifepristone (one 200 mg tablet) on Day 1, followed in 24-48 hours by 800 mcg buccal misoprostol for pregnancies through (b) (4) days gestation. In the amendment dated on February 25, 2016, the Sponsor proposed (b) (4) the gestation age for the termination (b) (4) (4) (b) (4) to 70 days and removing the currently approved regimen from the label.

In this efficacy supplement, the Sponsor submitted published literature findings, one study report by (b) (4) and a new label in compliance with the Physician Labeling Rule (PLR) format. The Sponsor did not conduct any new clinical pharmacology studies of Mifeprex[®] in support of this new regimen. Therefore, no new clinical pharmacology study reports of mifepristone were submitted in this efficacy supplement.

1.1 Recommendation

(b) (6) (b) (6) has reviewed the available clinical pharmacology information in relation to the newly proposed regimen for Mifeprex[®]. We find the application to be acceptable from a Clinical Pharmacology perspective. An agreement on the language in the package insert was reached between the Sponsor and the Division on March 29, 2016 and there are no pending issues from the (b) (6)

1.2 Post-Marketing Commitment/Requirement

None

1.3 Summary of Clinical Pharmacology Findings

While the currently approved regimen of Mifeprex[®] consists of 600 mg mifepristone (three tablets of a 200 mg tablet), the newly proposed treatment regimen recommends a lower dose of 200 mg mifepristone (one tablet).

The pharmacokinetics (PK) of 200 mg mifepristone tablet has not been characterized in women. However, the PK data of 200 mg mifepristone tablet in men are available (study 87/517/(b)(4), submitted to NDA 020687 on March 14, 1996):

PK parameters	Mean (\pm standard error)
C _{max}	1.77 (\pm 0.23) mg/L
T _{max}	0.81 (\pm 0.16) hour
AUC	25.8 (\pm 2.2) mg·h/L

C_{max}: the maximum concentration, T_{max}: the time to reach C_{max}, and AUC: the area-under the curve

While the effects of sex on the disposition of mifepristone have not been evaluated using Mifeprex[®], no sex differences in PK of mifepristone were seen with 300 mg mifepristone (Korlym[™], NDA 202107, Clinical Pharmacology review available from Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>). Therefore, Section 12.3 of the proposed label in a PLR format should include the available PK data of mifepristone 200 mg tablet.

Cytochrome P450 3A4 (CYP3A4) plays an important role in the metabolism of mifepristone. Therefore, concomitant intake of CYP3A4 inducers with mifepristone is anticipated to have a significant effect on the disposition of mifepristone. However, the Sponsor did not conduct any in vivo studies to evaluate the effect of CYP3A4 inducers on the PK of Mifeprex[®]. Although the lowest effective therapeutic margin of mifepristone for termination of pregnancy has been not characterized clearly, the use of misoprostol in the regimen for Mifeprex[®] contributes to efficacy for inducing termination of pregnancy. In addition, concomitant intake of CYP3A4 inducers does not appear to affect the systemic exposure of misoprostol. In the proposed new regimen, another dose of misoprostol can be administered following day 7 to 14 of post-treatment of mifepristone if termination of pregnancy does not occur. In summary, the contribution of misoprostol in termination of pregnancy and additional dosing option of misoprostol may compensate the possibly diminished efficacy of Mifeprex[®] in the users of CYP3A4 inducers. However, the follow-up assessment is very important to confirm complete termination in all women.

2 QUESTION-BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the currently approved Mifeprex[®]?

Mifeprex[®] (NDA 020687; approval date, September 28, 2000) is an immediate release tablet containing 200 mg of mifepristone which is a synthetic steroid derivative known as RU 38486. Mifepristone has a strong binding affinity to glucocorticoid as well as progesterone receptors and thus shows pharmacological antagonist activities. The anti-progestational activity of

mifepristone produces effects on the uterus and cervix that result in termination of an intrauterine pregnancy when combined with misoprostol.

