CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202107Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202107		
Proprietary Name: Korlym Established/Proper Name: mifepristone Dosage Form: Tablets Strengths: 300 mg		
Applicant: CORCEPT Therapeutics Agent for Applicant: N/A		
Date of Application: 4/15/11 Date of Receipt: 4/18/11 Date clock started after UN: N/A		
PDUFA Goal Date: 2/18/12	Action Goal Date (if different): **2/17/12**	
Filing Date: 6/17/11	Date of Filing Meeting: 6/14/11	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication: This new drug application provides for the use of Korlym (mifepristone) for the control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have diabetes mellitus type 2 or glucose intolerance and have failed surgery or are not candidates for surgery.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	Standard N/A	
Resubmission after withdrawal? No	Resubmission after refuse to file? No	
Part 3 Combination Product? No ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☐ Rolling Review X Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Numbers: (b) (4) and 076480	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:		✓		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Exempt (orphan)
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Not in arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		✓		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		✓		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		✓		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		✓		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		✓		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			✓	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **7 years requested exclusivity** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	✓			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	✓			
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***		✓		

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	All paper (except for COL)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1]				
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only)	✓			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	✓			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].***	✓			

Note: *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	✓			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			✓	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		✓		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s)				

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	✓			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***	✓			REMS plan submitted
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	Package Insert (PI), Medication Guide, Container Labels.			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	✓			
Is the PI submitted in PLR format?[4]	✓			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	✓			
Container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

OTC Labeling	**Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? ***If yes, specify consult(s) and date(s) sent:***	✓			QT Team. Maternal Health, DRUP
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**		✓		

Pre-NDA **Date:** 9/14/10	✓			
Any Special Protocol Assessments (SPAs)? **Date(s):**		✓		

NDA 202107 for mifepristone
Filing Meeting – Tuesday June 14, 2011

Sponsor: CORCEPT Drug: mifepristone 300mg Tablets
Indication: For the treatment of hypercortisolism associated with Cushing's Syndrome
505(b)(2) Orphan Drug designation
Paper submission

Review Team:

Division Director: Mary Parks, M.D.
OND DMEP PM: Jena Weber, BS/Julie Marchick, MS
CDTL: Dragos Roman, M.D.
Clinical: Marina Zemskova, M.D.
Chemistry: Xavier Ysern, Ph.D. (Su Tran, Ph.D., Ali Al-Hakim, Ph.D.)
ONDQA PM: Kushboo Sharma
Biopharm: Minerva Hughes, Ph.D. (Angelica Dorantes, Ph.D.)
Pharm/Tox: Pat Brundage, Ph.D. (Todd Bourcier, Ph.D.)
Pharm/Tox/Stats: Steve Thomson, Ph.D. (Karl Lin, Ph.D.)
Clin Pharm Jee Eun Lee, Ph.D (Jaya Vaidyanathan, Ph.D.)
Biometrics: Japo Choudhury, Ph.D. (Todd Sahlroot, Ph.D.)
DMEP Safety: Amy Egan, M.D., John Bishai, Ph.D.
DSI: Susan Leibenhaut, M.D. (Tejashri Purohit-Sheth, M.D.)
DRISK: Suzanne Robottom, PharmD
DDMAC: Sam Skariah, PharmD., Olga Salis, PharmD.
DMEPA: Lena Maslov, PharmD., Zach Oleszczuk
OSE: Rita Tossa, Claudia Karwoski, (Gerald Dal Pan, M.D.)
OCC: Carla Cartwright, JD
OC: Suzanne Barone
ORP: Kristen Miller, Kristen Everett, Liz Dickinson, JD
DCRP/QT: Devi Kozeli, RAC

Receipt Date: April 18, 2011
60-day Filing Date: June 17, 2011
74-day letter: July 1, 2011
Standard Review – 10 month Goal Date: February 17, 2012 (the 18th is a Sat).

Filing Meeting: June 14, 2011
Team Meeting#1: ~ August 2011
Team Meeting #2: ~ November 2011
Mid-Cycle Meeting: September 12, 2011
AC Meeting: NN
PeRC Meeting: N/A

Primary Reviews completed: January 13, 2012
Wrap-Up meeting: ~ January 13, 2012
Secondary reviews completed: January 20, 2012
DSI inspections complete: To be determined
Send labeling and PMR/PMC to sponsor: ~ January 27, 2012
CDTL review complete: January 27, 2012
Action Package to Division Director: January 28, 2012
Action letter sign-off: NLT February 17, 2012

Consults requested or to be requested prn:

DDMAC: labeling
TQT team
OSE: Trade Name
DRISK: Labeling, Med Guide
DSI: Clinical sites
DRUP: Possibility of pregnancy in Cushing's patients; what precautions or additional precautions should be taken?

Discussion Points:

Should an AC be scheduled? **No.**
REMS – specific to indication under this NDA
Inspections: DSI/clinical and CMC/EER
Exempt from PREA (Orphan)

Notes:

Additional info requested for TQT team to review
Review of PLR labeling underway
Employee list not to be included in NDA AP

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	JWeber	Y
	CPMS/TL:	JMarchick	Y
Cross-Discipline Team Leader (CDTL)	DRoman		Y
Clinical	Reviewer:	MZemskova	Y

	TL:	DRoman	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NN	NN
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	NN	NN
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NN	NN
	TL:		
Clinical Pharmacology	Reviewer:	JELee	Y
	TL:	JVaidyanathan	Y
Biostatistics	Reviewer:	JChoudhury	Y
	TL:	TSahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	PBrundage	Y
	TL:	TBourcier	Y
Statistics (carcinogenicity)	Reviewer:	SThomson	N
	TL:	KLin	N
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	NN	
	TL:	NN	
Product Quality (CMC)	Reviewer:	XYsern	Y
	TL:	STran	Y
Quality Microbiology *(for sterile products)*	Reviewer:	NN	
	TL:		
CMC Labeling Review	Reviewer:	XYsern	Y
	TL:	STran	Y
Facility Review/Inspection	Reviewer:	SLeibenhaut	Y
	TL:	TPurohit-Sheth	Y

OSE/DMEPA (proprietary name)	YMaslov	IChan	N
OSE/DRISK (REMS)	Reviewer:	SRobottom/RTossa	Y
	TL:		N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NN	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	NN	
	TL:	NN	
Controlled Substance Staff (CSS)	Reviewer:	NN	
	TL:	NN	
Other reviewers	DRUP, TQT, MHT		N
Other attendees			N

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? •	NO
• Per reviewers, are all parts in English or English translation?	YES
• Electronic Submission comments	Not Applicable
CLINICAL	FILE, review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	YES
• Advisory Committee Meeting needed? ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a***	NO

disease	
• Abuse Liability/Potential	Not Applicable
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?	NO
CLINICAL MICROBIOLOGY	Not Applicable
CLINICAL PHARMACOLOGY	FILE, review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	NO
BIOSTATISTICS	FILE, review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	FILE, review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	Not Applicable
PRODUCT QUALITY (CMC)	FILE, review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)?	Not Applicable YES ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	Not Applicable

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?	YES YES
Facility/Microbiology Review (BLAs only)	Not Applicable
CMC Labeling Review	NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Mary Parks, M.D., Division Director	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: review issues have been identified for the 74-day letter. Review Classification: Standard Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify OMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]

Jena M. Weber	February 16, 2012
Regulatory Project Manager	Date
Julie Marchick	February 21, 2012
Chief, Project Management Staff	Date

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

/s/

JENA M WEBER
02/21/2012

JULIE C MARCHICK
02/21/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name:	NDA 202107/Korlym (mifepristone)
PMR/PMC Description:	To obtain drug use data to better characterize the reporting rates of adverse events associated with the long-term use of Korlym (mifepristone).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/17/2012
	Interim report submissions:	08/17/2012
		02/17/2013
		02/17/2014
		02/17/2015
		02/17/2016
	Final Report Submission:	02/17/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☐ Life-threatening condition
   ☒ Long-term data needed
   ☒ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☒ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   Endogenous Cushing's syndrome is a rare disorder (~20,000 patients with Cushing's syndrome in the U.S.). The indication for Korlym (mifepristone) is for the control of hyperglycemia due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance who have failed surgery or who are not candidates for surgery. The estimated number of patients who would be candidates for Korlym (mifepristone) therapy is ~5,000. For these patients, there are currently no approved medical therapies. The clinical development program consisted of 1 trial enrolling 50 patients, 30 of whom were followed in an extension trial for a variable duration of time. The small size and the relatively short duration of the trials precluded an assessment of the potential long-term complications of Korlym treatment, including retinopathy, endometrial hyperplasia and/or vaginal bleeding, and major adverse cardiovascular events (due to reductions in HDL-cholesterol associated with Korlym [mifepristone] use). These adverse events will be collected using enhanced pharmacovigilance. The purpose of the drug use PMR is to provide a denominator for these adverse events to see if reporting rates in the Korlym-treated population exceed the background incidence rates in the Cushing's population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Potential adverse events associated with long-term exposure to Korlym (mifepristone) include endometrial hyperplasia and/or vaginal bleeding, retinopathy, and major adverse cardiovascular events, due to observed reductions in HDL-cholesterol. Because of the small size and short duration of the clinical trials, a determination regarding these risks could not be made. The drug use PMR will provide a denominator for the adverse events and will provide information on dose, duration of use of the product, patient age, patient gender, indication for treatment, and prescriber specialty.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☒ Assess a known serious risk related to the use of the drug?
     ☒ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A drug utilization study to provide the following information about users of Korlym (mifepristone): age, gender, dose, duration of use, indication for treatment, and prescriber specialty.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Drug utilization study

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name:	202107/Korlym (mifepristone)
PMR/PMC Description:	A drug-drug interaction clinical trial to determine a quantitative estimate of the change in exposure of mifepristone following co-administration with ketoconazole (a strong CYP3A4 inhibitor).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/18/2012
	Study/Trial Completion:	05/18/2013
	Final Report Submission:	08/18/2013
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☒ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

Endogenous Cushing's syndrome is a rare disorder (~20,000 patients with Cushing's syndrome in the U.S.). The indication for Korlym (mifepristone) is for the control of hyperglycemia due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance who have failed surgery or who are not candidates for surgery. The estimated number of patients who would be candidates for Korlym (mifepristone) therapy is ~5,000. For these patients, there are currently no approved medical therapies.

Cushing's syndrome patients may need to be prescribed other medications which are strong CYP3A4 inhibitors. Additionally, while not approved for use in this population, ketoconazole is frequently prescribed off-label to suppress glucocorticoid synthesis in Cushing's syndrome patients. Ketoconazole is a strong CYP3A4 inhibitor. The drug-drug interaction trial will allow for a quantification of the increase in exposure of mifepristone if it is co-administered with a strong CYP3A4 inhibitor. An increase in mifepristone exposure has the potential to increase serious side effects associated with Korlym use, such as adrenal insufficiency, and severe hypokalemia.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Mifepristone is a substrate of CYP 3A4; its three major active metabolites are formed via CYP3A4-mediated metabolism. The sponsor conducted a drug-drug interaction study with cimetidine, a mild CYP3A inhibitor. There was no effect of cimetidine on mifepristone exposure. The effect of moderate or strong CYP3A inhibitors on the pharmacokinetics of mifepristone has not been evaluated. (b) (4) Since ketoconazole, a strong CYP3A inhibitor has the potential for being used in the clinical management of the Korlym target population, there is a high potential for its concomitant use with mifepristone. The degree of change in exposure of mifepristone when co-administered with strong CYP3A inhibitors is unknown and may present a safety risk, or deprive patients on strong CYP3A4 inhibitors the use of mifepristone due to the lack of quantitative data on this potential drug interaction. Thus, this quantitative data is important for the safe and effective use of Korlym in the target population.

The goal of this study is to determine a quantitative estimate of the change in exposure of mifepristone following co-administration with ketoconazole. This will help provide more therapeutic options to Cushing's patients and appropriate labeling of mifepristone when co-administered with strong CYP3A inhibitors.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☒ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a pharmacokinetic drug-drug interaction trial in healthy subjects.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?

☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

/s/

AMY G EGAN
02/16/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Maternal Health Team Review

Date: February 14, 2012 **Date Consulted:** January 27, 2012

From: Upasana Bhatnagar, M.D.
Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari Ph.D.
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Lisa Mathis, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Metabolism and Endocrinology Products (DMEP)

Drug: **Korlym (mifepristone)- NDA 202107**

Sponsor: Corcept Therapeutics

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed: Sponsor's proposed labeling and medication guide

Consult Question: Please review and comment on the proposed labeling and medication guide.

INTRODUCTION

On April 15, 2011, Corcept Pharmaceuticals submitted a new drug application (NDA 202107) for Mifepristone (Corcept) 300mg tablets. The Sponsor proposed the treatment of patients with Cushing's disease who: have not adequately responded to or have relapsed after surgery, are not candidates for surgery, (b) (4) . After review of the NDA submission, DMEP determined that the approved indication should be limited to treatment of glucose intolerance or type 2 diabetes in adult patients with endogenous Cushing's syndrome who have failed surgery or are not candidates for surgery. The proposed dose is 300mg daily, which may be increased up to 1200mg daily. Mifepristone is a progesterone receptor modulator (PRM) that was approved on September 28, 2000, under the trade name Mifeprex, indicated for use for pregnancy termination at a 600 mg dose. The Division of Metabolism and Endocrinology Products (DMEP) consulted the Pediatric and Maternal Health Staff's Maternal Health Team (PMHS-MHT) to review the sponsor's proposed labeling and medication guide particularly focusing on the Pregnancy and Nursing Mothers subsections. This review provides the PMHS-MHT recommendations for revisions to the Sponsor's proposed labeling and medication guide.

BACKGROUND

Mifepristone, a norethindrone derivative, acts as an antiprogestin by binding the progesterone receptor. This progesterone receptor modulator (PRM) binds to the receptor with greater affinity than progesterone but does not activate the receptor. Mifepristone is also a glucocorticoid receptor antagonist, and is used in high doses for the treatment of Cushing's disease.[1]

Cushing's syndrome is defined as the set of clinical abnormalities resulting from chronic high levels of cortisol, whereas Cushing's disease is Cushing's syndrome that results from excess pituitary production of adrenocorticotropic hormone (ACTH) usually due to a pituitary adenoma.[2] Cushing's syndrome has a female preponderance with an estimated female to male ratio of 3:1.[3] Therefore, it is likely that mifepristone may be used in females of reproductive potential with Cushing's syndrome.

PRMs have various effects on the female genital tract that can be dose dependant. At higher doses, such as those used for the treatment of Cushing's syndrome, some of the uterine effects of mifepristone include softening of the cervix, necrotizing the decidua, and increasing uterine contractility. Therefore, mifepristone (200mg or 600mg) in combination with a prostaglandin analogue is commonly used as a medical abortion regimen.[4]

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[1] Spitz IM, Grunberg SM, Chabbert-Buffet N et al, Management of patients receiving long term treatment with mifepristone. *Fertil Steril*. 2005;84:1719-26.
[2] JUSTIN L. KAPLAN, MD, et al, eds. 2006. Merck Manual of Diagnosis and Therapy, The. Whitehouse Station, NJ. MERCK RESEARCH LABORATORIES. http://online.statref.com/document.aspx?fxid=21&docid=537. 8/15/2011 11:48:03 AM CDT (UTC -05:00).
[3] Steffensen C, Bak AM, Rubeck KZ et al. Epidemiology of Cushing's Syndrome. *Neuroendocrinology*. 2010. 92(1):1-5.
[4] ACOG Practice Bulletin. October 2005, Number 67. Medical Management of Abortion

Additionally, long-term use of mifepristone at higher doses has been shown to cause endometrial thickening and endometrial hyperplasia, which can symptomatically present as vaginal bleeding.[5] Women with a uterus receiving chronic treatment with mifepristone who experience irregular vaginal bleeding need a full evaluation by a gynecologist.

REVIEWED MATERIALS
Segments of Sponsors Proposed Labeling - see Appendix A

DISCUSSION

Korlym (mifepristone) is a progesterone receptor modulator that also acts as a glucocorticoid receptor antagonist at higher doses. After review of the Sponsor submission, Division of Metabolism and Endocrinology Products (DMEP) determined that the approved indication should be limited to treatment of glucose intolerance or type 2 diabetes in adult patients with endogenous Cushing's syndrome who have failed surgery or are not candidates for surgery. DMEP consulted the Pediatric and Maternal Health Staff's Maternal Health Team (PMHS-MHT) to review the proposed labeling and medication guide.

Because of mifepristone's effects as an inhibitor of the progesterone receptor causing pregnancy loss, PMHS-MHT recommends contraindicating the use of Korlym in women who are pregnant and classification with a pregnancy Category X. Furthermore, PMHS-MHT recommends the addition of section 8.8 Females of Reproductive Potential to include recommendations for pregnancy testing prior to initiation of Korlym therapy and for contraception during treatment.

Information was added in the human data subsection of 8.1 Pregnancy regarding pregnancy outcomes after exposure to mifepristone, administered in a single dose for pregnancy termination. In the Mifeprex (mifepristone) labeling, thirteen pregnancies occurring after exposure to mifepristone and resulting in live births were reported. Among these thirteen live births, no fetal abnormalities were noted. [6] This data may inform health care providers counseling patients regarding inadvertent exposure to Korlym during pregnancy.

Due to presence of mifepristone in human milk, even after single dose administration, and the unknown effects of long-term mifepristone exposure upon infants, the PMHS-MHT recommends contraindication of use of Korlym among nursing mothers. Lactation studies conducted after single dose administration of mifepristone indicate that as dosing was increased (from 200 mg to 600 mg), increasing levels of mifepristone were detectable in breast milk. However, no data was available regarding the long-term use of mifepristone and drug levels in breast milk or effects of chronic exposure on infants.[7]

[5] Grunberg SM, Weiss MH, Russell CA et al. Long Term Administration of Mifepristone (RU486): Clinical Tolerance During Extended Treatment of Meningioma. *Cancer Investigations*.2006.24;727-733.
[6] Mifeprex labeling, approved 4/22/2009.
[7] Saav I, Fiala C, Hamalainen JM, et al. Medical abortion in lactating women-low levels of mifepristone in breast milk. Acta Obstetricia et Gynecologica. 2010;89:618-622.

Because the data regarding transformation from endometrial thickening caused by mifepristone use to endometrial hyperplasia is varied, PMHS-MHT recommends that women who experience irregular bleeding on Korlym should have further evaluation by a gynecologist. To limit the risk of endometrial hyperplasia, Korlym treatment should be contraindicated in women with a history of unexplained vaginal bleeding, a history of endometrial hyperplasia, and precautions for female patients treated with Korlym that experience irregular vaginal bleeding should be included in labeling. Available data from Study 400 regarding endometrial changes caused by Korlym use resulting in abnormal endometrial thickening, vaginal bleeding, and cases of endometrial carcinoma should be included in labeling.

In the medication guide, PMHS-MHT recommends that females who can become pregnant have the option of a urine or serum pregnancy test prior to initiation of therapy with Korlym or if therapy is interrupted for 14 days because requiring a serum pregnancy test can be burdensome. Additionally, because no data regarding levels of drug in semen were available from the sponsor's application or in a review of the literature, the precautions for males regarding the use of condoms during intercourse are not supported. Finally, a women who are lactating should be included in the populations to avoid taking Korlym.

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. The Pregnancy and Nursing Mothers section of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus, and/or infant. PMHS-Maternal Health labeling recommendations not only comply with current regulations but also incorporate "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, the required regulatory language for the designated pregnancy category, and, when available, outcomes of studies conducted in pregnant women and studies conducted in animals. The paragraphs that follow provide more detailed descriptions of the available human and animal data and appropriate clinical information that may affect patient management.

RECOMMENDATIONS

1. The PMHS-Maternal Health team recommends labeling Korlym (mifepristone) Category X in pregnancy because of the concerns of pregnancy loss with use of Korlym. Recommendations for the pregnancy and lactation subsection labeling revisions are provided below.

2. The PMHS-MHT recommends adding section 8.6 Females of Reproductive Potential for the labeling of Korlym to inform healthcare providers about screening for pregnancy prior to use of Korlym and use of contraception during treatment with Korlym. These recommendations were added to the medication guide.

3. Because of the concern for abnormal endometrial thickening and vaginal bleeding as a symptom of endometrial pathology resulting from Korlym use, additional recommendations for revisions in sections 4.1, 5.3, and 6.3 as well as the medication guide were developed in conjunction with the DMEP review team and are included below.

PMHS – Maternal Health Team Labeling Recommendations

The PMHS-Maternal Health Team recommendations for labeling and the medication guide are provided below. Please see **Appendix B** for the track changes version.

Contraindications

- **Pregnancy** ***(4.1, 8.1)***

Use in Specific populations

- **Pregnancy-** Can cause pregnancy loss. Advise women of potential risk to the fetus *(8.1)*
- **Nursing Mothers-**discontinue drug or discontinue nursing *(8.3)*

4.1 Pregnancy Loss

Korlym is contraindicated in women who are pregnant. Pregnancy must be excluded before the initiation of treatment with Korlym. Non-hormonal contraceptives should be used during treatment and for one month after stopping treatment in all women of childbearing potential. *[see Use in Specific Populations (8.8) and Drug Interactions (7.6)]*

5.3 Vaginal Bleeding and Endometrial Changes

Being an antagonist of the progesterone receptor mifepristone promotes unopposed endometrial proliferation that may result in endometrium thickening, cystic dilatation of endometrial glands, and vaginal bleeding. Women who experience irregular vaginal bleeding during Korlym treatment should be referred to a gynecologist for further evaluation.

6.3 Vaginal Bleeding and Endometrial Changes

In Study 400, abnormally increased endometrial thickness was reported in 10/35 females (30%). Vaginal bleeding occurred in 5/35 females (14%), of these, two subjects had normal endometrial thickness. In all study patients, the thickness of the endometrium increased from a mean of 6.14 mm at baseline to 15.7 mm at end-of-trial in premenopausal women; in postmenopausal women the increase was from 2.75 mm to 7.35 mm. The endometrial thickness resolved with treatment cessation in the majority of patients after Korlym was discontinued. Endometrial biopsies were performed in a limited subset of patients with endometrial thickening; no endometrial carcinoma was detected in the sampled cases.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Category X

Korlym is contraindicated in pregnancy. Korlym can cause fetal harm when administered to a pregnant woman because the use of Korlym results in pregnancy loss. The inhibition of both

endogenous and exogenous progesterone by mifepristone at the progesterone-receptor results in pregnancy loss. If Korlym is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. *[see Contraindications (4.1)]*

Human Data
In a report of thirteen live births after single dose mifepristone exposure, no fetal abnormalities were noted.

Animal Data
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 level based on body surface area) were carried out. 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 decreased progesterone levels.

8.3 Nursing Mothers
Mifepristone is present in human milk. Because of the potential for serious adverse reactions in nursing infants from Korlym, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.8 Females of Reproductive Potential
Due to its antiprogestational activity, Korlym causes pregnancy loss. Exclude pregnancy before the initiation of treatment with Korlym or if treatment is interrupted for more than 14 days in females of reproductive potential. Recommend contraception for the duration of treatment and for one month after stopping treatment using a non-hormonal medically acceptable method of contraception. If the patient has had surgical sterilization, no additional contraception is needed.

17 PATIENT COUNSELING INFORMATION

17.1 Importance of Preventing Pregnancy

- Advise patients that Korlym will cause termination of pregnancy.
- Counsel females of reproductive potential regarding pregnancy prevention and planning with a non-hormonal contraceptive prior to use of Korlym and up to one month after the end of treatment.
- Instruct patients to contact immediately their physician if they suspect or confirm they are pregnant.

Medication Guide
Korlym™ (KOR-lim)
(mifepristone) Tablets

Read this medication guide before you start taking Korlym and each time before you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about Korlym?

Korlym can cause serious side effects.

1. Loss of a pregnancy

For women who can become pregnant, you must:

- Have a negative pregnancy test:
  - before starting Korlym
  - before restarting Korlym if you stop taking it for more than 14 days
- Use a non-hormonal form of birth control during treatment with Korlym and for 1 month after stopping treatment. Talk to your doctor to find out how to prevent pregnancy. Tell your doctor right away if you think you may be pregnant.

2. Too little adrenal hormone effect (adrenal insufficiency)

Korlym blocks the effects of cortisol, an adrenal hormone. The block could result in too little hormone effect in your body. Tell your doctor right away if you have any of these symptoms:

- Unusual tiredness or weakness
- Nausea, and/or vomiting
- Dizziness when standing
- Loss of appetite and weight loss
- Being irritable or depressed

3. Low blood potassium (hypokalemia)

Your doctor will check your blood potassium before you start Korlym and while you are taking it. Tell your doctor if you have these signs of low potassium:

- muscle weakness, aches, or cramps
- abnormal or irregular heartbeats (palpitations)

4. Bleeding from the vagina

Korlym may cause the lining of your uterus to thicken and cause vaginal bleeding. Tell your doctor right away about any unexpected vaginal bleeding.

Korlym has other serious side effects. See "What are the side effects of Korlym?" in this medication guide.

What is Korlym?

Korlym is a medicine that patients with Cushing's syndrome can take by mouth to reduce signs and symptoms of high cortisol levels. Korlym can cause serious side effects. See "What is the most important information I should know about Korlym?"

Cortisol is a hormone made in the adrenal glands. In Cushing's syndrome, your body makes too much cortisol. Korlym can reduce the effects of high cortisol levels. Korlym can lower blood sugar, help control high blood pressure and improve other signs and symptoms of Cushing's syndrome.

Who should not take Korlym?
Do not take Korlym if you:

- are pregnant
- are taking the following medicines
  - medicine for fungal infection: ketoconazole (Nizoral®)
  - medicine for depression: nefazodone (Serzone®)
  - medicines for HIV infection: ritonavir (Norvir®), nelfinavir (Viracept®), indinavir (Crixivan®), atazanavir (Reyetaz®), amprenavir (Agenerase®), and fosamprenavir (Lexiva®)
  - steroid medicines such as prednisone
  - the cholesterol lowering medicines simvastatin (Zocor®) and lovastatin (Mevacor®)
- are a woman who still has her uterus (womb) and have
  - a bleeding problem or are taking blood thinners
  - recently had unexplained bleeding from the vagina
  - cancer of the uterus or pre-cancerous growth in the uterus
- are allergic to mifepristone, the active ingredient in Korlym
- are nursing

Korlym has been studied in adults ages 26 to 71. Korlym has not been studied in children.

What should I tell my doctor before taking Korlym?
Before taking Korlym, tell your doctor if you:

- have infection with human immunodeficiency virus (HIV) or have AIDS
- have cancer
- have ever had unexplained bleeding from the vagina
- have any bleeding problem or are taking blood thinners
- have abnormal changes in your uterus
- **are or could be pregnant or plan to become pregnant.** Korlym will cause you to lose the baby. See "What is the most important information I should know about Korlym?" Tell your doctor right away if you become pregnant while taking Korlym.
- **are breastfeeding or plan to breastfeed.** It is not known if Korlym passes into your breast milk. You and your doctor should decide if you will take Korlym or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take. Include prescription and nonprescription medicines, vitamins and herbal supplements.
Korlym and certain other medicines can interact with each other, sometimes causing serious side effects. Especially tell your doctor if you take:

- medicine for fungal infection, such as ketoconazole
- medicine for depression, such as nefazodone
- medicines for HIV infection: ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, and fosamprenavir
- steroid medicines such as prednisone
- the cholesterol lowering medicines simvastatin (Zocor®) and lovastatin (Mevacor®)

These medicines should not be used with Korlym.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist. Do not take any new medicine without talking with your doctor first.

How should I take Korlym?
You get Korlym only through the Support Program for Access and Registration for Korlym (SPARK). Your doctor will talk with you about the SPARK. After your doctor registers you with the SPARK, a specialty pharmacy will deliver your Korlym directly to you.

- Take Korlym exactly as your doctor tells you. Your doctor will start Korlym at a low dose and may increase it over time.
- Take Korlym once a day, with a meal, at the same time each day.
- Do not split, crush or chew Korlym tablets.
- Do not stop taking Korlym without first talking to your doctor.
- If you miss a dose, take it as soon as you remember that day. Take your next dose at the regular time. Do not take 2 doses on the same day.
- Call your doctor or poison control center if you take more than your usual dose of Korlym.

What should I avoid while taking Korlym?

- If you are a woman who can become pregnant, do not get pregnant while taking Korlym. See "What is the most important information I should know about Korlym?" Call your doctor right away if you think you may be pregnant.
- Do not breastfeed while taking Korlym.

What are the possible side effects of Korlym?
Korlym can cause serious side effects. See "What is the most important information I should know about Korlym?" The most common side effects of Korlym in a clinical trial in patients with Cushing's syndrome are listed below.

- Fatigue
- Nausea
- Headache
- Decreased blood potassium
- Joint pain (arthalgia)
- Vomiting
- Fluid retention (edema)
- Hypertension
- Dizziness
- Thickening of the lining of the uterus (endometrial hypertrophy)
- Decreased appetite

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Korlym. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to Corcept at 1-800-XXX-XXXX or to the FDAat 1-800-FDA-1088.

How should I store Korlym?
• Store Korlym at room temperature, but not lower than 59°F and not higher than 86°F (15°C to 30°C).
• Store Korlym in the package it comes in.
• **Keep Korlym and all medicines out of the reach of children.**

General information about the safe and effective use of Korlym
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
Do not use Korlym for a condition for which it was not prescribed. Do not give Korlym to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about Korlym. For more information, talk with your doctor. You can ask your doctor or pharmacist for information about Korlym that is written for

healthcare professionals. For more information, call 1-xxx-xxx-xxxx or visit www.xxxxxxxx.com or www.corcept.com.

What are the ingredients in Korlym?
Active ingredient: mifepristone
Inactive ingredients: silicified microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, hypromellose, titanium dioxide, triacetin, D&C yellow 10 aluminum lake, polysorbate 80, and FD&C yellow 6 aluminum lake.

This Medication Guide has been approved by the US Food and Drug Administration.

Distributed by:
Corcept Therapeutics Incorporated
149 Commonwealth Avenue
Menlo Park, CA 94025
MMM 2011

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/s/

UPASANA BHATNAGAR
02/14/2012

MELISSA S TASSINARI
02/14/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Promotion (DPP)
Division of Direct-to-Consumer Promotion (DDTCP)

****Pre-decisional Agency Information****

Memorandum

Date: February 14, 2012

To: Jena Weber, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel M. Skariah, Regulatory Review Officer, DPP-OPDP
Kendra Y. Jones, Regulatory Review Officer, DDTCP-OPDP

CC: Lisa Hubbard, Group Leader, DPP-OPDP
Shefali Doshi, Group Leader, DDTCP-OPDP
Olga Salis, Regulatory Project Manager, OPDP

Subject: NDA #202107 Korlym™ (mifepristone) 300 mg Tablets

OPDP Labeling Review

OPDP has reviewed the proposed package insert (PI) and medication guide (MedGuide) for Korlym consulted from DMEP to OPDP on February 13, 2012.

General Comment

Comments regarding the PI and MedGuide are provided in the marked versions below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the PPI, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
02/14/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**February 13, 2012**
To:	Mary Parks, MD, Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
	Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	KORLYM (mifepristone)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 202-107
Applicant:	**Corcept Therapeutics Inc.**

1 INTRODUCTION

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for Korlym (mifepristone) Tablets.

On April 15, 2011, Corcept Therapeutics Inc. submitted a New Drug Application (NDA 202-107) for Korlym (mifepristone) Tablets, indicated for the treatment of the clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome.

2 MATERIAL REVIEWED

- Draft KORLYM (mifepristone) Medication Guide (MG) received on April 15, 2011 and received by DMPP on February 09, 2012.
- Draft KORLYM (mifepristone) Prescribing Information (PI) received on April 15, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on February 09, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.

- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
02/13/2012

MELISSA I HULETT
02/13/2012

LASHAWN M GRIFFITHS
02/13/2012

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

Application: NDA 202107

Name of Drug: Korlym (mifepristone) 300 mg Tablets

Applicant: CORCEPT

Labeling Reviewed

Submission Date: April 15, 2011 **Receipt Date:** April 18, 2011

Background and Summary Description

Korlym (mifepristone) is a cortisol receptor blocker indicated to treat the clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome, including:

- Patients with Cushing's disease who have not adequately responded to or relapsed after surgery
- Patients with Cushing's disease who are not candidates for surgery

(b) (4)

Review

Highlights Overview

Delete language that appears as ~~strikethrough.~~
Add language that appears underlined.

(b) (4) should be replaced by KORLYM, throughout the label

Add the year "2000" after "Initial U.S. Approval"

In the Boxed Warning, the initial presentation should read, **WARNING: TERMINATION OF PREGNANCY**

In the Boxed Warning, the last sentence, "See full prescribing information for complete boxed warning," should be moved and appear as the first sentence in this section right after **WARNING: TERMINATION OF PREGNANCY,** and be written in italic font.

(b) (4)

Under **DOSAGE AND ADMINISTRATION**:

Delete "dash" from 300 —mg

Under **CONTRAINDICATIONS:**

(b) (4)

Theoretical possibilities (i.e., hypersensitivity to the drug) should not be listed.

Under **WARNINGS AND PRECAUTIONS:**

Clinical team should concur that the order of importance or rates of occurrence as reported appear in the correct order.

Under **ADVERSE REACTIONS:**

Delete (b) (4) A general link to a company's website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting.

Capitalize **Drug Interactions** section

Under **USE IN SPECIFIC POPULATIONS:**

Remove first bullet; – (b) (4)

See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

- Remove (b) (4)
- May have to readjust contents to fit on half-page, or get waiver
- Some bullet points appear in a larger font than others

Contents – Table of Contents

- Insert asterisk after **FULL PRESCRIBING INFORMATION: Contents****
- A two-column format for the Table of Contents is recommended
- If Highlights cannot be revised to appear on a half-page format, the Table of Contents should appear on page 2. If revisions can be made, a horizontal line (in **bold** type) must be inserted between the Highlights and Table of Contents.
- Remove all corresponding page numbers.
- The Table of Contents sections must be in **bold** type.
- As SPL R4 validation does not permit the inclusion of the MG as a subsection under Patient Counseling information section, do not include the MG or PPI as a subsection heading in the Table of Contents. Therefore, remove (b) (4)
- Remove (b) (4) Although the content ("Patients should be advised not to split, crush, or chew tablets") is useful, it should not appear under this section, but under **DOSAGE AND ADMINISTRATION.**

Full Prescribing Information – Overview

- Add **Labor and Delivery** subsection (**8.2**) to **USE IN SPECIFIC POPULATIONS** section if applicable (it may not be). If not applicable, should a statement indicating such be inserted?

Full Prescribing Information – Details

BOXED WARNING

Wherever there is a reference in the label to the Boxed Warning, it should appear as *[see **Boxed Warning**]*; that is, in bold type and italics.

This section needs to be rewritten. (b) (4)

1. INDICTIONS AND USAGE

- No comments at this time.

2. DOSAGE AND ADMINIATRATION

- Add the term "oral" to this section when describing the tablets. Delete the "dash" from 300 —mg

3. DOSAGE FORMS AND STRENGTHS

- Add comment whether tablets are scored.
- State if tablets are coated and include this description under **HOW**

SUPPLIED/STORAGE AND HANDLING section.

4. CONTRAINDICATIONS

- Section to be re-written

5. WARNINGS AND PRECAUTIONS

- Determine order of importance in decreasing order for each subsection mentioned.
- Reviewers should determine if absolute risk/rate of adverse reaction(s) are known.

6. ADVERSE REACTIONS

- Section should be re-written; are potentially fatal adverse reactions that are mentioned in **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS** all mentioned here (if applicable). Clinical will have to provide language.

6.1 Clinical Trials Experience

- No mention of drug comparator of placebo noted; this is probably not necessary or required. Entire section (including Table 1) needs re-writing.
  Section 6.2 must be reserved for postmarketing experience.
  Laboratory Tests and Additional Data from Clinical Trials can be subsections of 6.1.
- Subsection 6.3**Additional Data from Clinical Trials** needs rewriting; a Table appearance may be better.

7. DRUG INTERACTIONS

- Section should be re-written; if know, mention of any foods, dietary supplements, grapefruit juice, etc should be documented. Comments such, (b) (4) should be removed.

8. USE IN SPECIFIC POPULATIONS

- Whether known or not (probably not), should we add subsection **7.2 Labor and Delivery**?
- Pregnancy Category not identified any where in the label (Highlights, Table of Contents, Full Prescribing Info).
- Are pregnancy data available (unlikely)?
- Section should be re-written. Clinical input needed to insert precise information/data.

8.5 Insufficient numbers; however, should we include what information we can? Add additional information if drug is excreted by the kidney.

8.6 Additional Subsections

- Note: no PK/PD information mentioned.

11. DESCRIPTION

- Add pharmacologic or therapeutic class of drug

12. CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

- Data on exposure-response relationship not stated (concentration-response, dose-response) and time course of PD response . . .

12.3 Pharmacokinetics

- Not identified in this section C_{min}, $C_{max,}$ $T_{max,}$ AUC, route of elimination, drug/drug interactions, Vd, non-linearity in PK parameters, changes in PK over time, binding, other info about BE among marketed formulation.

13. NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

- Not identified; should this be included?

14. CLINICAL STUDIES

- Should be re-written. Should p-values be represented? Include patient variability, effects in age, gender . . . Population studies is small so we may not be able to adequately incorporate this into the label(s).

15. HOW SUPPLIED/STORAGE AND HANDLING

- Add "scored" (if appropriate) to tablet. Information presented does not mention this. Should identify "scored" only if tablet appears as such.

Conclusions/Recommendations

To be completed and conveyed to applicant. Reviewers evaluating WORD copy of initial labeling.