The US FDA approved Mifeprex[®] for the medical termination of pregnancy through 49 days gestation in 2000. The currently approved regimen is 600 mg mifepristone (3 tablets of Mifeprex[®] 200 mg tablet) on Day 1, followed on Day 3 by 400 mcg oral misoprostol.

2.1.2 What is the proposed new regimen?

The proposed new treatment regimen is one 200 mg tablet of Mifeprex[®], on Day 1, followed in 24-48 hours by 800 mcg buccal misoprostol for pregnancies through 70 days gestation. The new regimen is composed of one-third the approved dose of mifepristone and double the double dose of misoprostol. However, unlike the currently approved regimen, misoprostol is to be taken buccally.

2.1.3 What are the clinical and clinical pharmacology data submitted to support the new regimen?

The Sponsor submitted publications and 1 study report to support the approval of this efficacy supplement. The submitted articles are categorized as follows:

Type of article
Comparative (randomized) efficacy studies in different gestational ages using different regimens
Feasibility studies of combination (mifepristone + misoprostol) or single (mifepristone or misoprostol) regimen
Acceptability studies of early termination procedures
Retrospective cohort or meta-analysis studies (systematic review)
Medical practice proposed from the specialist society (review articles)
Comparative PK studies of misoprostol*
Others

* includes 1 study report by (b) (4).

The effectiveness and safety of regimens using 200 mg mifepristone with different doses and/or administration routes of misoprostol have been evaluated by the independent research groups and the study findings published in literature. In addition, the 200 mg mifepristone has been commonly used as an off-label regimen for the termination of pregnancy.

The Sponsor did not submit any new clinical pharmacology study reports of mifepristone in support of this new regimen. However, in response to the Division's information request dated on August 11 and October 30, 2015, the Sponsor submitted the following two published articles to address the effects of CYP3A4 inducers on the PK and efficacy of 200 mg mifepristone

[REDACTED] (b) (4)

These two published papers were not reviewed because they did not address the effect of CYP3A4 inducers on the PK of mifepristone. The first publication [REDACTED] (b) (4)

[REDACTED] The second publication [REDACTED] (b) (4)

[REDACTED] (b) (4). These two reports are not relevant to address the effect of CYP3A4 inducers on the disposition of mifepristone.

This supplementary submission also included 2 published papers and 1 study report on PK of misoprostol following different routes of administration. It is noted that the assessment of misoprostol in the proposed new regimen is beyond the scope of the current clinical pharmacology review because buccal route administration of misoprostol has not been approved officially for any indication including termination of pregnancy in the United States. In addition, in the Type B meeting on January 29, 2015 to discuss an efficacy supplement, the Sponsor stated that they plan to [REDACTED] (b) (4)

[REDACTED]

2.2 General Clinical Pharmacology

2.2.1 What are the major features of the clinical pharmacology in relation to the new regimen?

- The new regimen includes one-third the currently approved dose of mifepristone.
- Mifepristone has nonlinear PK due to saturation of binding capacity to the major binding protein, α_1 -acid glycoprotein. Two PK studies submitted at the time of original submission showed that systemic exposure to mifepristone does not increase in a dose-proportional manner in the doses exceeding 50mg (Table 1).

Table 1. Summary of two PK studies showing dose non-proportionality

Study title	Study design	Mean PK parameters (mean \pm standard error)
-------------	--------------	--

Changes in the plasma concentration of RU 38486 and RU 42633 in women during pregnancy termination (87/486/15)	<ul style="list-style-type: none"> Open, randomized, parallel, single dose trial in healthy females (18-45 years) in the pregnancy of less than 49 days Treatment doses: 400 or 600mg (20 subjects per each group) 		C_{max} (mg/L)	AUC (mg·h/L)
		400mg	2.70±0.23	78.7±8.0
		600mg	2.56±0.18	106±16
Plasma kinetics of RU 38486 and some of its metabolites in female subjects after a single oral administration of 50, 150 or 450 mg linearity study (86/257/(b) (4))	<ul style="list-style-type: none"> Open, randomized, crossover, single dose trial in healthy non-pregnant females (20-40 years) Treatment doses: 50, 150, and 450mg using 50mg tablet 		C_{max} (mg/L)	AUC (mg·h/L)
		50mg	1.22±0.14	17.4±1.8
		150mg	1.75±0.23	28.8±3.9
		450mg	2.05±0.16	63.6±5.9