Regulatory Project Manager Date

Chief, Project Management Staff Date

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/s/

JENA M WEBER
02/06/2012

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: December 8, 2011

TO: Jena Weber, Regulatory Project Manager
Marina Zemskova, Clinical Reviewer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202107

APPLICANT: Corcept Therapeutics

DRUG: mifepristone

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: treatment of the signs and symptoms of hypercortisolemia in subjects with endogenous Cushing's syndrome (b) (4)

CONSULTATION REQUEST DATE: June 28, 2011

DIVISION ACTION GOAL DATE: January 6, 2012

PDUFA DATE: February 17, 2012

I. BACKGROUND:

Corcept Therapeutics submitted NDA 202107 for Mifepristone (CORLUX) for the indication of treatment of the signs and symptoms of hypercortisolemia in subjects with endogenous Cushing's syndrome (b) (4). This is a routine audit request to assess data integrity and human subject protection for a clinical trial submitted in support of this indication.

The protocol inspected was C1073-400 entitled "An Open-label Study of the Efficacy and Safety of CORLUX® (mifepristone) in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome." The study was conducted at 20 sites in the US from August 12, 2008 to January 10, 2011. A total of 29 subjects were enrolled in the cohort of subjects with diabetes mellitus and/or impaired glucose tolerance (C-DM cohort) and 21 subjects were enrolled in the cohort of subjects with hypertension (C-HT cohort). The primary endpoint for the C-DM cohort was change in the area under the concentration-time curve for glucose (AUCglucose) in the 2-hour oral glucose tolerance test (oGTT) from baseline to Week 24. For the C-HT cohort it was the change in diastolic blood pressure from baseline to Week 24.

Two clinical investigator sites were inspected in support of this application. The choice of sites was based on site enrollment.

II. RESULTS (by Site):

Name of Clinical Investigator (CI)	**Protocol #/ # Subjects Randomized**	**Inspection Date**	**Final Classification**
Dr. David Schteingart University of Michigan Medical Center Division of Endocrinology 5570 MSRB II Spc 5678 1150 W Medical Center Drive Ann Arbor, MI 48109-0678	Protocol C1073-400/ 8 Subjects	August 3 to 25, 2011	VAI
Dr. Maria Grama Fleseriu Oregon Health Sciences University Dept of Endo/Pituitary Unit 3515 SW US Veterans Hospital Road BTE472 Portland, OR 97239	Protocol C1073-400/ 8 Subjects	August 17 and 26, 2011	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Dr. David Schteingart**
University of Michigan Medical Center, Division of Endocrinology
5570 MSRB II Spc 5678, 1150 W Medical Center Drive
Ann Arbor, MI 48109-0678

a. **What was inspected**: For Protocol C1073-400at this site, 10 subjects were screened and two subjects were considered screen failures. A total of 8 subjects were enrolled. Two subjects (Subjects #004 and 010) completed the study, and Subject 004 continues to survive on the drug in the Extension study, C1073-405. Five subjects withdrew due to SAEs or AEs (3 deaths, 2 worsening of disease), and Subject 002 withdrew consent. An audit of all 10 subjects' records was conducted. During the inspection the following areas were covered: protocol compliance, test article accountability and storage, informed consent process, data accuracy, and site training and monitoring.

b. **General observations/commentary:** The primary endpoint data were verified and there was no evidence of under reporting of adverse events. A Form FDA 483 was issued for violations below. These items were discussed with the review division in August 2011. The following are some of the items cited on the Form FDA 483:
   1. Failure to follow the investigational plan:
      i. The protocol stated that initiation or dose changes are not allowed for anti-diabetic medications or antihypertensive medications and subjects who require additional medications should be removed from the study.
         1. Subject 004 was enrolled to the study under the Diabetes Mellitus (DM) arm on 12/1/08. Diabetes medication (Lantus) was increased from 50 units to 90 units on 1/17/09.
         2. Subject 006 was enrolled to the study under the Hypertension (HT) arm on 2/19/09. Hypertension medication (c1onidine) was begun approximately 3/12/09.
         3. Subject 008 was enrolled to the study under the Hypertension (HT) arm on 7/14/09. Hypertension medication (Lisinopril) was increased from 5 mg per day to 10 mg on 8/10/09.

Reviewer note: For protocol violations concerning medications, the data were submitted in the NDA as either a protocol violation or listed as a concomitant medication. In addition, these items can be explained by additional information supplied by the CI. For Item #1, this medication was initiated by the patient's primary care physician. For Item #2, this observation is not correct because clonidine was an ongoing medication. For Item #3, the subject was subsequently enrolled into the DM cohort. These findings are considered isolated findings and are unlikely to impact data reliability.

      ii. Poorly controlled hypertension defined as systolic blood pressure >170 mm Hg or diastolic blood pressure >110 mmHg at screening was an exclusionary criterion but Subjects 002 and 003 were enrolled with BP that were above these values.

Reviewer note: These data were submitted in the NDA. The CI requested and received

permission from the sponsor to continue these subjects in the study.

iii. The protocol states "Blood pressure in both arms should be measured at Screening and the arm with the higher diastolic reading should be recorded and used for all subsequent measurement. Two blood pressure measurements in the designated arm are required at all visits, including Screening. These measurements must be separated by an interval of at least 2 minutes. If the 2 sequential readings differ by >5mmHg (systolic or diastolic), repeat the measurement until consecutive readings are within 5 mmHg of each other." Of the deviations listed on the FDA Form 483, only subjects 006, 007, 009, and 010 were in the hypertension arm of the study. Of these, only subject 009 had diastolic blood pressure vary by >5 mmHg at visits where primary study efficacy was evaluated (baseline and end of treatment visits).

Reviewer note: These data were submitted in the NDA, including the variability in the BP readings are included in the NDA. This finding was discussed with the review division in August 2011. It is an isolated finding and unlikely to impact data reliability.

Dr. Schteingart responded adequately to the findings in a written response of September 15, 2011. Also, it was determined that the protocol was vague concerning the requirements to obtain blood pressures and it was difficult to adhere to some of the requirements for taking repeat blood pressures in this vulnerable population. In addition, although there were violations concerning the primary endpoint for hypertension, the actual blood pressures obtained at this site, were contained in the data listings submitted to the FDA, so the review division could perform an analysis on the actual blood pressures that were obtained.

c. **Assessment of data integrity**: The violations noted above are isolated and are not considered to have impacted significantly on the conduct of the study or on data reliability. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. **Dr. Maria Fleseriu**
Oregon Health Sciences University
3515 S.W. Sam Jackson Park Rd, BTE 472, Portland, OR 97239

a. **What was inspected**: For Protocol C1073-400 at this site, at this site, a total of 14 subjects were screened, eight subjects were enrolled into the study. Five subjects completed the study and three subjects were terminated from the study due to adverse events or non-compliance with treatment. An audit of all eight enrolled subjects' records was conducted. Review of 100% of informed consent documents was performed. The review covered all eight subjects' records and included a comparison of source documentation to (CRFs) and data listings submitted to the NDA. Specific records reviewed included, but were not limited to, adverse event reporting; inclusion/exclusion criteria; test article

accountability; informed consent form approvals; monitoring records; adherence to protocol-specified procedures for blinding and randomization.

b. **General observations/commentary**: Verification of data line listings for efficacy endpoint data was conducted. There were no discrepancies and there was no evidence of under-reporting of adverse events. No violations were cited, and a Form FDA 483 was not issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites were inspected in support of this NDA. The primary endpoint data were verified at all sites and there was no evidence of underreporting of adverse events. No violations were found on inspection of Dr. Fleseriu's site. Inspection of Dr. Schteingart's site detected protocol violations that were isolated and not likely to impact data integrity. These violations are included in the data submitted by the sponsor to the NDA so that the review team is able to analyze the data taking into account the actual study conduct.

Based on results of these inspections it appears that data submitted by the Applicant in support of the requested indication should be considered reliable.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
12/08/2011

TEJASHRI S PUROHIT-SHETH
12/08/2011

DRUP Track Correspondence # 258

NDA 202107 Consult Request

From: [redacted] (b) (6)
Division of Metabolic and Endocrine Products

Document: **NDA for treatment of Cushing's syndrome with mifepristone**
Applicant: **Corcept Therapeutics**

Reviewer: [redacted] (b) (6)
Division of Reproductive and Urologic Products (DRUP)

Through [redacted] (b) (6)**, DRUP**
[redacted] (b) (6)**, DRUP**

Date **November 17, 2011**

Request: **Please evaluate whether pregnancy is possible in females with Cushing's disease on the proposed mifepristone doses. Do the proposed doses of mifepristone when taken chronically carry the risk of pregnancy loss in patients with Cushing's syndrome? Do additional precautions need to be given to the female patients of child-bearing age while taking mifepristone?**

Background Information:
This NDA is for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome. In the clinical trials, dosing started with 300 mg of mifepristone once per day for 14 days. After 14 days, if no clinical improvement was seen, but the drug had been well tolerated, the dose of mifepristone was increased to 600 mg once per day. After 4 weeks of dosing at 600 mg once per day, if no clinical improvement was seen, but the drug had been well tolerated, the dose could be increased to 900 mg once per day. Subjects weighing < 60 kg did not have the dose escalated beyond 900 mg once per day throughout the study. In heavier subjects, after 4 weeks of dosing at 900 mg once per day, if no clinical improvement was seen, but the drug had been well tolerated, the dose could be increased to 1200 mg once per day. If significant clinical improvement was noted, the dose of mifepristone could be maintained or reduced at the discretion of the physician. These varying doses were given to 50 subjects for up to 24 weeks in Study C1073-400; 34 subjects completed the study.

Subjects completing 24 weeks of mifepristone treatment under protocol C1073-400 were eligible to continue treatment for an additional 1 year or longer In Study C1073-415 at the discretion of the Investigator. Mifepristone at doses from 300 mg/day up to 1200 mg/day daily were used. Assessments of safety, as evaluated by physical examinations, vital signs, laboratory tests, and adverse events, were made at entry and throughout the study.

In the above studies, women of childbearing potential had to have a negative serum pregnancy test at study entry and be willing to use non-hormonal, medically acceptable methods of contraception during the study. Proposed labeling contradicts use in women

who are pregnant or may become pregnant. A black box warning states "Pregnancy must therefore be excluded before the initiation of treatment with (b) (4) and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization in which case no additional contraception is needed." [For Study 410 synopsis- see page 7 of Consult; Study 415 synopsis- see page 611.]

Note from the primary medical officer Marina Zemskova, MD: If the drug is approved, the starting dose will be 300 mg. Titration is still a review issue, but, yes, it is based on safety and efficacy, and most likely the maximum dose will be no more than 20 mg/kg (1200 mg for the patients > 60 kg weight).

Mifepristone has been studied extensively for over 30 years. French trials for medical abortion began in the 1980s. In 1988, mifepristone was approved and brought to market in France. In the US it was approved in 2000 for early medical abortion with a single dose of **600 mg** followed in 24-48 hours by 400-800 µg of misoprostol if needed. In current clinical practice, it is commonly used at a dose of 200 mg, followed by misoprostol, for medical abortion. In other countries, mifepristone has been approved for other reproductive-related indications such as emergency contraception, and in single doses up to 600 mg for both late first trimester (9–14 weeks) and second trimester (14–22 weeks) abortions.

Questions and DRUP Responses:

Question 1. Is pregnancy possible in females with Cushing's disease on the proposed mifepristone doses?

DRUP Consult Response:

Pregnancy is possible but is likely to occur at a significantly reduced rate in women with Cushing's disease who are being treated with daily doses of mifepristone of at least 300 mg. Studies have demonstrated that low daily doses of mifepristone can prevent ovulation in 13-20% of women or disrupt/delay normal endometrial maturation which is needed for implantation of an early (day 3-8 post fertilization) pregnancy.[1, 2] To our knowledge, however, there have been no adequate and well-controlled trials to assess the effectiveness of mifepristone in preventing pregnancy.

Question 2. Do the proposed doses of mifepristone when taken chronically carry the risk of pregnancy loss in patients with Cushing's syndrome?

DRUP Consult Response:

Yes.

Mifepristone alone is less effective for pregnancy termination when compared to the combined regimen mifepristone/prostaglandin. In three studies when a single or multiple doses (2 or 3) of 200 to 600 mg of mifepristone were administered alone to women ≤ 49

[1] Chen Y et al. Effects of low-dose mifepristone administration in two different 14-day regimens on the menstrual cycle and endometrial development. Contraception 2011;84:64-70.
[2] Irving Spitz. Mifepristone: where do we come from and where do we go? Clinical development over a quarter of a century. Contraception 2010;82:442-452.

days pregnant, the rate of successful termination ranged from 64 to 85%. With the addition of a prostaglandin, such as misoprostol, given 36 to 60 hours after the mifepristone, the success rate increases to 92 to 97%.

In the US trial submitted for the NDA approval of a single dose of mifepristone 600 mg for medical abortion up to 49 days pregnant, followed 24-48 hours later with 400-800 µg of misoprostol if needed, the effectiveness for a complete abortion was 92.1%, while the French data showed 95.5% effectiveness. With a combined regimen of mifepristone/prostaglandin, mifepristone 600 mg compared to 200 mg shows similar effectiveness in achieving complete abortion (2010 Cochrane review of 4 trials, RR 1.07, 95% CI 0.87 to 1.32).

Question 3. Do additional precautions need to be given to the female patients of child-bearing age while taking mifepristone?

DRUP Consult Response:

Back up nonhormonal contraception is strongly recommended throughout the use of the proposed mifepristone doses because there is a chance that a women could conceive while being treated with mifepristone. Similarly, should she become pregnant while taking mifepristone, there is a high probability of pregnancy loss. Furthermore, we recommend urine pregnancy testing at a 4-8 week interval in women with amenorrhea to reassure that pregnancy is not the cause.

A recent article[3] showed that following medical abortion with oral mifepristone 200 mg + vaginal misoprostol 800 µg ovulation occurred 20.6 ± 5.1 days (range 8-36) after mifepristone administration. Therefore, we also recommend that adequate contraception be continued after mifepristone treatment is stopped in women who do not want to become pregnant.

(b) (6)

11-17-11
DRUP Tracking # 258

[3] Schreiber CA et al. Ovulation resumption after medical abortion with mifepristone and misoprostol. Contraception 2011; 84:230-233.

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/s/

(b) (6)

11/17/2011

(b) (6)

11/18/2011

(b) (6)

11/18/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	October 26, 2011
Reviewer:	Yelena Maslov, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Zachary Oleszczuk, Pharm.D., Team Leader Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Mifepristone Tablets, 300 mg
Application Type/Number:	NDA 202107
Applicant/sponsor:	Corcept Therapeutics
OSE RCM #:	2011-1989

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1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis's (DMEPA's) evaluation of the proposed packaging, container labels and prescribing information labeling of Mifepristone Tablets for vulnerabilities to confusion that may lead to medication errors.

1.1 REGULATORY HISTORY

Mifepristone Tablets, NDA 202107, was submitted to the FDA on April 18, 2011. This NDA is a subject of a 505(b)(2) application referencing Mifeprex (NDA 020687) that was approved on September 28, 2000.

Currently, the product does not have a proprietary name. The first proposed proprietary name, (b) (4) was found unacceptable by DMEPA in OSE Review #2010-1719, dated December 28, 2010, while the product was in IND stage of development (IND 076480). The second proposed proprietary name, (b) (4), was found unacceptable by DMEPA in OSE Review #2011-1353, dated July 14, 2011, during review of the NDA. The third proposed proprietary name, Korlym, is currently under review with DMEPA.

1.2 PRODUCT INFORMATION

(b) (4) (Mifepristone) Tablets is a cortisol receptor blocking agent indicated to treat the clinical and metabolic effects of hypercortisolism in patients with endogenous Cushing's syndrome, including:

- Patients with Cushing's disease who have not adequately responded to or relapsed after surgery
- Patients with Cushing's disease who are not candidates for surgery

(b) (4)

The recommended dose of Mifepristone is 300 mg to 1200 mg (1 tablet to 4 tablets) administered orally once daily. However, for patients with severe renal function the maximum daily dose is 600 mg. It will be available in a single strength of 300 mg packaged in bottles of 28 and 280 counts. (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1], the principles of human factors, and lessons learned from the post-marketing experience, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted on April 25, 2011 (See Appendix A)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Insert Labeling submitted on April 25, 2011 (no image)

Additionally, since the reference listed drug, Mifeprex, is currently marketed and has the REMS program, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Mifeprex because errors with reference listed drug may be indicative of error that would occur with the proposed product once marketed. The AERS search conducted on July 22, 2011, used the following search terms: active ingredient "Mifepristone", trade name "Mifeprex", and verbatim term "Mifep%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". No time limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error (i.e., adverse reactions, abortion inductions).

We identified twenty-one reports (n=21) in the AERS database. Following exclusions, we evaluated one case (n=1) relevant to this review.

The case (ISR 3987400-9) from 2002 involved a wrong drug error between Mifepristone and Misoprostol. The case reported that prescription for Mifepristone 200 mg was filled with Misoprostol 200 mcg. The patient administered the wrong medication for two weeks until the error was discovered by the pharmacist. The patient did not suffer any harm. The case stated that the error occurred due to phonetic similarity between the two names, same strength, and similar measurement units (mg vs. mcg).

3 DISCUSSION

The following section discusses the medication error as well as product packaging and labeling.

3.1 MEDICATION ERROR

Mifepristone and Misoprostol are orthographically and phonetically similar and share several product characteristics. Both products share the first letter string 'Mi'. Additionally, the letter string 'epristo' in Mifepristone may appear similar to the letter string 'oprosto' in Misoprostol when scripted. When spoken, the names sound similar as well. In addition to orthographic and phonetic similarities, the products share product characteristics such as dosage form (tablet), route of administration (oral), and strength (200 mg vs. 200 mcg). This name pair also appears on ISMP's List of Confused Drug Names.[2]

Although the established names are similar, this error was reported once in 2002 and appears transient. Additionally, the proposed product, Mifepristone Tablets, will have a

[2] ISMP's List of Confused Drug Names, http://www.ismp.org/Tools/confuseddrugnames.pdf [Accessed October 26, 2011)

proprietary name that may help additional differentiation between Mifepristone and Misoprostol.

3.2 PRODUCT PACKAGING

Mifepristone will be packaged in plastic bottles with child-resistant container closures, which is acceptable for this product. The product can be repackaged into different pharmacy containers and since the dose is once tablet to four tablets daily, the package sizes (i.e., 28 count and 280 count) are appropriate.

3.3 CONTAINER LABELS

The container label carries the proposed proprietary name (b) (4). However, this name was found unacceptable by DMEPA in OSE Review 2011-1353, dated July 14, 2011. Additionally, the net quantity appears in the same size as the strength of the product, and thus, may be misinterpreted as the strength and lead to medication errors. Furthermore, a prominent triangular-shaped image in the left upper corner of the principle display panel intervenes with the proprietary name and may be distracting. Also, patient information labeling states that Mifepristone tablets should be (b) (4). However, this important information is not presented on the container labels. Thus, a statement regarding administration of the product whole, without splitting, crushing, or chewing should be made more prominent by adding it to the principle display panel of the container label.

3.4 INSERT LABELING

(b) (4)

Additionally, as stated in Section 8.6, *Renal Impairment*, the maximum dose of Mifepristone for patients with severe renal impairment (i.e., Glomerular filtration rate [GFR] is less than 30 mL/min/1.73 m^2, but not on dialysis) is 600 mg per day. This information is important for healthcare practitioners to know prior to adjusting dose of Mifepristone. However, this information is not present *Dosage and Administration* Section. Thus, the dosage in the severe renal impairment should be made more prominent by adding this information to the *Dosage and Administration* Section of the prescribing information.

Additionally, patient information labeling states that Mifepristone tablets should be split, crushed, or chewed. However, this important information is not presented in *Dosage and Administration* Section. Thus, a statement regarding administration of the product whole,

[3] Medical Abbreviations Dictionary [Internet]. MediLexicon International Ltd; © 2004-2011 [cited 2011 July 22]. Available from http://www.medilexicon.com/medicalabbreviations.php

without splitting, crushing, or chewing should be added to the *Dosage and Administration* Section.

3.5 Risk Evaluation and Mitigation Strategy (REMS)

The Applicant indicates that Mifepristone will have a REMS program and will be available through only restricted distribution. The REMS program is comprised of (b) (4) and medication guide. (b) (4) . As the part of the program female patients of child-bearing age will be ordered a pregnancy test prior to starting therapy and if treatment is interrupted for more than 14 days. Additionally, all patients will receive educational materials such as medication guide and patient information and at each visit patients will be counseled regarding the risks associated with Mifepristone treatment including the risk of pregnancy termination, adrenal insufficiency, potential hypokalemia, and drug interactions. Patients will also be educated about the need for non-hormonal, medically-acceptable contraception.

The inclusion of REMS for this product is appropriate due to multiple safety risks including termination of pregnancy and possible adverse events. Additionally, REMS helps prevent the abuse potential of this medication since Mifepristone is indicated for pregnancy termination under a proprietary name RU-486.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed packaging configuration of Mifepristone Tables is acceptable because the container closure system is child-resistant. However, container label and prescriber information labeling introduce vulnerability that can lead to medication errors. As a result we recommend labeling revisions outlined below be implemented prior to the approval of this product. Section 5.1 *Comments to the Division* contains our recommendations regarding prescribing information labeling. Section 5.2 *Comments to the Applicant* contains our recommendations regarding container labels. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Ermias Zerislassie at 301-796-0097.

4.1 Comments to the Division

1. General Comments

    a. Because there are multiple safety risks including termination of pregnancy and possible adverse events associated with this product, the Applicant proposes the implementation of Risk Evaluation and Mitigation Strategy (REMS) that will include (b) (4) and medication guide. The inclusion of Mifepristone REMS is appropriate to help reduce multiple safety risks and possible abuse potential. DMEPA requests that we are included in further evaluation of REMS.

b. Delete proprietary name (b) (4) from the prescribing information and patient information labeling and use the established name throughout labeling.

2. *Indication and Usage* Section, *Highlights of Prescribing Information* and *Full Prescribing Information*

(b) (4)

3. *Dosage and Administration* Section, *Full Prescribing Information*

a. We request addition of the Section 2.2, *Special Populations* to *Dosage and Administration* Section that will state that patients with severe renal impairment (i.e., Glomerular filtration rate [GFR] is less than 30 mL/min/1.73 m^2, but not on dialysis) should not exceed a maximum 600 mg dose per day. This dosing information is currently presented only in Section 8.6, *Renal Impairment*. We recommend this change because this information is important for dosing of patients with impaired renal function and should be made more prominent. See example below:

Patients with severe renal impairment (Glomerular filtration rate [GFR] is less than 30 mL/min/1.73 m^2, but not on dialysis): no change in the initial dose of Mifepristone is needed. Maximum dose should not exceed 600 mg per day.

b. We request that a statement be added after the last sentence in the first paragraph to Section 2.1, *Adult Dosage*, that reads "Mifepristone tablets should be taken whole. Do not split, crush, or chew." We recommend this change because this information is important for correct administration of the product and should be made more prominent.

4.2 COMMENTS TO THE APPLICANT

A. Container Labels (28 tablets and 280 tablets)

1. Delete the proprietary name (b) (4) and use the established name on the container label.

2. Once the proprietary name is identified, ensure the size of the established name is at least ½ size the letters comprising the proprietary name and has prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10(g)(2).

3. Delete or reduce size of the (b) (4) placed on top of the proprietary name in accordance with 21 CFR 202.1(a)(1). This (b) (4) is intervening matter that decreases the visibility of the proprietary name. Additionally, this graphic is prominent and distracting. However, the proprietary

[4] Medical Abbreviations Dictionary [Internet]. MediLexicon International Ltd; © 2004-2011 [cited 2011 July 22]. Available from http://www.medilexicon.com/medicalabbreviations.php

and established names, dosage form, and strength should be the most prominent items on the principle display panel.

4. Add the statement to the principle display panel that reads “Take tablets whole. Do not split, crush, or chew”. We request this change because this information is important for the correct administration of the product and thus, should be made more prominent.
5. Increase the prominence of the strength by increasing the font size. As currently presented, the strength and the net quantity (i.e., 28 tablets or 280 tablets) appear in the same prominence. As a result, the net quantity may be misinterpreted as the strength.
6. Change medication guide statement to be consistent with other medication guide statements for other product. For example, you medication guide statement can read as follows “ATTENTION PHARMACIST: Dispense attached Medication Guide to each patient”.

APPENDICES

Appendix A: Container Labels (Submitted to the FDA on April 25, 2011)

Appendix B: Case Listings from AERS database

3606826	6797254
3812740	7220567
4055210	7910627
5838355	7910628
5851866	7910635
5996567	7910641
6002829	7910811
6010334	7985454
6168417	7990198
6256372	8036780

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/s/

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10/26/2011

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10/27/2011

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10/31/2011

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	202107
Drug Name	Corlux®
Generic Name	Mifepristone
Sponsor	Corcept Therapeutics
Indication	To Reduce Effects of Hypercortisolism in Patients with Endogenous Cushing's Syndrome
Dosage Form	Tablets
Drug Class	Corticosteroid
Therapeutic Dosing Regimen	300 – 1200 mg Once-daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1200 mg Once-Daily
Submission Number and Date	SDN 001 18 Apr 2011
Review Division	DMEP/ HFD 510

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The thorough QT study (TQT) is inconclusive. The assay sensitivity was not established, as the largest lower bound of the two-sided 90% confidence interval (CI) for the placebo-adjusted, baseline-corrected QTcI (ΔΔQTcI) for moxifloxacin was less than 5 ms (Table 1). Therefore small changes in QTc interval, defined by ICH E14 guidance, cannot be excluded from the current TQT study.

In this randomized, blinded, parallel design study, 180 healthy male subjects were randomized to receive mifepristone 600 mg, mifepristone 1800 mg, placebo, and a single oral dose of moxifloxacin 400 mg. All of them finished Day 7, but only 128 subjects finished Day 14, among them, 21 were in mifepristone 1800-mg group. Overall summary of findings for analysis on Day 7 data is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for mifepristone (600 mg and 1800 mg, Day 7) and the Largest Lower Bound for Moxifloxacin (Day 14) (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
mifepristone 600 mg	12	4.2	(-0.4, 8.8)
mifepristone 1800 mg	12	7.4	(2.8, 12.0)
Moxifloxacin 400 mg*	8	6.8	(1.8, 11.9)

* The largest lower bound is after Bonferroni adjustment for 3 timepoints.

The supratherapeutic dose (1800 mg) produces mean C_{max} values 20% higher than the mean C_{max} for the therapeutic dose (600 mg) at steady-state. These concentrations are similar to those for the predicted worst case scenario (1200-mg dose in patients with mild renal impairment). At these concentrations there is no detectable relationship between mifeprisone exposure and the ΔΔQTcI-interval. However, there is a dose-dependent increase observed in the response at steady-state. It is likely that the response has reached a plateau and ΔΔQTcI-interval prolongation is not anticipated at higher exposures.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- Assay sensitivity was not established in the thorough QT study. Therefore, small increase in QTc interval cannot be ruled out under the therapeutic dose of 600 mg, even though the observed upper bound of 90% two-sided confidence interval for the largest QTc interval change is less than 10 ms. In addition, the upper bound of two-sided 90% confidence interval for the largest QTc interval change is greater than 10 ms under supratherapeutic dose. As a result, treating mifepristone as a compound with modest QTc interval prolongation (i.e., ~10 ms for the mean QT effect), as the sponsor proposed in the W&P section of the label, seems to be reasonable. Because the trial failed to demonstrate assay sensitivity, we propose that no study description should be included in the label.
- If the sponsor intends to change the label, we have the following recommendations.
    - The sponsor may further analyze the moxifloxacin data to determine why assay sensitivity was failed in the study. For example, the sponsor may analyze the moxifloxacin concentration to determine whether low QT effect in moxifloxacin is associated with decreased moxifloxacin exposure. Furthermore, the sponsor may determine whether large variability in heart rate changes was observed at nominal times where ECGs were extracted.
    - Another thorough QT study may be required; if there is no evidence that assay sensitivity can be restored from the current QT study.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL:

The sponsor proposed the following language in the label.

5.4 QT Interval Prolongation

Mifepristone and its metabolites block IKr. (b) (4) prolongs the QTc interval in a dose-related manner. There is little or no experience with high exposure, concomitant dosing with other QT-prolonging drugs, or potassium channel variants resulting in a long QT interval. To minimize risk, the lowest effective dose should always be used.

Reviewer's comment: No recommended changes from QT-IRT.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Mifepristone is a relatively selective antagonist of the progesterone receptor at low doses and also effectively blocks glucocorticoid receptors at higher doses. The effects of mifepristone on glucocorticoid receptors appear to be quite specific. Mifepristone has a high affinity for the GR II receptor but little affinity for the GR I (mineralcorticoid) receptor.

3.2 MARKET APPROVAL STATUS

Mifepristone is approved and marketed for single dose use in termination of pregnancy in several countries.

3.3 PRECLINICAL INFORMATION

From package insert (Warning and Precaution section)

"Mifepristone and its metabolites block IKr. (b) (4) prolongs the QTc interval in a dose-related manner."

(b) (4)

(b) (4)

3.4 PREVIOUS CLINICAL EXPERIENCE

From Summary of Clinical Safety (Section 2.7.4)

"This Summary of Clinical Safety comprises data from 29 clinical studies of (b) (4) (mifepristone) (also referred to as CORLUX and C1073 in older studies): These studies include two studies in the primary indication of endogenous Cushing's syndrome, 14 studies in healthy subjects (two of which included subjects with hepatic or renal impairment), nine studies in subjects with psychotic depression, three studies of olanzapine- or risperidone-induced weight gain, and one study in subjects with Alzheimer's disease.

"For the proposed indication of mifepristone in the treatment of Cushing's syndrome, the safety data from the phase 3 study (C1073-400) and its long-term extension study (C1073-415) are considered the primary safety data, and the safety data from all other studies are considered supportive.

"A total of 1349 subjects have been exposed to mifepristone in the 29 Corcept-sponsored studies of mifepristone. The longest exposure to mifepristone in these trials has been in the pivotal studies of endogenous Cushing's syndrome (studies C1073-400 and C1073-415).

"Study C1073-400 - An Open-label Study of the Efficacy and Safety of Mifepristone in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome Study C1073-400 was a 24-week, open-label study of the administration of mifepristone to subjects with Cushing's syndrome. Following a screening period of up to 6 weeks, 50 subjects began treatment with 300 mg mifepristone once daily (QD). Because the optimal dose of mifepristone for each subject was not known, dose escalation was undertaken cautiously. Doses of mifepristone ranged from 300 mg to 1200 mg.

"Study C1073-415 was an open-label extension study of the administration of mifepristone to subjects with Cushing's syndrome. Individuals completing C1073-400 were given the opportunity to enter this extension study. Subjects must have completed the C1073-400 Week 24 and 6-week follow-up study visits; during the interval between those 2 visits, mifepristone was not administered. The initial dose of mifepristone was the same dose that was being administered at the Week 24 visit in study C1073-400.

"All 50 subjects who participated in the study experienced a treatment-emergent adverse event (TEAE) at some time during the study. The most frequently reported TEAEs (occurring in 10 or more subjects [20%]) were nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy (endometrial thickening). Events occurring in ≥10% of subjects regardless of relationship to study medication are listed in Table 13 of the report (not included in the review). The majority of TEAEs were considered mild or moderate in severity.

"In study C1073-400 and its extension (study C1073-415), when hypokalemia was reported as an AE, the MedDRA dictionary coded the event as "decreased blood potassium." Seventeen subjects in study C1073-400 had reported TEAEs of decreased blood potassium (three of these 17 subjects had reported TEAEs of hypokalemia but did not have corresponding laboratory values of low potassium recorded by the central laboratory). Four subjects had potassium values that met the definition of severe hypokalemia (≤2.5 mEq/L); in three of these subjects, there were previous potassium values that were low, although not in the severe hypokalemic range, and these subjects were receiving treatment with potassium or spironolactone. The one subject who developed severe hypokalemia without a previously low potassium level had values within the normal range that were declining prior to the development of severe hypokalemia. In one of the subjects with severe hypokalemia, the event occurred at the follow-up visit when the subject had been off study drug for 6 weeks. In study C1073-415, three subjects had reported AEs of decreased blood potassium, and seven subjects overall had potassium values indicative of hypokalemia (≤3.4 mEq/L); no subjects had severe hypokalemia."

Reviewer's comments: There were no Torsade de pointes or other ventricular arrhythmias reported in mifepristone clinical programs. Hypokalemia was a common AE in all indications but was more frequent (34%) in the Cushing population. Twenty-four percent of the subjects in the Cushing population reported hypertension as a TEAE.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of mifepristone's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report C-1073-300 for the study drug mifepristone, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Thorough ECG Trial Comparing Mifepristone and Placebo

4.2.2 Protocol Number

1245.16

4.2.3 Study Dates

18 January 2006 to 20 September 2006

4.2.4 Objectives

This study was designed to evaluate the effect of mifepristone on cardiac repolarization, as detected by QT/QTc prolongation in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a double-blinded (except for the use of moxifloxacin, which was single-blinded), randomized, placebo-controlled, single-site, parallel design study in healthy male subjects.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded except for moxifloxacin.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were randomly assigned to treatment for 14 days with either of two doses of mifepristone (600 mg and 1800 mg), placebo or placebo followed by a single dose of moxifloxacin on Day 14.

- Placebo (PLAC group; six placebo tablets each day)
- Moxifloxacin (MOXI group; placebo six tablets each day plus a single dose of moxifloxacin 400 mg on Day 14)
- Mifepristone 600 mg (MIFE 600 group; two 300-mg tablets, plus four placebo tablets each day)
- Mifepristone 1800 mg (MIFE 1800 group; six 300-mg tablets each day)

4.2.6.2 Sponsor's Justification for Doses

"Due to the long half-life of mifepristone, a parallel design with multiple dosing over 14 days was chosen for this TQT study. A crossover study would have been problematic, as a prolonged washout would be required and elimination of carryover effects would be difficult to ensure. A 14-day dosing period was chosen to ensure that steady state had been obtained for both mifepristone parent and metabolites.

"The proposed clinical dose of mifepristone for endogenous Cushing's syndrome ranges from 300 mg to 1200 mg daily. A daily mifepristone dose of 1800 mg was chosen as the highest supratherapeutic dose likely to be tolerated, based on the induction of adrenal insufficiency in a Cushing's disease patient on chronic treatment up to 2000 mg. To date, the maximum dose given to human subjects has been 2000 mg per day.

"In addition to the placebo control, the study also included a positive control to demonstrate that the study was sufficiently sensitive to detect a small QTc prolongation. Moxifloxacin, a fluoroquinolone antibiotic, was used as the positive control as it has been demonstrated to reproducibly increase the QTc interval with about 8 to 14 ms in TQT studies."

Reviewer's Comment: The sponsor's selection of dose is acceptable. The sponsor chose a dose near the maximum tolerated dose that produces exposures similar to that for the clinical use high exposure scenario (1200 mg in patients with Cushing's syndrome). The CL appears to be reduced in patients with Cushing's syndrome. As a result the AUC for the maximum expected dose in the clinic (1200 mg) is 1.1-fold the AUC for the supratherapeutic dose in healthy volunteers in the TQT study.

Intrinsic factors other than disease state and extrinsic factors did not play a role in the high exposure scenario. The C_{max} and AUC of mifeprestone are increased by ~30% in patients with end stage renal disease. However, the maximum dose for patients with severe renal impairment is 600 mg. Although drug-drug interactions increased the exposure of mifepristone more than 100%, mifepristone is contraindicated for use with these strong CYP3A inhibitors.

4.2.6.3 Instructions with Regard to Meals

(b) (4) was administered after an overnight fast.

Reviewer's Comment: The proposed package insert indicates that (b) (4) *should always be taken with a meal. Taking* (b) (4) *with food has been shown to increase the exposure by as much as 60 percent. The data in support of the high clinical exposure scenario (see Appendix 6.1) from study C1073-400 was not specified in the protocol; however, the company believes that most patients took* (b) (4) *with a meal.*

4.2.6.4 ECG and PK Assessments

ECG Assessments:

Three ECGs about 1 minute apart were recorded at the corresponding times after dosing on Days -1, 7, and 14: 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 23.5 hours. The baseline time points were matched to the on-treatment time points relative to dosing on Day 7.

PK Assessments:

In the thorough ECG study, blood samples for PK analysis were obtained from all subjects within 2 hours before the first dose (Day 1). Pre-dose (trough samples) were taken on Days 10 and 12. On Days 7 and 14, blood samples were obtained pre-dose (trough level), and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 23.5 hours post-dose.

Reviewer's Comment: The timing of ECG measurements and PK sampling is sufficient to describe the time course of these endpoints over the dosing interval at steady-state.

4.2.6.5 Baseline

Time matched ECG measures at Day -1 before dose were used as baseline.

4.2.7 ECG Collection

Electrocardiograms were obtained digitally using a Mortara Instrument H-12 ECG continuous 12-lead digital recorder on Day -1 (baseline) and on Days 7 and 14. The ECGs were stored on a flash card about every 10 seconds and were not available for review until the card was received by the central ECG laboratory.

Five ECGs extracted at a total of 14 time points resulted in 70 ECGs for analysis at baseline and on Day 7 and Day 14. ECGs were measured at the central ECG laboratory on lead II in 3 beats per replicate (10-second strip) using a high-resolution manual on-screen caliper method with annotations.

Subjects were required to lie down for approximately 10 minutes prior to and 5 minutes after the scheduled ECG time point.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

One-hundred-eighty male subjects were enrolled into Part II of the study.

Table 2: Summary of Mean Demographic Data (± SD)

Characteristic	All Subjects (N=195)
Age (years)	25.5 (±6.3)
Weight (pounds)	179.3 (±24.3)
Height (inches)	69.6 (±2.7)
Body Mass Index	26.1 (±3.1)

Sources: Table 14.1, Appendix 16.2.4, Listing 16.2.4

Source: CSR, Table 11.2

Forty-five subjects were randomized to each of the four treatment groups. Overall, 39, 38, 28 and 21 subjects from the PLAC, MOXI, MIFE 600 and MIFE 1800 groups constituted the QT/QTc completers set, in total 126 subjects.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

"The protocol for study C-1073-300 was approved in January 2006 and the study was conducted between January and September 2006. It was stopped prematurely after completion of the third cohort of 60 subjects because of an unexpected frequency of adverse event.