In particular, the dose non-proportionality of C_{max} appeared to be more pronounced in the tested dose range (50 to 600 mg). This PK feature might provide plausibility that the effectiveness for inducing termination of pregnancy is likely preserved in the doses lower than the approved dose (600 mg) including the new regimen, 200 mg mifepristone.

2.2.2 What are the pharmacokinetic characteristics of a single dose of 200mg mifepristone?

- The PK information of 200 mg mifepristone (one tablet Mifeprex[®]) has not been addressed in women. When considering the non-linearity PK of mifepristone in the dose range of mifepristone in the approved and new regimen, the PK information of one tablet Mifeprex[®] should also be included in the new label.
- To address the PK characteristics of single dose of 200 mg mifepristone, the Sponsor submitted a list of PK studies conducted to support the approval of original NDA 020687 (initial submission date: 03/14/1996; approval date: 9/28/2000) including a PK study report of 200 mg mifepristone (Study 87/517/(b) (4)), entitled "Bioequivalence study of 4 dosage forms of RU 38486 administered orally to healthy male volunteers"). This study is summarized in Table 2.

Table 2. Summary of 87/517/(b) (4) study

Study title	Bioequivalence study of 4 dosage forms of RU 38486 administered orally to healthy male volunteers
Design	<ul style="list-style-type: none"> Open, randomized, crossover, single dose trial in male subjects Treatment doses: A - 20mL solution (5mg/mL, 200mg mifepristone) B - 4 × 50mg tablets C - 1 × 200mg tablet (batch (b) (4) 20780-32) D - 1 × 200mg tablet (batch (b) (4) 20236-12)

PK results of mifepristone (mean ± standard error)		A	B	C	D
	C _{max} (mg·h/L)	2.39±0.23	1.81±0.32	1.87±0.18	1.77±0.23
	T _{max} (h)	0.81±0.14	0.81±0.13	0.81±0.10	0.81±0.16
	AUC (mg·h/L)	24.0±2.2	24.4±2.1	31.1±3.9	25.8±2.2
	t _{1/2} (h)	14.5±0.8	15.6±1.3	17.1±1.3	16.8±1.6
Study conclusion	The different type of formulation tablets tested in this study are bioequivalent and may be used without distinction clinically.				

- This study provides the PK profile of 200mg mifepristone using various formulations including two batches of 200mg tablet formulations (C: batch ^{(b) (4)} 20780-32 and D: batch ^{(b) (4)} 21236-12). The Sponsor confirmed that the tested D is the same formulation as the currently approved Mifeprex[®] tablet in the response dated on September 22, 2015. However, it should be noted that this study was conducted in the healthy male subjects.
- The PK of 200mg and 600mg mifepristone is summarized in table 3.

Table 3. Cross-comparison of PK parameters between 200mg and 600mg mifepristone

		200mg	600mg
Study	Study number	87/517/ ^{(b) (4)}	87/593/ ^{(b) (4)}
	Study title	Bioequivalence study of 4 dosage forms of RU 38486 administered orally to healthy male volunteers	Study of the plasma PK parameters of RU 38486 administered in a single oral dose of 600 mg to women
	Population	Male	Female
PK parameters (Mean ± standard error)	C _{max} (mg/L)	1.77±0.23	1.98±0.31*
	T _{max} (h)	0.81±0.16	1.35±0.31
	AUC (mg·h/L)	25.8±2.2	71±10
	t _{1/2} (h)	16.8±1.6	17.5±1.0 *

* The results are included in the current labelling information.

In this comparison, there was no significant difference in the mean C_{max} values between two dose strengths, but the T_{max} was delayed with 600 mg mifepristone. The mean AUC value appeared to be higher 2.75-fold with 600 mg when compared with that of 200 mg in men. The terminal half-life was comparable.

2.2.3 Is there any sex effect on the PK of mifepristone?

Mifeprex[®] is prescribed for women in early pregnancy (through 70 days gestation for the new regimen). However, the PK data of 200 mg mifepristone is available only from the study (87/517 (b) (4)) conducted in the healthy male subjects. For using the PK data from male population as new labeling information of Mifeprex[®], it should be proved that there is no pharmacokinetic difference between male and female. However, in the developmental program of Mifeprex[®], the effect of sex on the disposition of mifepristone has not been addressed. The Clinical Pharmacology review for the NDA approval of 300 mg mifepristone (Korlym[™], NDA 202107) indicated for endogenous Cushing's syndrome described that sex did not affect PK of mifepristone (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202107Orig1s000ClinPharmR.pdf). Based on this information, the PK data of 200 mg mifepristone in the male subjects provided by the 87/517 (b) (4) study can be considered for new PK information of single dose administration of 200 mg mifepristone in the new label.

2.2.4 What is the effect of CYP3A4 inducers on the disposition of mifepristone?

- Mifepristone is a CYP3A4 substrate. The in vitro study demonstrated that CYP3A inhibitors and CYP3A4 antibodies inhibit major metabolic pathways of mifepristone by 65 to 82%. Given the major contribution of CYP3A4 in the metabolism of mifepristone, it is anticipated that the exposure to mifepristone can be significantly reduced in the users of strong CYP3A4 inducers such as rifampin and carbamazepine. However, the Sponsor did not conduct any in vivo studies to evaluate the effect of CYP3A4 inducers on the PK of Mifeprex[®]. In addition, the currently proposed dose of mifepristone, 200 mg, is one-third dose of the approved dose (600mg).
- In the current submission, the Sponsor proposed the labeling language in relation to the use of CYP3A4 inducers: (b) (4).

2.2.5 What is the clinical relevance of decreased exposure to mifepristone?

- Although concomitant use of CYP3A4 inducers is anticipated to have a significant effect on the disposition of mifepristone, the change in the exposure to mifepristone in relation to the CYP3A4 inducers has not been reported and evaluated. While 100 mg mifepristone regimen combined with misoprostol has been demonstrated to be an effective alternative to 200 or 600 mg for the termination of pregnancy in the literatures (Creinin et al. 2001), the effective lowest therapeutic margin of mifepristone for termination of pregnancy has been not characterized clearly (*Creinin MD, Pymar HC, Schwartz JL. Mifepristone 100 mg in abortion regimens. Obstet Gynecol. 2001;98:434-9*).
- The use of misoprostol in the regimen also contributes to efficacy for inducing termination of pregnancy. In addition, it has not been reported that CYP3A4 inducers decrease the exposure

of misoprostol significantly. In the new regimen, the Sponsor also proposed the option of a repeat dose of misoprostol with the supporting data: another dose of misoprostol can be administered following day 7 to 14 of post-treatment of mifepristone if termination of pregnancy does not occur. The contribution of misoprostol in efficacy and additional dosing option of misoprostol may compensate the possibly diminished efficacy of Mifeprex® in the users of CYP3A4 inducers. However, clinical interpretation of this interaction potential in the user of CYP3A4 inducers is deferred to the medical reviewer. In clinical practice, the follow-up assessment is very important to confirm the complete termination in all women who are treated with Mifeprex®.