"The study has been reanalyzed taking into account the state-of-the-art statistical methodology for TQT studies and the information available on the PK of mifepristone. Moreover, since a substantial proportion of subjects dropped out between day 7 and day 14, the primary analysis has been performed on day 7 data and additional analyses have been performed to investigate any bias that may have been introduced by this change of the analysis strategy.

"On Day 7, a supratherapeutic dose of mifepristone (1800 mg) caused a small QTc prolongation of 3 to 7 ms (ΔΔQTcI) between 6 and 20 hours post-dosing; an effect exceeding 11 ms could be excluded at all time points. On the same day, the mean ΔΔQTcI in MIFE 600 was below 5 ms and an effect exceeding 10 ms could be excluded at all post-dosing time points. On Day 14, ΔΔQTcI was somewhat larger in MIFE 1800 and reached 9 and 10 ms at 6 and 16 hours. Based on the relatively small sample size in this group (n=21), the width of the 90% confidence interval was wider and the upper

bound reached 14 and 15 ms at these time points. Similarly, ΔΔQTcI was slightly higher in MIFE 600 with a peak effect of 6.9 ms. The observed differences between Day 7 and Day 14 were small and since plasma concentrations of mifepristone and its metabolites were comparable on both days, it seems unlikely that the QTc prolongation at the level observed on Day 7 would increase further on chronic dosing. The concentration effect analysis, which correlated plasma concentrations of mifepristone and its metabolites and ΔΔQTcI separately, did not demonstrate that the observed QTc prolongation can easily be attributed to either parent or any of the metabolites alone.

"The placebo-corrected, change-from-average-baseline QTcI (ΔΔQTcI) ranged between 3 and 7 ms in MIFE 1800 from 6 to 20 hours post-dosing and the upper bound (UB) of the 2-sided 90% confidence interval (CI) exceeded 10 ms at 6 hours (10.6 ms), 14 hours (10.6 ms) and 16 hours (10.0 ms). The largest ΔΔQTcI observed in MIFE 600 was 4.6 ms at 12 hours and the UB of CI did not exceed 10 ms at any time point. The pattern was the same for ΔΔQTcF with values between 4.6 and 6.3 ms at 6 and 10 to 20 hours post-dosing in MIFE 1800 with the UB of CI exceeding 10 ms at 16 hours only (10.0). In MIFE 600, ΔΔQTcF was smaller with a peak value of 4.7 ms at 16 hours and with none of the UB of CI above 10 ms.

"Placebo-adjusted changes (ΔΔQTc) seemed somewhat larger on Day 14 as compared to Day 7 with the largest mean ΔΔQTcI of 8.8 ms (CI: 3.6 to 14.1) at 6 hours and 10.3 ms (CI: 5.4 to 15.3) at 16 hours in MIFE 1800. The upper bound of the CI exceeded 10 ms at multiple time points. In MIFE 600, mean ΔΔQTcI reached 6.9 ms at 6 and 16 hours, with the UB of CI below 12 ms."

Reviewer's Comments: The largest upper bound forΔΔQTcI was above 10 ms in mifepristone 1800-mg group, Please see the reviewer's analysis is section 5.2.

4.2.8.2.2 Assay Sensitivity

"The analysis to show assay sensitivity was based on the same model, but using Day 14 data. For the time points 2, 3 and 4 hours the contrast moxifloxacin – placebo – 5 ms has been computed and a t-distribution-based one-sided p-value calculated. The three p-values were submitted to a Hochberg procedure. If at least one of them is significant, assay sensitivity is deemed to be shown.

"The change-from-baseline QTc was only mildly or not at all prolonged at 2, 3 and 4 hours after dosing of 400 mg moxifloxacin on Day 14, whereas negative values were seen in PLAC at corresponding time points. The mean ΔΔQTcI varied between 5.0 and 6.3 ms and mean ΔΔQTcF between 4.9 and 6.4 ms and in consequence, none of the lower bounds of the CI exceeded 5 ms. The largest mean ΔΔQTc was observed at 6 hours post-dosing with similar values for ΔΔQTcI and ΔΔQTcF (8.2 ms (3.8 to 12.5) and 7.6 ms (3.1 to 12.0), respectively.

"On Day 7, the average ΔΔQTcI and ΔΔQTcF across all time points was 3.7 ms (CI: 0.9 to 6.6) and 3.7 ms (CI: 0.9 to 6.5), respectively."

Reviewer's Comments: For parallel studies, the time between baseline and treatment should be similar for moxifloxacin and drug treatment groups. The reviewer's assay sensitivity analysis using Day 14 data is in section 5.2.

4.2.8.2.3 Categorical Analysis

"At baseline, there were no subjects with a QTcI value exceeding 450 ms, whereas this was observed in 1 subject on MIFE 1800 on Day 7 and in 1 in the same group on Day 14. 1 subject had a QTcF value exceeding 450 ms at baseline and the two subjects with QTcI exceeding 450 ms on Day 7 and Day 14 respectively also had QTcF exceeding this threshold at the same timepoints. No subjects had a QTcI or QTcF value exceeding 480 ms at any time point during the study.

"No subject had an increase from baseline of QTcI or QTcF exceeding 60 ms (Table 14.3.12) on either Day 7 or Day 14."

4.2.8.2.4 Additional Analyses

"Time matched ΔΔPR values for both MIFE groups on Day 7 were consequently small at all time points. In MIFE 1800, ΔΔPR ranged between 0 and -3 ms at all post-dosing time points except at 20 hours (-6.7 ms, CI: -10.3 to -3.2 ms) and in MIFE 600 ΔΔPR was between 0 and -7 ms at all time points (Table 14.3.10.1). On Day 14, the ΔΔPR shortening was somewhat larger at late time points in MIFE 1800, ranging between -5 and -12 ms between 12 and 20 hours.

"On Day 7, no subjects in MIFE 600 or MIFE 1800 had a PR interval exceeding 200 ms with the change-from-baseline exceeding 25%, whereas 1 subject (of 45) in PLAC demonstrated such a change. On Day 14, no subjects met this outlier criterion.

"The placebo-corrected, change from baseline (ΔΔQRS) for MIFE 1800 was significantly reduced at several time points; this reduction never exceeded -2.7 ms (at 12 and 18 hours). On Day 14, mean ΔΔQRS ranged between 0.5 and -2 ms at all time points in all treatment groups.

"On Day 7, 1 subject in the placebo and 1 in moxifloxacin (who received placebo on this day), demonstrated a QRS interval exceeding 100 ms with the change-from-baseline exceeding 25%."

4.2.8.3 Safety Analysis

Of 52 subjects who discontinued Part II of the study, 45 were withdrawn due to cutaneous adverse events (AE) of rash (variously described as rash, drug sensitivity rash, urticaria, red bumps, and drug sensitivity folliculitis). In PLAC, 4 of 6 discontinuations due to AEs were cutaneous reactions, and in MOXI, MIFE 600 and MIFE 1800 the corresponding numbers were 4 of 6, 15 of 16 and 22 of 24, respectively. All of the cutaneous AEs except 3 led to discontinuation between Day 7 and Day 14.

No deaths or serious adverse events were reported over the course of the study.

Overall, "headache" was the most common AE term, reported by 43 of 195 subjects (22.0%). Of 325 total AEs reported, 68 were reports of 'headache' (20.9%). The second most common AE term was 'drug hypersensitivity' as manifest by some form of rash,

reported by 42 of 195 subjects (21.5%). Of 325 total AEs reported, 42 were reports of hypersensitivity (12.9%). The treatment group with the greatest number of AEs (144 AEs of the 325 AEs reported; 44.3%) was the mifepristone 1800-mg group.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for mifeprisone and its metabolites are presented in Table 3 (600 mg dose) and Table 4 (1800 mg dose). C_{max} and AUC values in the thorough QT study were 20% higher following administration of 1800 mg mifepristone Supra compared with 600 mg mifeprisone, the intended clinical dose.

Table 3: Day 7 and Day 14 Pharmacokinetic Parameters for 600 mg Mifepristone Dose.

		Day 7			Day 14		
Analyte		Tmax (hr)	Cmax (ng/mL)	AUC_{0-24} (hr*ng/mL)	Tmax (hr)	Cmax (ng/mL)	AUC_{0-24} (hr*ng/mL)
Mifepristone	N	29	29	29	29	29	28
	Mean (SD)	2 (1.3)	3081 (1060)	44327 (15385)	2.9 (3.9)	2410 (1021)	34703 (14743)
	%CV	68.6	34.4	34.7	131.8	42.4	42.5
RU 42633	N	29	29	27	29	29	26
	Mean (SD)	6.4 (5.5)	2277 (891)	43557 (18118)	6.6 (6.3)	1622 (725)	30783 (15931)
	%CV	86.2	39.1	41.6	95.8	44.7	51.8
RU 42698	N	29	29	28	29	29	27
	Mean (SD)	6.5 (3.7)	741 (266)	13496 (4796)	6.1 (4.1)	554 (196)	9829 (3264)
	%CV	56.6	35.9	35.5	67.2	35.4	33.2
RU 42848	N	29	29	29	29	29	29
	Mean (SD)	12.2 (8.4)	1286 (361)	24806 (7579)	11.1 (8.9)	926 (349)	16367 (5061)
	%CV	68.9	28.1	30.6	79.9	37.7	30.9

(Source: Sponsor's Thorough QT Study Report, Table 11.8)

Table 4: Day 7 and Day 14 Pharmacokinetic Parameters for 1800 mg Mifepristone.

		Day 7			Day 14		
Analyte		Tmax (hr)	Cmax (ng/mL)	AUC_{0-24} (hr*ng/mL)	Tmax (hr)	Cmax (ng/mL)	AUC_{0-24} (hr*ng/mL)
Mifepristone	N	21	21	21	21	21	20
	Mean (SD)	2.6 (1.4)	3416 (941)	51165 (13918)	2.8 (1.5)	2926 (810)	39359 (12319)
	%CV	53	27.5	27.2	54.8	27.7	31.3
RU 42633	N	21	21	20	21	21	17
	Mean (SD)	6.4 (4.3)	2216 (505)	43494 (9025)	8.4 (7.5)	1754 (428)	30131 (8471)
	%CV	66.8	22.8	20.8	89.3	24.4	28.1
RU 42698	N	21	21	21	21	21	18
	Mean (SD)	6 (3.4)	667 (210)	12832 (4480)	7.7 (4.8)	547 (188)	9862 (4098)
	%CV	55.7	31.5	34.9	62.3	34.3	41.5
RU 42848	N	21	21	21	21	21	21
	Mean (SD)	9.4 (9.2)	1366 (330)	25890 (6129)	10.7 (9.7)	1057 (295)	17155 (4815)
	%CV	97.7	24.2	23.7	90.6	27.9	28.1

(Source: Sponsor's Thorough QT Study Report, Table 11.9)

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 5, it appears that QTcI had smaller absolute slopes than QTcF. Therefore, QTcI is a better correction method for the study data.

Table 5: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI	diff p value
Overall	0.02325	0.02101	0.20193
Mifepristone 1800 mg	0.02221	0.01576	0.05344
Mifepristone 600 mg	0.02185	0.01594	0.12251
Moxifloxacin	0.01986	0.01866	0.74193
Placebo	0.02913	0.03452	0.11138

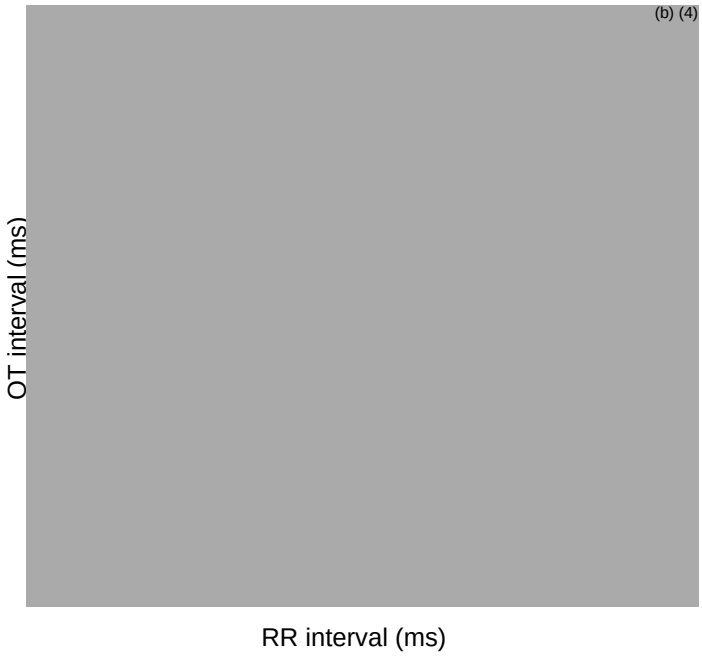
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it also appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment									
	Mifepristone 1800 mg		Mifepristone 600 mg		Moxifloxacin		Placebo		Overall	
Method	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcF	43	0.0023	42	0.0024	43	0.0029	45	0.0023	173	0.0025
QTcI	43	0.0015	41	0.0018	42	0.0027	45	0.0023	171	0.0021

The relationship between different correction methods and RR is presented in Figure 1.

Figure 1: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Mifepristone

The statistical reviewer used linear model by time point to analyze the ΔQTcI effect. The model includes gender, baseline values as covariates. The analysis results are listed in the following tables.

Table 7: Analysis Results of ΔQTcI and ΔΔQTcI for Treatment Group = Mifepristone 600 mg on Day 7

	Mifepristone 600 mg	Placebo	ΔΔQTcI	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0	-3.0	-1.8	-1.2	(-6.1, 3.7)
1	-5.4	-5.4	-0.0	(-4.6, 4.6)
2	-8.2	-9.6	1.3	(-3.1, 5.8)
3	-1.9	-2.7	0.7	(-4.0, 5.4)
4	1.7	-0.1	1.8	(-2.9, 6.5)
6	0.1	-3.6	3.7	(-1.3, 8.8)
8	-7.3	-4.5	-2.8	(-7.7, 2.1)
10	-6.4	-7.1	0.7	(-3.7, 5.1)
12	-1.3	-5.5	4.2	(-0.4, 8.8)
14	-3.6	-6.1	2.6	(-2.0, 7.1)
16	-1.4	-4.3	2.9	(-2.0, 7.9)
18	-4.3	-2.4	-1.9	(-7.1, 3.4)
20	-4.2	-4.5	0.3	(-5.0, 5.5)
23.5	-0.3	1.9	-2.2	(-7.0, 2.7)

Table 8: Analysis Results of ΔQTcI and ΔΔQTcI for Treatment Group = Mifepristone 1800 mg on Day 7

	Mifepristone 1800 mg	Placebo	ΔΔQTcI	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0	-1.3	-1.8	0.5	(-4.3, 5.3)
1	-3.7	-5.4	1.7	(-2.8, 6.2)
2	-5.8	-9.6	3.8	(-0.6, 8.2)
3	-0.3	-2.7	2.4	(-2.3, 7.1)
4	-0.1	-0.1	-0.0	(-4.7, 4.6)
6	2.4	-3.6	6.0	(1.0, 11.0)
8	-0.7	-4.5	3.8	(-1.0, 8.6)
10	0.4	-7.1	7.6	(3.2, 11.9)
12	1.9	-5.5	7.4	(2.8, 12.0)
14	1.1	-6.1	7.3	(2.7, 11.8)
16	1.4	-4.3	5.7	(1.0, 10.5)
18	1.7	-2.4	4.2	(-0.9, 9.2)
20	-2.1	-4.5	2.4	(-2.7, 7.5)
23.5	-0.2	1.9	-2.1	(-6.9, 2.7)

The largest upper bounds of the 2-sided 90% CI for the mean difference between mifepristone 600 mg and placebo, and between mifepristone 1800 mg and placebo were 8.8 ms and 12.0 ms, respectively.

The reviewer also used data on Day 14 as well as time-averaged baseline instead of time-matched baseline. The results are similar: the upper bounds of ΔΔQTcI for mifepristone 600 mg are all below 10 ms but the upper bounds of ΔΔQTcI for mifepristone 1800 mg are all above 10 ms.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data on Day 14. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval considering Bonferroni multiple endpoint adjustment of 3 time points is -4.3 ms , which indicates that an at least 5 ms QTcI effect for moxifloxacin was not detected from the study. The reviewer also used time-averaged baseline to

compute ΔΔQTcI, as well as ΔΔQTcI for moxifloxacin on Day 7, and the conclusion is the same.

Table 9: Analysis Results of ΔQTcI and ΔΔQTcI for Moxifloxacin on Day 14

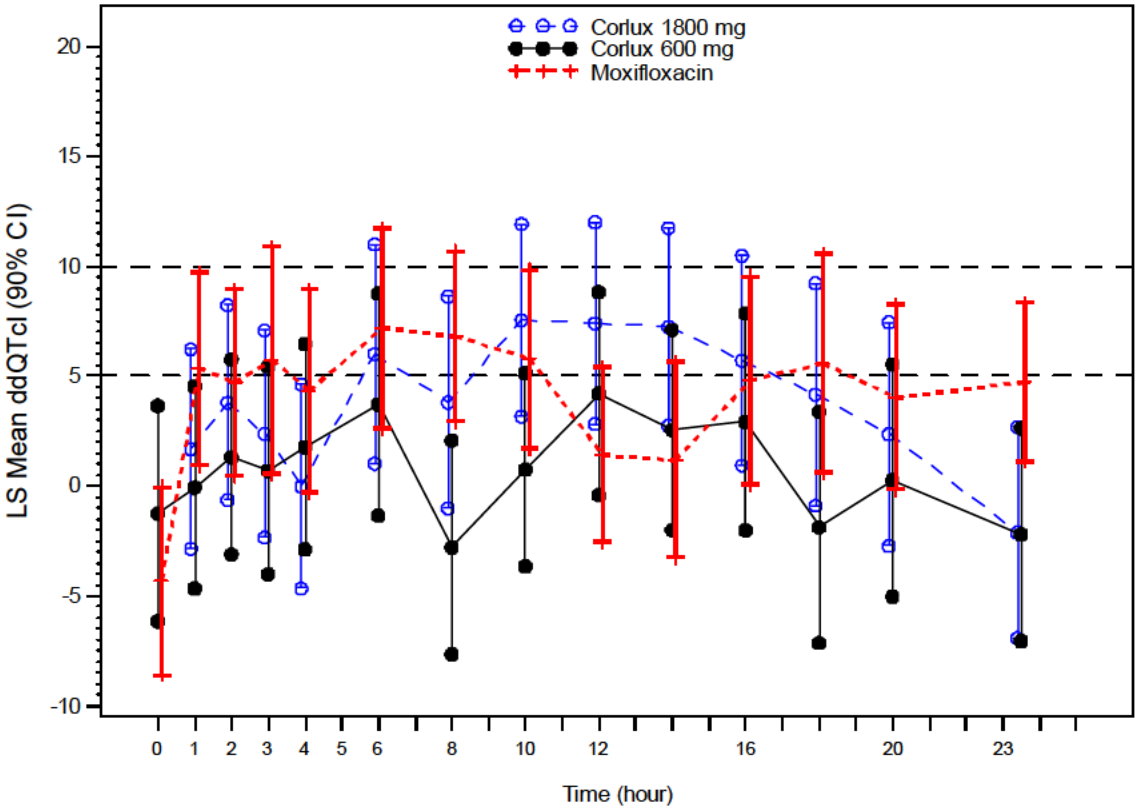
	Moxifloxacin	Placebo	ΔΔQTcI	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0	-4.4	-0.1	-4.3	(-9.9, 1.3)
1	2.5	-2.8	5.3	(-0.4, 11.0)
2	-3.9	-8.5	4.7	(-0.9, 10.2)
3	3.4	-2.3	5.7	(-1.0, 12.5)
4	6.0	1.7	4.3	(-1.7, 10.3)
6	-0.3	-7.5	7.2	(1.3, 13.1)
8	-0.1	-6.9	6.8	(1.8, 11.9)
10	0.6	-5.2	5.8	(0.4, 11.1)
12	-3.5	-5.0	1.4	(-3.8, 6.6)
14	-2.9	-4.1	1.2	(-4.6, 7.0)
16	-2.4	-7.2	4.8	(-1.3, 11.0)
18	4.1	-1.5	5.6	(-0.9, 12.1)
20	-0.8	-4.8	4.1	(-1.4, 9.5)
23.5	1.1	-3.6	4.7	(0.0, 9.4)

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of ΔΔQTcI Over Time

The following figure displays the time profile of ΔΔQTcI for different treatment groups.