3 LABELING RECOMMENDATIONS

Sponsor's initial proposal	Reviewer's recommendations
<p>7 DRUG INTERACTIONS</p> <p>7.1 CYP 3A4 Inhibitors</p> <p>Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Mifeprex should be used with caution in patients currently or recently treated with CYP 3A4 inhibitors.</p> <p>7.2 CYP 3A4 Inducers</p> <p>Rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (such as phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone). (b) (4)</p> <p>7.3 CYP 3A4 Substrates</p> <p>Based on <i>in vitro</i> inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range (b) (4)</p>	<ol style="list-style-type: none"> Rearrange the order of subsections to reflect its clinical relevance and the role of Mifeprex in the interaction as a victim or perpetrator. <ol style="list-style-type: none"> CYP3A4 inducers as a victim CYP3A4 inhibitors as a victim CYP3A4 substrates as a perpetrator Each header in the subsections needs to be described in detail for summary concept (e.g. CYP3A4 inducer → Effect of CYP3A4 inducer on Mifeprex). Provide a practical clinical guidance such as the follow-up assessment for the users of CYP3A4 inducers.
<p>12.3 Pharmacokinetics</p> <p><u>Absorption</u></p> <p>(b) (4)</p> <p><u>Distribution</u></p> <p>Mifepristone is 98% bound to plasma proteins, albumin, and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the</p>	<ol style="list-style-type: none"> This section should be revised based on the Guidance for Industry: Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products. In particular, it should begin with a brief introduction that describes the clinically significant PK properties of mifepristone such as PK nonlinearity ahead of the following subsections.

drug displays nonlinear kinetics with respect to plasma concentration and clearance. (b) (4)

Elimination

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

2. Insert the single dose PK data (200mg) using (b) (4) 20236-12 formulation from 87/517 (b) (4) study. State that the study was conducted in the male subjects.

4 APPENDIX
4.1 Filing Review

Application Information			
NDA Number	020687	SDN	629
Applicant	Danco Laboratories LLC	Submission Date	05/29/ 2015
Generic Name	Mifepristone	Brand Name	MIFEPREX
Drug Class	Progestin antagonist		
Indication	The medical termination of intrauterine pregnancy		
Dosage Regimen	<ul style="list-style-type: none"> • (b) (4) (for pregnancies through (b) (4) days gestation): 200 mg Mifeprex on Day 1, followed on Day 2 (minimum 24-hour interval between Mifeprex and misoprostol) or Day 3 by 800 mcg buccal misoprostol 		
Dosage Form	Tablets	Route of Administration	Oral
(b) (6) Division	(b) (6)	(b) (6) Division	(b) (6)
(b) (6) Review Team	Primary Reviewer(s)		(b) (6)
Division	(b) (6)	(b) (6)	(b) (6)
Pharmacometrics	N/A	N/A	N/A
Genomics	N/A	N/A	N/A
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	7/28/2015	74-Day Letter Date	8/11/2015
Review Due Date	1/29/2016	PDUFA Goal Date	3/29/2016
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
<input checked="" type="checkbox"/> Yes			
<input type="checkbox"/> No			
If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
<input checked="" type="checkbox"/> Yes			
<input type="checkbox"/> No			
Major review issues:			
<ul style="list-style-type: none"> • Mifepristone is a CYP3A4 substrate. Therefore, there is a drug interaction potential between CYP3A4 inducers and mifepristone. In addition, the currently proposed dose, 200mg, is lower than the approved dose (600mg). The decreased exposure of 			

mifepristone due to a drug-drug interaction with CYP3A4 inducers may reduce the efficacy (abortion failure). The effect of CYP3A4 inducers on the pharmacokinetics (PK) and clinical efficacy of mifepristone will be a major review issue.

- While the PK of mifepristone 600 mg is described in the proposed label, the PK of mifepristone 200 mg is not available under Section 12.3 of the proposed label. Mifepristone has non-linear PK characteristics. The PK information of a single dose of 200mg and a non-linear PK profile will be a review issue.

Information request:

- Address the effect of CYP3A4 inducers on the PK and efficacy of 200 mg mifepristone. This can be done by providing any published literature on the drug interaction between CYP3A4 inducers and mifepristone.
- Provide the PK characteristics of a single dose of 200mg mifepristone and address non-linear PK characteristics in the range of available doses (200 to 600mg).

Is there a need for clinical trial(s) inspection?

Yes

No

If yes explain

Filing Memo

Introduction

The Sponsor submitted the efficacy supplement for Mifeprex[®] (NDA20687, mifepristone, approval date of September 28, 2000), on May 28, 2015. Mifeprex[®] is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy. The approved dosage is 600 mg mifepristone on Day 1, followed on day 3 by 400 mcg oral misoprostol for pregnancies through 49 days gestation. The current efficacy supplement proposes (b) (4): 200 mg mifepristone on Day 1, followed on Day 2 (minimum 24-hour interval between mifepristone and misoprostol) or Day 3 by 800 mcg buccal misoprostol for pregnancies through (b) (4) days gestation. The clinical efficacy and safety of the new regimen have been evaluated by the independent study groups. This regimen has been commonly used as an off-label regimen. The Sponsor also submitted a new label in compliance with the Physician Labeling Rule (PLR) format. To support the approval of the new regimen, the Sponsor submitted 53 published literatures and 1 study report, of which 3 studies compared the PK of misoprostol in different routes.

Reviewer's Note:

- The Sponsor proposed a new label that conforms to the PLR with the information regarding the new dosing regimen.
- The Sponsor submitted 53 publications and 1 study report to support the approval of this efficacy supplement. The submitted articles can be categorized as follows:

Type of article	Number of articles
-----------------	--------------------

Comparative (randomized) efficacy study of diverse regimens or in diverse gestational ages	18
Feasibility study of combination (mifepristone + misoprostol) or single (mifepristone or misoprostol) regimen	6
Acceptability study of early termination procedures	13
Retrospective cohort or meta-analysis study (systematic review)	8
Medical practice proposed from the specialist society (review article)	4
Comparative PK studies of misoprostol	3*
Others	2

* includes 1 study report from (b) (4).

- This supplementary submission includes 2 published papers and 1 study report on PK of misoprostol following different routes of administration.

Title	Major findings
Comparison of misoprostol plasma concentrations following buccal and sublingual administration (Schaff et al. 2005)	Sublingual administration of misoprostol had a higher AUC and C _{max} compared with buccal administration
Pharmacokinetics of different routes of administration of misoprostol. (Tang et al. 2002)	The AUC up to 360 min in the sublingual group (743.7±291.2 pg.h/ml) was significantly greater than those in oral (402.8±151.6 pg.h/ml, P < 0.05) and vaginal (433.7±182.6 pg.h/ml, P < 0.05) groups, but no significant difference was found between sublingual and vaginal administration if water (649.3± 333.8 pg.h/ml) was added.

(b) (4)

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

/s/

(b) (6)
03/29/2016

(b) (6)
03/29/2016

I concur as the (b) (6).

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	020687	SDN	629
Applicant	Danco Laboratories LLC	Submission Date	05/29/ 2015
Generic Name	Mifepristone	Brand Name	MIFEPREX
Drug Class	Progestin antagonist		
Indication	The medical termination of intrauterine pregnancy		
Dosage Regimen	• (b) (4) for pregnancies through (b) (4) days gestation): 200 mg Mifeprex on Day 1, followed on Day 2 (minimum 24-hour interval between Mifeprex and misoprostol) or Day 3 by 800 mcg buccal misoprostol (b) (4)		
Dosage Form	Tablets	Route of Administration	Oral
(b) (6) Division	(b) (6)	(b) (6) Division	(b) (6)
(b) (6) Review Team	Primary Reviewer(s)		(b) (6)
Division	(b) (6)	(b) (6)	(b) (6)
Pharmacometrics	N/A	N/A	
Genomics	N/A	N/A	
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	7/28/2015	74-Day Letter Date	8/11/2015
Review Due Date	1/29/2016	PDUFA Goal Date	3/29/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