Figure 2: Mean and 90% CI ΔΔQTcI Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcI values are ≤450 ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

Table 10: Categorical Analysis for QTcI

	Total N		Value<=450 ms		450 ms<Value<=480 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Baseline	178	2270	177 (99.4%)	2269 (100%)	1 (0.6%)	1 (0.0%)
mifepristone 1800 mg	43	556	42 (97.7%)	554 (99.6%)	1 (2.3%)	2 (0.4%)
mifepristone 600 mg	42	538	42 (100%)	538 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin	39	498	39 (100%)	498 (100%)	0 (0.0%)	0 (0.0%)
Placebo	45	585	45 (100%)	585 (100%)	0 (0.0%)	0 (0.0%)

Table 11 lists the categorical analysis results for ΔQTcI. No subject's change from baseline was above 60 ms.

Table 11: Categorical Analysis of ΔQTcI

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
mifepristone 1800 mg	43	547	37 (86.0%)	540 (98.7%)	6 (14.0%)	7 (1.3%)
mifepristone 600 mg	41	517	36 (87.8%)	512 (99.0%)	5 (12.2%)	5 (1.0%)
Moxifloxacin	38	480	35 (92.1%)	477 (99.4%)	3 (7.9%)	3 (0.6%)
Placebo	45	572	43 (95.6%)	567 (99.1%)	2 (4.4%)	5 (0.9%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12 and Table 13. The largest upper limits of 90% CI for the HR mean differences between mifepristone 600 mg and placebo, and between mifepristone 1800 mg and placebo were 8.3 bpm and 9.3 bpm, respectively.

Table 12: Analysis Results of ΔHR and ΔΔHR for Treatment Group = Mifepristone 600 mg on Day 7

	Mifepristone 600 mg	Placebo	ΔΔHR	
Time/(h)	Mean (bpm)	Mean (bpm)	Diff LS Mean bpm	90% CI (bpm)
0	4.1	4.7	-0.6	(-4.9, 3.7)
1	5.1	6.6	-1.6	(-4.8, 1.7)
2	0.6	-0.8	1.4	(-2.4, 5.2)
3	-1.6	-2.4	0.9	(-3.1, 4.8)
4	1.5	-1.4	2.9	(-0.9, 6.6)
6	11.4	7.4	4.0	(-0.2, 8.3)
8	8.5	8.0	0.5	(-3.8, 4.8)
10	8.2	4.3	4.0	(0.2, 7.7)
12	3.0	3.2	-0.2	(-4.9, 4.4)
14	2.4	1.9	0.5	(-3.6, 4.5)
16	4.6	5.4	-0.7	(-4.8, 3.3)
18	6.5	7.2	-0.7	(-5.1, 3.8)
20	7.8	6.7	1.1	(-2.7, 4.8)
23.5	3.3	2.1	1.2	(-3.2, 5.5)

Table 13: Analysis Results of ΔHR and ΔΔHR for Treatment Group = Mifepristone 1800 mg on Day 7

	Mifepristone 1800 mg	Placebo	ΔΔHR	
Time/(h)	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0	4.0	4.7	-0.8	(-5.5, 4.0)
1	9.6	6.6	3.0	(-0.6, 6.6)
2	1.9	-0.8	2.7	(-1.5, 6.9)
3	1.0	-2.4	3.5	(-0.9, 7.9)
4	2.4	-1.4	3.8	(-0.4, 8.0)
6	11.9	7.4	4.5	(-0.2, 9.3)
8	9.4	8.0	1.4	(-3.4, 6.1)
10	7.7	4.3	3.4	(-0.7, 7.6)
12	4.6	3.2	1.3	(-3.7, 6.4)
14	5.4	1.9	3.5	(-0.9, 8.0)
16	6.7	5.4	1.4	(-3.1, 5.8)
18	8.5	7.2	1.3	(-3.5, 6.1)
20	8.2	6.7	1.4	(-2.6, 5.5)
23.5	3.6	2.1	1.4	(-3.2, 6.1)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14 and Table 15. The largest upper limits of 90% CI for the PR mean differences between mifepristone 600 mg and placebo, and between mifepristone 1800 mg and placebo were 8.3 ms and 9.3 ms, respectively.

The outlier analysis results for PR are presented in Table 16.

Table 14: Analysis Results of ΔPR and ΔΔPR for Treatment Group = Mifepristone 600 mg on Day 7

	Mifepristone 600 mg	Placebo	ΔΔPR	
Time/(h)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0	-2.5	3.1	-5.6	(-10.4, -0.7)
1	-3.5	0.4	-4.0	(-9.0, 1.1)
2	-3.9	1.1	-5.0	(-10.0, -0.0)
3	-2.1	3.8	-5.9	(-10.9, -0.9)
4	-1.1	6.4	-7.5	(-12.8, -2.1)
6	-0.0	1.8	-1.9	(-6.9, 3.2)
8	-5.6	0.1	-5.7	(-10.2, -1.2)
10	-7.1	-0.5	-6.6	(-11.2, -2.0)
12	-2.8	3.2	-5.9	(-11.0, -0.9)
14	-2.5	3.9	-6.4	(-11.8, -1.0)
16	-5.8	1.5	-7.2	(-12.7, -1.8)
18	-7.5	0.4	-8.0	(-13.4, -2.5)
20	-8.1	0.8	-9.0	(-14.0, -3.9)
23.5	-1.6	2.6	-4.2	(-9.8, 1.5)

Table 15: Analysis Results of ΔPR and ΔΔPR for Treatment Group = Mifepristone 1800 mg on Day 7

	Mifepristone 1800 mg	Placebo	ΔΔPR	
Time/(h)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0	0.2	3.1	-2.9	(-8.2, 2.4)
1	-0.9	0.4	-1.3	(-7.0, 4.3)
2	0.5	1.1	-0.6	(-6.2, 5.0)
3	1.6	3.8	-2.3	(-7.9, 3.4)
4	0.4	6.4	-6.0	(-12.0, 0.1)
6	3.3	1.8	1.4	(-4.1, 7.0)
8	-0.3	0.1	-0.5	(-5.5, 4.5)
10	-0.6	-0.5	-0.1	(-5.2, 5.0)
12	-3.9	3.2	-7.1	(-12.7, -1.5)
14	2.7	3.9	-1.2	(-7.1, 4.7)
16	-2.2	1.5	-3.7	(-9.6, 2.2)
18	-6.7	0.4	-7.1	(-13.1, -1.1)
20	-9.0	0.8	-9.9	(-15.4, -4.3)
23.5	4.8	2.6	2.3	(-3.9, 8.4)

Table 16: Categorical Analysis for PR

	Total		Value<=200 ms		Value>200 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Baseline	178	2270	169 (94.9%)	2243 (98.8%)	9 (5.1%)	27 (1.2%)
mifepristone 1800 mg	43	556	42 (97.7%)	549 (98.7%)	1 (2.3%)	7 (1.3%)
mifepristone 600 mg	42	538	42 (100%)	538 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin	39	498	38 (97.4%)	493 (99.0%)	1 (2.6%)	5 (1.0%)
Placebo	45	585	43 (95.6%)	582 (99.5%)	2 (4.4%)	3 (0.5%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 17 and Table 18. The largest upper limits of 90% CI for the QRS mean differences between mifepristone 600 mg and placebo, and between mifepristone 1800 mg and placebo were 1.6 ms and 3.2 ms, respectively. There is one subjects who experienced QRS interval greater than 110 ms in mifepristone 1800-mg group.

The outlier analysis results for QRS are presented in Table 19.

Table 17: Analysis Results of ΔQRS and ΔΔ QRS for Treatment Group = Mifepristone 600 mg on Day 7

	Mifepristone 600 mg	Placebo	ΔΔQRS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0	-0.4	1.0	-1.4	(-3.5, 0.7)
1	-0.5	0.7	-1.2	(-3.1, 0.8)
2	-0.6	0.9	-1.5	(-3.7, 0.6)
3	-0.8	0.3	-1.1	(-3.2, 1.1)
4	-0.8	0.9	-1.7	(-3.8, 0.4)
6	0.8	1.6	-0.8	(-2.7, 1.1)
8	-0.1	0.7	-0.9	(-2.7, 0.9)
10	0.4	0.7	-0.3	(-2.1, 1.6)
12	-0.5	0.8	-1.3	(-3.1, 0.5)
14	-0.7	0.1	-0.8	(-2.8, 1.2)
16	-1.4	-1.0	-0.4	(-2.5, 1.6)
18	-1.9	-0.3	-1.6	(-3.6, 0.5)
20	-1.2	-0.6	-0.6	(-2.5, 1.3)
23.5	0.3	1.5	-1.2	(-3.2, 0.8)

Table 18: Analysis Results of Δ QRS and ΔΔ QRS for Treatment Group = Mifepristone 1800 mg on Day 7

	Mifepristone 1800 mg	Placebo	ΔΔQRS	
Time/(h)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0	0.0	1.0	-0.9	(-3.3, 1.4)
1	-0.0	0.7	-0.7	(-2.8, 1.4)
2	0.7	0.9	-0.2	(-2.7, 2.2)
3	0.9	0.3	0.6	(-1.8, 3.0)
4	1.8	0.9	0.9	(-1.5, 3.2)

	Mifepristone 1800 mg	Placebo	ΔΔQRS	
Time/(h)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
6	2.2	1.6	0.6	(-1.5, 2.7)
8	1.0	0.7	0.3	(-1.7, 2.3)
10	1.1	0.7	0.5	(-1.6, 2.5)
12	-0.3	0.8	-1.1	(-3.1, 0.9)
14	0.1	0.1	-0.1	(-2.2, 2.1)
16	-0.5	-1.0	0.5	(-1.7, 2.7)
18	-1.7	-0.3	-1.3	(-3.6, 0.9)
20	-0.5	-0.6	0.1	(-1.9, 2.2)
23.5	1.7	1.5	0.2	(-1.9, 2.4)

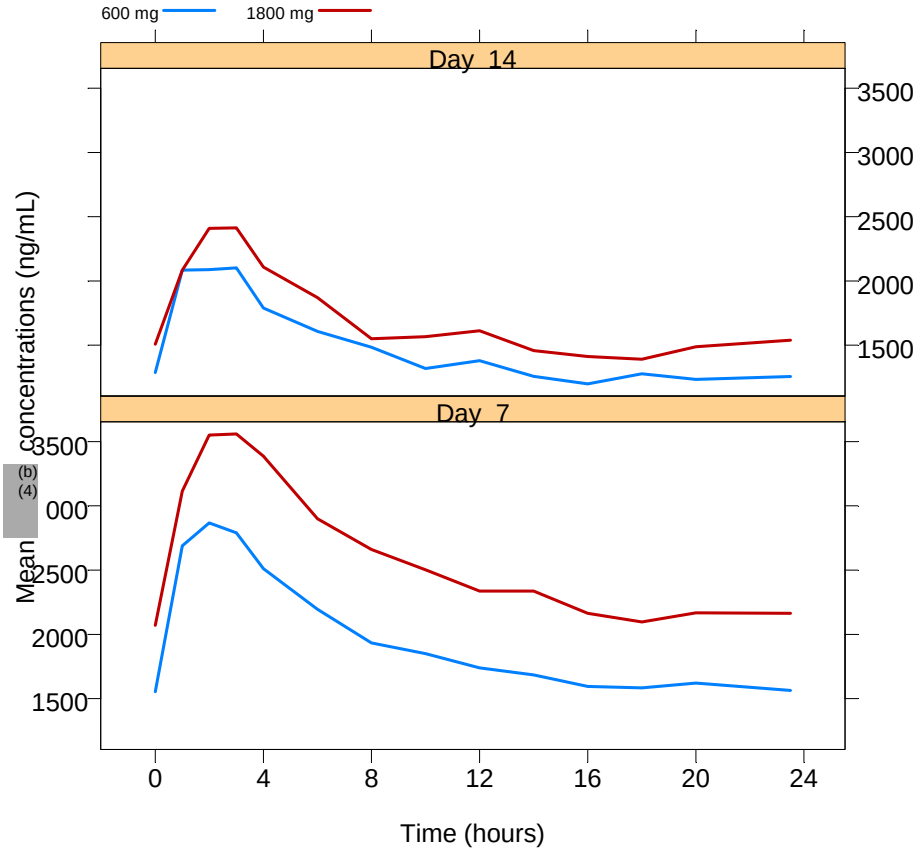
Table 19: Categorical Analysis for QRS

	Total		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	178	2270	112 (62.9%)	1852 (81.6%)	63 (35.4%)	402 (17.7%)	3 (1.7%)	16 (0.7%)
Mifepristone 1800 mg	43	556	20 (46.5%)	432 (77.7%)	22 (51.2%)	115 (20.7%)	1 (2.3%)	9 (1.6%)
Mifepristone 600 mg	42	538	27 (64.3%)	462 (85.9%)	15 (35.7%)	76 (14.1%)	0 (0.0%)	0 (0.0%)
Moxifloxacin	39	498	27 (69.2%)	402 (80.7%)	12 (30.8%)	96 (19.3%)	0 (0.0%)	0 (0.0%)
Placebo	45	585	24 (53.3%)	425 (72.6%)	17 (37.8%)	128 (21.9%)	4 (8.9%)	32 (5.5%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 3.

Figure 3: Mean Mifepristone Concentration-time Profiles for 600 mg (Blue Line) and 1800 mg Mifepristone (Red Line)



5.3.1 Mifepristone Concentration-QTcI Analysis

The relationship between ΔΔ QTcI and mifepristone concentrations was investigated by linear mixed-effects modeling. The relationship between mifepristone metabolite concentrations and ΔΔ QTcI was also explored but changes in ΔΔ QTcI were not better explained by the metabolite concentrations. The analysis below shows the relationship between the metabolite and ΔΔ QTcI.

The following three linear models were considered:

- Model 1 is a linear model with an intercept;
- Model 2 is a linear/ model with mean intercept fixed to 0 (with variability);
- Model 3 is a linear model with no intercept.

Table 20 summarizes the results of the mifepristone concentration - QTcI analyses. Model 1 was used for further analysis since the model with a positive intercept was found

to fit the data best. The predicted ΔΔ QTcI at mean peak mifepristone concentration can be found in Table 21.

Table 20: Exposure-Response Analysis of Mifepristone Associated ΔΔQTcI Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ddQTcI = Intercept + slope * Mifepristone Concentration		
Intercept (ms)	3.45 (1.53; 5.37) 0.0039	7.07
Slope (ms per ng/mL)	0.000164 (0.00092; 0.000592) 0.718	2.23
Residual Variability (ms)	10.57	--
Model 2: ddQTcI = Intercept + slope * Mifepristone Concentration (Fixed Intercept)		
Intercept (ms)	0	7.78
Slope (ms per ng/mL)	0.00089 (0.000409; 0.00137) 0.003	2.46
Residual Variability (ms)	10.57	--
Model 3: ddQTcI = slope * Mifepristone Concentration (No Intercept)		
Slope (ms per ng/mL)	0.0013 (0.000732; 0.00187) 0.0003	2.88
Residual Variability (ms)	10.81	--

Table 21: Predicted Change of ΔΔQTcI Interval at Mean Peak Mifepristone Concentration using Model 1.

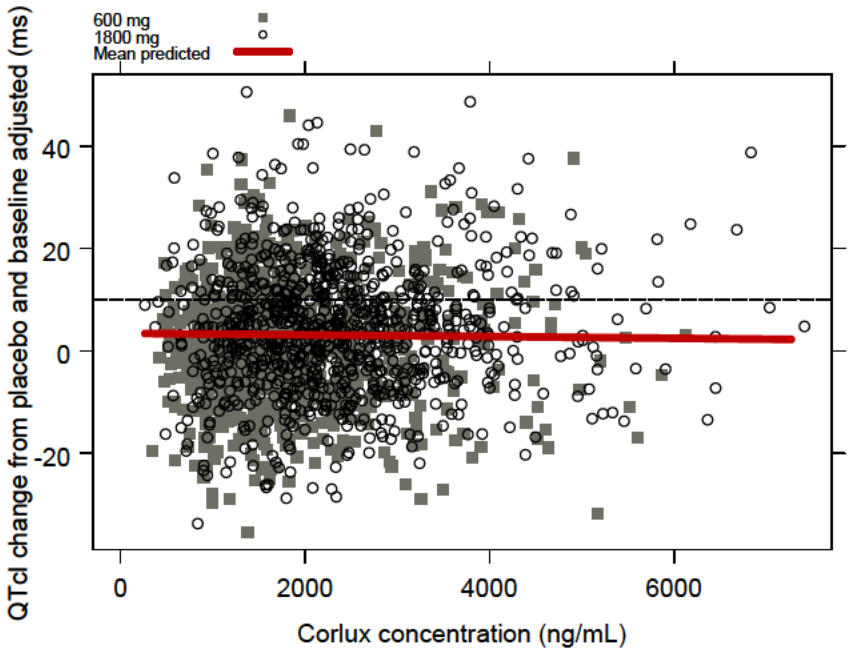
Dose Group	Predicted change in ΔΔ QTcI interval (ms)	
	Mean	90% Confidence Interval
Mifepristone 600 mg		
Mean Metabolite C_{max} (2250 ng/mL)	3.08	(1.85; 4.31)
Mifepristone 1800 mg		
Mean Metabolite C_{max} (2800 ng/mL)	2.99	(1.62, 4.35)

The relationship between mifepristone concentrations and ΔΔ QTcI is visualized in Figure 4 where the raw data is shown on top together with the population predictions.

The goodness-of-fit is illustrated in the bottom left graph of Figure 4 showing the observed median-quantile concentrations and associated mean ΔΔ QTcI (90% CI) together with the mean (90% CI) predicted ΔΔ QTcI (black line with shaded grey area).

The mean (90% CI) predicted ΔΔ QTcI at mean C_{max} is shown in the bottom right graph of Figure 4.