- Yes
 No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

- Yes
 No

Major review issues:

- Mifepristone is a CYP3A4 substrate. Therefore, there is a drug interaction potential between CYP3A4 inducers and mifepristone. In addition, the currently proposed dose, 200mg, is lower than the approved dose (600mg). The decreased exposure of mifepristone due to a drug-drug interaction with CYP3A4 inducers may reduce the efficacy (abortion failure). The effect of CYP3A4 inducers on the pharmacokinetics (PK) and clinical efficacy of mifepristone will be a major review issue.
- While the PK of mifepristone 600 mg is described in the proposed label, the PK of mifepristone 200 mg is not available under Section 12.3 of the proposed label. Mifepristone has non-linear PK characteristics. The PK information of a single dose of 200mg and a non-linear PK profile will be a review issue.

Information request:

- Address the effect of CYP3A4 inducers on the PK and efficacy of 200 mg mifepristone. This can be done by providing any published literature on the drug interaction between CYP3A4 inducers and mifepristone.
- Provide the PK characteristics of a single dose of 200mg mifepristone and address non-linear PK characteristics in the range of available doses (200 to 600mg).

Is there a need for clinical trial(s) inspection?

Yes

No

If yes explain

Filing Memo

Introduction

The Sponsor submitted the efficacy supplement for Mifeprex[®] (NDA20687, mifepristone, approval date of September 28, 2000), on May 28, 2015. Mifeprex[®] is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy. The approved dosage is 600 mg mifepristone on Day 1, followed on day 3 by 400 mcg oral misoprostol for pregnancies through 49 days gestation. The current efficacy supplement proposes adding a new treatment regimen: 200 mg mifepristone on Day 1, followed on Day 2 (minimum 24-hour interval between mifepristone and misoprostol) or Day 3 by 800 mcg buccal misoprostol for pregnancies through (b) (4) days gestation. The clinical efficacy and safety of the new regimen have been evaluated by the independent study groups. This regimen has been commonly used as an off-label regimen. The Sponsor also submitted a new label in compliance with the Physician Labeling Rule (PLR) format. To support the approval of the new regimen, the Sponsor submitted 53 published literatures and 1 study report, of which 3 studies compared the PK of misoprostol in different routes.

Reviewer’s Note:

- The Sponsor proposed a new label that conforms to the PLR with the information regarding the new dosing regimen.
- The Sponsor submitted 53 publications and 1 study report to support the approval of this efficacy supplement. The submitted articles can be categorized as follows:

Type of article	Number of articles
Comparative (randomized) efficacy study of diverse regimens or in diverse gestational ages	18
Feasibility study of combination (mifepristone + misoprostol) or single (mifepristone or misoprostol) regimen	6
Acceptability study of early termination procedures	13
Retrospective cohort or meta-analysis study (systematic review)	8
Medical practice proposed from the specialist society (review article)	4

Comparative PK studies of misoprostol	3*
Others	2

* include 1 study report from (b) (4).

- This supplementary submission includes 2 published papers and 1 study report on PK of misoprostol following different routes of administration.

Title	Major findings
Comparison of misoprostol plasma concentrations following buccal and sublingual administration (Schaff et al. 2005)	Sublingual administration of misoprostol had a higher AUC and C _{max} compared with buccal administration
Pharmacokinetics of different routes of administration of misoprostol. (Tang et al. 2002)	The AUC up to 360 min in the sublingual group (743.7±291.2 pg.h/ml) was significantly greater than those in oral (402.8±151.6 pg.h/ml, P < 0.05) and vaginal (433.7±182.6 pg.h/ml, P < 0.05) groups, but no significant difference was found between sublingual and vaginal administration if water (649.3± 333.8 pg.h/ml) was added.

(b) (4)

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

/s/

(b) (6)

08/13/2015

(b) (6)

08/13/2015