Figure 4 : ΔΔ QTcI vs. Mifepristone Concentration.



Reviewer's Comments: The relationship between mifepristone concentrations and ΔΔQTcI prolongation appears to be flat. This is likely because the change in ΔΔQTcI has reached a plateau by day 14. Based on this, increasing exposures further is not anticipated to increase the ΔΔQTcI interval.

5.4 Clinical Assessments

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 91.5% of the ECGs were annotated in the primary lead II, with less than 1% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

One subject had a PR>200 ms and another had a QRS >110 ms at baseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

<table>
<tr><td>Therapeutic dose</td><td>The recommended starting dose is 300 mg once daily (OD). Based on assessments of clinical response and tolerability, doses may be increased to 600 mg OD. Further escalation in 300 mg-increments to a maximum of 1200 mg OD may be appropriate in some patients, with increased monitoring for risk factors associated with the drug. [(b) (4)] must be given as a single daily dose. [(b) (4)] should always be taken with a meal.</td></tr>
<tr><td>Maximum tolerated dose</td><td>1800 mg OD in healthy subjects and up to 1200 mg in Cushing's Syndrome Patients</td></tr>
<tr><td>Principal adverse events (Study C1073-400)</td><td>Treatment Emergent Adverse Events Occurring in ≥10% of Cushing's Syndrome Patients Receiving [(b) (4)]
<table>
<tr><th>Body System/Adverse Reaction</th><th>Percent of Patients Reporting Event</th></tr>
<tr><td>Gastrointestinal disorders</td><td></td></tr>
<tr><td>Nausea</td><td>48.0</td></tr>
<tr><td>Vomiting</td><td>26.0</td></tr>
<tr><td>Dry mouth</td><td>18.0</td></tr>
<tr><td>Diarrh a</td><td>12.0</td></tr>
<tr><td>Constipation</td><td>10.0</td></tr>
<tr><td>General disorders and administration/site conditions</td><td></td></tr>
<tr><td>Fatigue</td><td>48.0</td></tr>
<tr><td>Edema peripheral</td><td>26.0</td></tr>
<tr><td>Pain</td><td>14.0</td></tr>
<tr><td>Nervous system disorders</td><td></td></tr>
<tr><td>Headache</td><td>44.0</td></tr>
<tr><td>Dizziness</td><td>22.0</td></tr>
<tr><td>Somnolence</td><td>10.0</td></tr>
<tr><td>Musculoskeletal and connective tissue disorders</td><td></td></tr>
<tr><td>Arthralgia</td><td>30.0</td></tr>
<tr><td>Back pain</td><td>16.0</td></tr>
<tr><td>Myalgia</td><td>14.0</td></tr>
<tr><td>Pain in extremity</td><td>12.0</td></tr>
<tr><td>Investigations</td><td></td></tr>
<tr><td>Blood potassium decreased</td><td>34.0</td></tr>
<tr><td>Thyroid function test abnormal</td><td>18.0</td></tr>
<tr><td>Infections and infestations</td><td></td></tr>
<tr><td>Sinusitis</td><td>14.0</td></tr>
<tr><td>Nasopharyngitis</td><td>12.0</td></tr>
<tr><td>Metabolism and nutrition disorders</td><td></td></tr>
<tr><td>Decreased appetite</td><td>20.0</td></tr>
<tr><td>Anorexia</td><td>10.0</td></tr>
<tr><td>Vascular disorders</td><td></td></tr>
<tr><td>Hypertension</td><td>24.0</td></tr>
<tr><td>Reproductive system and breast disorders</td><td></td></tr>
<tr><td>Endometrial hypertrophy</td><td>20.0</td></tr>
<tr><td>Respiratory, thoracic, and mediastinal disorders</td><td></td></tr>
<tr><td>Dyspnea</td><td>16.0</td></tr>
<tr><td>Psychiatric disorders</td><td></td></tr>
<tr><td>Anxiety</td><td>10.0</td></tr>
</table></td></tr>
</table>

<table>
<tr><td rowspan="2">Maximum dose tested (Studies C1073-20, 27 and 300)</td><td>Single Dose</td><td>1800 mg to fasted subjects, 1200 mg with food</td></tr>
<tr><td>Multiple Dose</td><td>1800 mg OD for 14 days to fasted subjects, 1200 mg OD for 7 days to healthy subjects with a medium fat (34%) meal</td></tr>
<tr><td rowspan="2">Exposures Achieved at Maximum Tested Dose</td><td>Single Dose (Study C1073-20)</td><td>PK data not available for 1800 mg to fasted subjects

Mean (%CV) for C_{max} and AUC_{inf} from 1200 mg with a standard high fat meal:

<table>
<tr><th>Analyte</th><th>C_{max} (ng/mL)</th><th>AUC_{inf} (ng.hr/mL)</th></tr>
<tr><td>Mifepristone</td><td>3830 (35)</td><td>206633 (46)</td></tr>
<tr><td>RU 42633</td><td>3022 (30)</td><td>273314 (39)</td></tr>
<tr><td>RU 42698</td><td>705 (27)</td><td>73165 (48)</td></tr>
<tr><td>RU 42848</td><td>1555 (33)</td><td>216544 (34)</td></tr>
</table></td></tr>
<tr><td>Multiple Dose (Studies C1073-300 and C1073-27)</td><td>Mean (%CV) for C_{max} and AUC_{24} on days 7 and 14 for fasted subjects from study C1073-300 at 1800 mg/day (includes those who terminated early prior to day 14):
<table>
<tr><th>Analyte</th><th>Day</th><th>C_{max} (ng/mL)</th><th>AUC_{24} (ng.hr/mL)</th></tr>
<tr><td>Mifepristone</td><td>7</td><td>3922 (34.8)</td><td>59475 (33.5)</td></tr>
<tr><td>RU 42633</td><td>7</td><td>2302 (31.5)</td><td>46139 (29.0)</td></tr>
<tr><td>RU 42698</td><td>7</td><td>796 (35.7)</td><td>15439 (35.7)</td></tr>
<tr><td>RU 42848</td><td>7</td><td>1566 (32.5)</td><td>29961 (33.7)</td></tr>
<tr><td>Mifepristone</td><td>14</td><td>3205 (32.4)</td><td>44545 (34.6)</td></tr>
<tr><td>RU 42633</td><td>14</td><td>1902 (23.8)</td><td>35259 (28.7)</td></tr>
<tr><td>RU 42698</td><td>14</td><td>614 (39.9)</td><td>11511 (41.4)</td></tr>
<tr><td>RU 42848</td><td>14</td><td>1429 (47.5)</td><td>25687 (55.5)</td></tr>
</table>
Mean (%CV) for C_{max} (ng/mL) and AUC_{24} (ng.hr/mL) on day 7 for subjects treated in study C1073-27 with 1200 mg/d with a medium fat (34%) meal:
<table>
<tr><th>Analyte</th><th>C_{max} (ng/mL)</th><th>AUC_{24} (ng hr/mL)</th></tr>
<tr><td>Mifepristone</td><td>5237 (28)</td><td>75428 (27)</td></tr>
<tr><td>RU 42633</td><td>2264 (30)</td><td>48858 (28)</td></tr>
<tr><td>RU 42698</td><td>850 (30)</td><td>17601 (30)</td></tr>
<tr><td>RU 42848</td><td>1867 (31)</td><td>41571 (31)</td></tr>
</table></td></tr>
</table>

Range of linear PK (Shi (1993), Heikinheimo (1989a), Section 2.7.2.3)	Both single-dose and multiple-dose studies in the literature demonstrate nonlinearity of the parent compound at doses greater than 25 mg. In a crossover study comparing single doses ranging from 25 to 600 mg (a 24-fold increase) in non-pregnant women, there was only a 3-fold increase in the maximal mifepristone concentration (C_{max}) and a 10-fold increase in the mifepristone AUC. A parallel-group study of volunteers receiving 12.5, 25, 50, or 100 mg of mifepristone twice per day for 4 days similarly showed only a 2.3-fold increase in trough serum concentrations over this 8-fold dose range. Data from Corcept-sponsored single and multiple-dose studies to fasted volunteers and patients also demonstrated less than proportional increases in exposure with increasing dose. Multiple-dose data pooled from Corcept-sponsored multiple dose studies with healthy fasted volunteers are summarized below:

Parameter	Dose Level	N	Geo. Mean	%CV
C_{max} (ng/mL)	300 mg	20	2604	35.6
	600 mg	52	3041	34.8
	1200 mg	30	3151	37.7
	1800 mg	58	3701	34.8
% increase	300 to 600		16.8	
	600 to 1200		3.6	
	1200 to 1800		17.5	
AUC_{24} (ng.hr/mL)	300 mg	20	34836	32.5
	600 mg	52	43564	35.5
	1200 mg	30	44137	36.1
	1800 mg	58	56349	33.5
% increase	300 to 600		25.1	
	600 to 1200		1.3	
	1200 to 1800		27.7	
C_{trough} (ng/mL)	300 mg	20	1166	27.7
	600 mg	52	1461	38.2
	1200 mg	30	1493	35.8
	1800 mg	58	1945	33.8
% increase	300 to 600		25.3	
	600 to 1200		2.2	
	1200 to 1800		30.3	

<table>
<tr><td>Accumulation at steady state
(Section 2.7.2.3)</td><td colspan="2">Data were pooled across Corcept-sponsored multiple-dose studies in fasted healthy volunteers with PK evaluations after the 1st dose and at presumed steady-state. The multiple-dose to single-dose ratios for the mifepristone PK parameters are summarized below.

<table><tr><th>Parameter</th><th>N</th><th>Geo. Mean</th><th>%CV</th></tr><tr><td>MD/SD C_{max}</td><td>52</td><td>1.219</td><td>31.6</td></tr><tr><td>MD/SD AUC_{24}</td><td>52</td><td>1.547</td><td>25.1</td></tr></table></td></tr>
<tr><td>Metabolites
(Jan (1997), Wu (1999), Lahteenmaki (1987), Heikinheimo (1987))</td><td colspan="2">As reported in the literature, cytochrome P450 3A4 (CYP3A4) has been shown to be the only isoenzyme involved in mifepristone metabolism in human liver microsomes. Two of the known active metabolites are the product of demethylation (monodemethylated RU 42633 and di-demethylated RU 42848), while a third active metabolite (RU 42698) results from nondemethylated hydroxylation. In addition, another three minor metabolites (M4, M5, M6) resulting from further hydroxylation or acetylation were identified in S9 protein fractions from human hepatocytes. However, these additional metabolites only account for 15% of the analytes at the end of the 60 minute incubation period, Also reported in the literature, mifepristone and its three metabolites (RU 42633, RU 42848 and RU 42689) have greater affinity for the glucocorticoid receptor (100%, 61%, 48%, and 45%, respectively) than either dexamethasone (23%) or cortisol (9%). Based on plasma concentrations and receptor affinity, the theoretical contribution of the metabolites to antiglucocorticoid activity is estimated as 47% at 1 hour and 61% at 24 hours.</td></tr>
<tr><td rowspan="3">Absorption</td><td>Absolute/Relative Bioavailability
(Summary Basis of Approval for Mifeprex Tablets)</td><td>Absolute bioavailability at doses >100 mg has not been studied. Data from the Mifeprex Summary Basis of Approval indicate that the absolute bioavailability of 100 mg is approximately 40% (range, 30-56%),while that of lower doses is higher, 72% for 40 mg and 69% for 20 mg.</td></tr>
<tr><td rowspan="2">Tmax
(Studies C1073-5, 12, 20, 26 and 27)</td><td><u>Mifepristone:</u> Based on data pooled across Corcept-sponsored studies, the mean mifepristone T_{max} values for 300, 600 and 1200 mg single doses to fasted subjects have ranged from approximately 1.7 – 2.7 hr. Mean T_{max} from multiple-doses of 300, 600, 1200 and 1800 mg/day to fasted subjects have ranged from 1.5 – 2.7 hr. Mean T_{max} from 1200 mg single and multiple doses with food is 2.9 - 4.0 hr.</td></tr>
<tr><td><u>Metabolites</u>: T_{max} values for the metabolites are prolonged relative to parent mifepristone. Based on data pooled across Corcept-sponsored studies, the mean single-dose metabolite T_{max} values for 300, 600 and 1200 mg doses to fasted volunteers are summarized below:</td></tr>
</table>

		Analyte / Dose (mg) / Fed/Fasted / Range of mean Tmax (hr) RU 42633 / 300-1200 / Fasted / 3.0 – 5.6 RU 42698 / 300-1200 / Fasted / 4.1 – 6.8 RU 42898 / 300-1200 / Fasted / 19.4 – 26.7
Distribution	Vd/F (Studies C1073-05, -12, -26, -27)	When data were pooled from Corcept-sponsored studies, mean values of Vdβ/F ranged from 220 – 362 L for single-doses of 300, 600 and 1200 mg to fasted subjects. Mean values of Vdβ/F ranged from 1270 – 4520 L for multiple-doses of 600, 1200 and 1800 mg daily to fasted subjects.
	% bound (Wu (1999), Lahteenmaki (1987), Charles River Laboratory Report (2006))	Based on literature, mifepristone is highly bound to α1-acid glycoprotein (AAG) and approaches saturation at doses of 100 mg (2.5 μM) or more. Mifepristone and its metabolites also bind to albumin. In a Corcept-sponsored study, binding to human plasma proteins was approximately 99.2% for mifepristone, 98.9% for RU 42633, 97.8% for RU 42698, and 96.1% RU 42848 at clinically relevant concentrations, with binding being only slightly concentration-dependent.
Elimination	Route (Summary Basis of Approval for Mifeprex Tablets)	90% of a radiolabeled dose of mifepristone was recovered in the feces, with biliary excretion as the primary route of elimination.
		Urinary elimination accounted for <10% of the dose radiolabelled dose, with 0.5% of the dose being receptor-reactive.
	Terminal t½ (Summary Basis of Approval for Mifeprex Tablets, Lahteenmaki, et al., (1987), Heikinheimo, et al., (1989b), Section 2.7.2.2)	Based on studies reported in the literature of moderate-to-high single and multiple doses (200 to 800 mg) of mifepristone with sampling periods of 5 or 7 days, the mean observed half-life of the parent compound ranged from 24 to 50 hours. In Corcept-sponsored studies which utilized a longer sampling period of 14 days, median half-life ranged from 25.0 to 43.0 hours for a single dose and from 35.9 to 90.8 hours following multiple dose administration.
		Median half-life for metabolites in Corcept-sponsored studies: RU 42633 single dose 28 to 40 hours; multiple dose 51 to 64 hours. RU 42698 single dose 33 to 47 hours; multiple dose 49 to 50 hours. RU 42848 single dose 34 to 45 hours; multiple dose 42 to 73 hours.
	CL/F (Studies C-1073-05,12,19, 20, 22, 26, 27, 300)	When data were pooled from Corcept-sponsored studies, mean values of CL/F ranged from 6.04 – 9.81 L/h for single-doses of 300, 600 and 1200 mg to fasted subjects. Mean values of CL/F ranged from 9.0 – 37.9 L/hr for multiple-doses of 300, 600, 1200 and 1800 mg to fasted subjects.

<table>
<tr><td rowspan="5">Intrinsic Factors</td><td>Age (Section 2.7.2.3)</td><td>In a comparison of data pooled across the clinical pharmacology studies (see section 2.7.2.3), there was no obvious age-related effect on PK.</td></tr>
<tr><td>Sex (Section 2.7.2.3)</td><td>In a comparison of data pooled across the clinical pharmacology studies (see section 2.7.2.3), there was no consistent sex-related effect on PK.</td></tr>
<tr><td>Race (Section 2.7.2.3)</td><td>In a comparison of data pooled across the clinical pharmacology studies (see section 2.7.2.3), there was no obvious race-related effect on PK.</td></tr>
<tr><td>Hepatic Impairment (Study C-1073-05)</td><td>Change in parameters from moderately hepatically impaired subjects relative to healthy volunteers administered mifepristone 600 mg/day:
<table><tr><th>Analyte</th><th>Study Day</th><th>C_{max}</th><th>AUC_{inf}</th></tr><tr><td>Mifepristone</td><td>1</td><td>-23%</td><td>-21%</td></tr><tr><td></td><td>7</td><td>-8%</td><td>-10 %</td></tr><tr><td>RU 42633</td><td>1</td><td>-38%</td><td>-29%</td></tr><tr><td></td><td>7</td><td>-29%</td><td>-29%</td></tr><tr><td>RU 42698</td><td>1</td><td>-20%</td><td>-10%</td></tr><tr><td></td><td>7</td><td>+6%</td><td>+9%</td></tr><tr><td>RU 42848</td><td>1</td><td>-42%</td><td>-43%</td></tr><tr><td></td><td>7</td><td>-45%</td><td>-45%</td></tr></table></td></tr>
<tr><td>Renal Impairment Study (C1073-19)</td><td>Change in parameters from end stage renal disease patients (creatinine clearances of 21.2 to 24.8 mL/min/1.73m^2) relative to healthy volunteers administered mifepristone 1200 mg/day for 7 days:
<table><tr><th>Analyte</th><th>C_{max}</th><th>AUC_{24}</th></tr><tr><td>Mifepristone</td><td>+30%</td><td>+31%</td></tr><tr><td>RU 42633</td><td>+50%</td><td>+56%</td></tr><tr><td>RU 42698</td><td>+33%</td><td>+35%</td></tr><tr><td>RU 42848</td><td>+12%</td><td>+ 6%</td></tr></table></td></tr>
<tr><td>Extrinsic Factors</td><td>Drug Interactions (Woodland (2003), Corcept Studies MC05728, MC05745, 5CORCP1R1, and clinical studies C1073-16, 23, 24, 25 and 26.)</td><td>Mifepristone is a substrate for CYP3A4. In vitro studies indicate a medium potential for CYP-mediated drug interactions by mifepristone and/or its metabolites via mifepristone inhibition of CYPs 2A6, 2C8/2C9, 2C19 and 3A4. Mifepristone also inhibited P-gp and BCRP in in vitro studies. Results of clinical drug-drug interaction studies sponsored by Corcept with healthy volunteers:

<u>Inhibition of CYP3A by mifepristone</u>: Mifepristone increased exposure to simvastatin and simvastatin acid by more than 10-fold. Mifepristone also increased exposure to alprazolam by 70%. Drugs with high first pass metabolism in which CYP3A is the primary route of metabolism such as triazolam, felodipine,</td></tr>
</table>

		cyclosporine, everolimus or sildenafil, should be used with extreme caution when co-administered with mifepristone. The lowest possible dose and/or a decreased frequency of dosing must be used, with therapeutic drug monitoring. While such large magnitude drug interactions may be successfully managed, use of alternative drugs without these metabolic characteristics is advised wherever possible with concomitant mifepristone. Mifepristone increased exposure to alprazolam by 70%. Co-administration of mifepristone with other drugs of similar low first pass metabolism by CYP3A or of drugs in which CYP3A is not the sole or major route should use the lowest dose necessary with appropriate monitoring and follow-up. *Drugs Metabolized by CYP2C9/2C8:* Mifepristone increased the exposure to fluvastatin by 2.7-fold. When given concomitantly with mifepristone, drugs in which CYP2C9/2C8-mediated metabolism has a major role (including non-steroidal anti-inflammatory drugs, warfarin, and repaglinide) should be used at the smallest recommended doses and closely monitored for adverse effects. *Effect of CYP3A inhibition on PK of mifepristone:* Co-administration of mifepristone with cimetidine (800 mg/day, a mild-moderate inhibitor of CYP3A) in healthy subjects showed no evidence of a changed exposure to mifepristone. Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone may be required. Ketoconazole and other strong inhibitors of CYP3A, such as itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, and fosamprenavir, may significantly increase exposure to mifepristone. The clinical impact of this interaction has not been studied. Therefore, these drugs are contraindicated and must not be prescribed in combination with mifepristone. Based on the results of the cimetidine interaction study, no dose adjustment of mifepristone is needed when co-administered with mild to moderate inhibitors of CYP3A. *CYP3A Inducers:* No medications that induce CYP3A have been studied when co-administered with mifepristone. Avoid co-administration of

		mifepristone and CYP3A inducers such as rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, and St. John's wort. *Inhibition of transport by P-gp:* Mifepristone increased mean digoxin exposure by 40%. No initial dose adjustment is needed for 0.125 mg digoxin once daily given with mifepristone. Plasma digoxin concentration should be measured after 1 to 2 weeks of concomitant use and following usual clinical practice at appropriate intervals therafter. In general, the extent of this interaction indicates only minor effects are likely for other drugs with P-gp mediated drug transport. *Inhibition of transport by BCRP:* No clinical studies have been performed to evaluate the inhibitory effect of mifepristone on BCRP. When given concomitantly with mifepristone, drugs in which BCRP has a major role in disposition should be used at the smallest recommended doses and patients closely monitored for adverse effects.
	Food Effects (Studies C1073-20 and 27)	Fed:fasted geometric mean ratio (90% CI) for administration of 1200 mg single dose with/without a standard high-fat (50%) meal: Analyte C_{max} AUC_{inf} Mifepristone 1.30 (1.16-1.45) 1.42 (1.23-1.65) RU 42633 1.15 (1.05-1.25) 1.37 (1.20-1.57) RU 42698 1.09 (1.00-1.20) 1.34 (1.17-1.53) RU 42848 1.32 (1.20-1.45) 1.51 (1.31-1.75) Fed:fasted geometric mean ratio (90% confidence interval) for 7 days multiple-dose administration with a 34% fat meal: Analyte C_{max} AUC_{24} Mifepristone 1.56 (1.41-1.74) 1.65 (1.52-1.79) RU 42633 1.17 (1.11-1.22) 1.21 (1.15-1.28) RU 42698 1.34 (1.26-1.43) 1.34 (1.27-1.43) RU 42848 1.29 (1.21-1.37) 1.29 (1.20-1.38) Meals appear to increase exposure to mifepristone, more so for multiple dosing vs single dose. No difference whether the meal has high fat (50%) or medium fat (34%) content. Mifepristone should be administered once daily with a meal.

Expected High Clinical Exposure Scenario	The following table shows the mean and median MIFE-C_{trough} concentrations for the TQT study on Day 7 and for Cushing's patients who were rated "responders" for the key secondary endpoint in Study C1073-400, at steady state:

Study #	Cushing's C1073-400				TQT C1073-300	
MIFE Dose (mg)	300	600	900	1200	1800	600
N	30	29	23	14	58	42
Mean	1774	1952	2108	2293	2047	1554
Ratio to TQT 1800 mg mean	0.87	0.95	1.03	1.12	1	0.76
Median	1455	1630	1820	2023	1889	1422
Ratio to TQT 1800 mg median	0.77	0.86	0.96	1.07	1	0.75

MIFE = mifepristone
Source: Study C1073-400 CSR, Appendix 16.5.3 (NDA Section 5.3.5.2.1)

The 300 mg dose has exposures similar to that of the 600 mg dose in the TQT; the 900 mg dose has exposures close to that of the 1800 mg dose in the TQT.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review

Date:	September 19, 2011
Reviewer(s):	Patty Greene, Pharm.D., Drug Use Data Analyst Division of Epidemiology II (DEPI II)
Team Leader:	Grace Chai, Pharm.D. Division of Epidemiology II (DEPI II)
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Drug Name(s):	Mifeprex® (mifepristone)
Application Type/Number:	NDA 20-687
Applicant/sponsor:	Danco Laboratories, LLC
OSE RCM #:	2011-3147

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EXECUTIVE SUMMARY

The Division of Risk Management (DRISK) is reviewing a Risk Evaluation and Mitigation Strategy (REMS) proposal for NDA 202107, mifepristone tablet, for the treatment of Cushing's syndrome. Mifepristone is currently marketed under restricted distribution under the brand name Mifeprex® Tablets, 200 mg, for the indication of medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period. To determine the extent of use, including off-labeled use for Cushing's syndrome, DRISK is requesting drug utilization data to quantify the number of patients treated with Mifeprex® (mifepristone) each year and to determine the amount distributed to clinics, medical offices, and hospitals.

- There were (b) (4) patients a year with a medical claim for Mifeprex® (mifepristone) in a sample of medical offices and outpatient clinics (n=350 facilities) for years 2008-2010.
    - Of these patients, two patients were captured with a medical claim for "Cushing's Syndrome" (ICD-9 255.0) over the study period.
- In the hospital setting, projected numbers of (b) (4) patients a year were billed for Mifeprex® (mifepristone) for years 2004-2011, primarily in *outpatient* hospital settings. No diagnosis codes for Cushing's syndrome were captured with a billing for Mifeprex® (mifepristone) in the hospital setting.

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review examines patient utilization for Mifeprex® (mifepristone) in the off-label treatment of Cushing's Syndrome from years 2004 through 2011, annually.

1.1 BACKGROUND

Mifeprex® (mifepristone) is an antiprogesterone product indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy.[1] Mifeprex® (mifepristone) was approved under a restricted distribution program on September 28, 2000 under NDA 21-793 and is currently available in 200 mg tablets. On June 8, 2011, a Risk Evaluation and Mitigation Strategy (REMS) was approved for Mifeprex® (mifepristone) which included a medication guide with Elements To Assure Safe Use (ETASU) to communicate the benefits and risk of Mifeprex® (mifepristone). Mifeprex® (mifepristone) is available from the manufacturer and sold to certified distributors through clinics, medical offices, and hospitals only. Since the REMS was recently approved, no drug utilization information or assessment is available from the sponsor of Mifeprex® at this time.

A new drug application for mifepristone (NDA 202107) with a REMS proposal was submitted by Corcept Therapeutics, Inc. for the treatment of hypercortisolism in patients with endogenous Cushing's syndrome on April 18, 2011. To determine whether a REMS

[1] Mifeprex label sponsor's website: www.earlyoptionpill.com

will be necessary to ensure the safe use of mifepristone for Cushing's syndrome, DRISK has requested a drug utilization analysis for mifepristone, including off-labeled use for Cushing's Syndrome, from year 2000 through 2011, or as many years available for analysis. In addition, sales distribution data were requested to determine the amount distributed to clinics, medical offices, and hospitals.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTING OF CARE

Mifeprex® (mifepristone) is available through a restricted distribution program available only from clinics, medical offices, and hospitals (non-retail pharmacy settings). As a result, non-retail pharmacy utilization patterns were examined. Neither mail order nor outpatient retail pharmacy settings were included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

The IMS Health, National Sales Perspectives™ and the Wolters Kluwer PHAST Institutional databases were searched to determine the amount distributed to clinics, medical offices, and hospitals.

Wolters Kluwer Health's Source® Lx database was used to obtain estimates of the number of patients receiving a medical claim for Mifeprex® (mifepristone) in an unprojected sample of patients, stratified by selected diagnosis groups, in the non-retail pharmacy setting from January 1, 2008 to December 31, 2010, annually. Patients with a medical claim for Mifeprex® (mifepristone) were searched using the healthcare common procedure coding system/current procedural terminology code (HCPCS/CPT code) S0190 and selected ICD-9 diagnosis codes. Off-labeled diagnoses such as Disorders of Adrenal (ICD-9 255), and Spontaneous Abortion (ICD-9 634) were grouped together ***(see Appendix 3 for ICD-9 Diagnosis Group).*** Other off-labeled diagnoses included in the search were Emergency Contraception (V25.04), and Malignant Neoplasm of Ovary (183). All other claims with other or unspecified diagnoses captured under the HCPCS code S0190 were grouped as "All Other Diagnosis."

Hospital utilization was obtained from SDI's Inpatient HealthCare Utilization System (IHCarUS) database to determine the number of projected discharges or patients associated with a hospital billing for Mifeprex® (mifepristone), stratified by inpatient and outpatient encounters, from January 1, 2004 through June 30, 2011, annually.

3 RESULTS

3.1 SALES DISTRIBUTION DATA

A extensive search of sales data using IMS Health, National Sales Perspectives™ and the Wolters Kluwer PHAST Institutional databases for Mifeprex® (mifepristone) was searched. No sales information were captured in either databases for the review period.

3.2 MIFEPREX® MEDICAL CLAIMS IN A SAMPLE OF NON-RETAIL PHARMACY SETTINGS

Table 1 in Appendix 1 displays the unprojected number of patients (b) (4), stratified by selected diagnoses group, with a medical claim for Mifeprex® (mifepristone) in a sample of medical offices and outpatient clinics (n=350 facilities), years 2008-2010. The unprojected number of patients with a medical claim for Mifeprex® (mifepristone) ranged from (b) (4) patients annually, for years 2008 through 2010. Of these patients, a total of two patients were captured with a medical claim for "Cushing's Syndrome" (ICD-9 255.0) during the study period. Off-label use of Mifeprex® (mifepristone) for the treatment of Spontaneous Abortion (ICD-9 634.0) and Emergency Contraception (V25.04) accounted for approximately (b) (4) of total patients, respectively, for the cumulative time period.

3.3 PROJECTED NUMBER OF DISCHARGES AND UNIQUE PATIENTS ASSOCIATED WITH A HOSPITAL BILLING FOR MIFEPREX®

Table 2 in Appendix 1 displays the projected number of discharges and unique patients associated with a hospital billing for Mifeprex® (mifepristone), for years 2004 through June 2011, annually. The majority of patients were billed for Mifeprex® (mifepristone) from the outpatient hospital setting. The projected number of patients billed for Mifeprex® (mifepristone) ranged from (b) (4) patients a year. In year 2010, roughly (b) (4) patients or discharges were billed for Mifeprex® (mifepristone), a (b) (4) increase from year 2004.

4 DISCUSSION

Our findings suggest that off-label use of Mifeprex® (mifepristone) in the treatment Cushing's syndrome is uncommon. DRISK also requested information on the amount of Mifeprex® (mifepristone) distributed to individual physician offices compared to family planning clinics. In the sample of medical offices and outpatient clinics, no information was available from the data vendor regarding the amount of Mifeprex® (mifepristone) distributed by facility type.

Data from Wolters Kluwer Source Lx® provides unprojected patient counts with a medical and prescription claim for Mifeprex®. Only 350 clinics/medical offices could be identified through (b) (4) for the reported number of patients who received a *medical claim* for Mifeprex during the study period. Therefore, due to the small sample size and the inability to characterize clinic or pharmacy information, there are limitations in the ability to identify national trends in the data. In addition, the universe of specialty pharmacies and outpatient clinics contributing to these data are unknown, therefore, nationwide projections are not available at this time.

Outpatient hospital visits are encounters where a patient is not hospitalized for 24 hours or more, but visits a hospital emergency room for diagnosis or treatment. The SDI Hospital CDM sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals, and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the SDI CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations

of SDI's Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown SDI's patient level data to be representative and accurate across multiple therapeutic areas.

5 CONCLUSIONS

Our findings suggest that off-label use of Mifeprex® (mifepristone) in the treatment Cushing's syndrome is uncommon. In a sample of medical offices and outpatient clinics (n=350 facilities), the unprojected number of patients with a medical claim for Mifeprex® (mifepristone) ranged from (b) (4) patients annually for years 2008-2010. A total of (b) (4) patients with a claim for Mifeprex® were captured with a medical claim for "Cushing's syndrome" (ICD-9 255.0) during the study period. In the hospital setting, the projected number of patients billed for Mifeprex® (mifepristone) ranged from (b) (4) patients or discharges, annually for years 2004-2011.

APPENDICES

APPENDIX 1: TABLES

APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

Wolters Kluwer SOURCE Lx®

The Wolters Kluwer Source® Lx database a longitudinal patient data source which capture adjudicated claims across the United States from a mix of prescription claims from commercial plans, Medicare Part D plans, Cash and Medicaid claims. The database contains approximately 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

SDI, Inpatient HealthCare Utilization System (IHCarUS)

The SDI, Inpatient HealthCare Utilization System (IHCarUS) provides hospital inpatient and outpatient emergency department encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from mid-2001, are collected weekly and monthly and are available 25-30 days after the end of each monthly period. This robust data set includes > 650 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include >7 million annual hospital inpatient encounters and >60 million annual hospital outpatient encounters (including ED visits) representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. SDI's datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

APPENDIX 3: ICD-9 DIAGNOSIS GROUPS

Diagnosis Group Name	*Code*	*Description*
255 DISORDERS OF ADRENAL (CUSHING'S SYNDROME)		
	255	DISORDERS OF ADRENAL GLANDS
	255.0	CUSHING'S SYNDROME
	255.1	HYPERALDOSTERONISM
	255.2	ADRENOGENITAL DISORDERS
	255.3	CORTICOADREN OVERACT NEC
	255.4	CORTICOADRENAL INSUFFIC
	255.5	ADRENAL HYPOFUNCTION NEC
	255.6	MEDULLOADRENAL HYPERFUNC
	255.8	ADRENAL DISORDER NEC
	255.9	ADRENAL DISORDER NOS
	255.10	HYPERALDOSTERONISM UNSPEC
	255.11	GLUCRTCOD-REM ALDSTERNSM
	255.12	CONN'S SYNDROME
	255.13	BARTTER'S SYNDROME
	255.14	SECONDRY ALDOSTERNSM NEC
	255.41	GLUCOCORTICOID DEFICIENCY
	255.42	MINERALOCORTICOID DEFICIENCY
V25.04 POSTCOITAL CONTRACEPTION		
	V25.04	CONTRACEPT MGMT-EMERGNCY
183 MALIGNANT NEOPLASM OF OVARY		
	183	MALIGNANT NEOPLASM OF OVARY
634 SPONTANEOUS ABORTION		
	634	SPONTANEOUS ABORTION
	634.0	SPON ABORT W PELVIC INFECT
	634.00	SPON ABOR W PEL INF-UNSP
	634.01	SPON ABOR W PELV INF-INC
	634.02	SPON ABOR W PEL INF-COMP
	634.1	SPON ABORT W HEMORRHAGE
	634.10	SPON ABORT W HEMORR-UNSP
	634.11	SPON ABORT W HEMORR-INC
	634.12	SPON ABORT W HEMORR-COMP
	634.2	SPON ABORT W PELVIC DAMAGE
	634.20	SPON AB W PEL DAMAG-UNSP
	634.21	SPON AB W PELV DAMAG-INC
	634.22	SPON AB W PEL DAMAG-COMP
	634.3	SPON ABORT W RENAL FAILURE
	634.30	SPON AB W REN FAIL-UNSP
	634.31	SPON AB W REN FAIL-INC
	634.32	SPON AB W REN FAIL-COMP
	634.4	SPON ABORT W METAB DISORDER
	634.40	SPON AB W METAB DIS-UNSP
	634.41	SPON AB W METAB DIS-INC
	634.42	SPON AB W METAB DIS-COMP
	634.5	SPON ABORT W SHOCK
	634.50	SPON ABORT W SHOCK-UNSP
	634.51	SPON ABORT W SHOCK-INC
	634.52	SPON ABORT W SHOCK-COMP
	634.6	SPON ABORT W EMBOLISM
	634.60	SPON ABORT W EMBOL-UNSP
	634.61	SPON ABORT W EMBOL-INC
	634.62	SPON ABORT W EMBOL-COMP
	634.7	SPON ABORT W OT COMPLICA
	634.70	SPON AB W COMPL NEC-UNSP
	634.71	SPON AB W COMPL NEC-INC
	634.72	SPON AB W COMPL NEC-COMP
	634.8	SPON ABORT W UN COMPLICA
	634.80	SPON AB W COMPL NOS-UNSP
	634.81	SPON AB W COMPL NOS-INC
	634.82	SPON AB W COMPL NOS-COMP
	634.9	SPON ABORT WO COMPLICAT
	634.90	SPON ABORT UNCOMPL-UNSP
	634.91	SPON ABORT UNCOMPL-INC
	634.92	SPON ABORT UNCOMPL-COMP

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09/19/2011
drug use data cleared

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Maternal Health Team Review

Date: September 9, 2011 **Date Consulted:** August 1, 2011

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Medical Officer, Maternal Health Team
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Through: Karen B. Feibus, M.D.
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Pediatric and Maternal Health Staff

To: **Office of Surveillance and Epidemiology, Division of Risk Management (OSE/DRISK)**

Drug: (b) (4) **(Mifepristone tablets 300mg)- NDA 202107**

Subject: Assess the need for REMS to address the risk of pregnancy termination associated with the use of Mifepristone for the treatment of Cushing's syndrome.

Materials Reviewed:

Sponsor's submitted labeling, published literature about Cushing's disease and the menstrual cycle, Use of Mifepristone for treatment of Cushing's disease and side effects of this treatment

INTRODUCTION

On April 15, 2011, Corcept Pharmaceuticals submitted a new drug application (NDA 202107) for Mifepristone (Corcept) 300mg tablets. The Sponsor has proposed the treatment of patients with Cushing's disease who: have not adequately responded to or have relapsed after surgery, are not candidates for surgery, (b) (4) . The proposed dose is 300mg daily, which may be increased up to 1200mg daily. Mifepristone is a progesterone receptor modulator (PRM) that was approved on September 28, 2000, under the trade name Mifeprex, indicated for use for pregnancy termination at a 600 mg dose.

On August 1, 2011, the DRISK consulted the Pediatric and Maternal Health Staff's Maternal Health Team (PMHS-MHT) to assess the need for a Risk Evaluation and Mitigation Strategy (REMS) to address the risk of pregnancy termination associated with the use of Mifepristone for the treatment of Cushing's disease. This review includes a current literature search and a discussion of unique drug risks and potential indication for risk management strategies for the use of Mifepristone in the proposed patient populations.

BACKGROUND

Mifepristone, a norethindrone derivative, acts as an antiprogestin by binding the progesterone receptor. This progesterone receptor modulator (PRM) binds to the receptor with greater affinity than progesterone but does not activate the receptor. Mifepristone is also a glucocorticoid receptor antagonist, and is used in high doses for the treatment of Cushing's disease.[1] The Sponsor is seeking approval for the use of Mifepristone for the treatment of patients with Cushing's disease who have not adequately responded to or have relapsed after surgery, who are not candidates for surgery, and who have (b) (4) . The proposed dose is 300mg daily, which may be increased up to 1200mg daily.

Cushing's syndrome is defined as the set of clinical abnormalities resulting from chronic high levels of cortisol, whereas Cushing's disease is Cushing's syndrome that results from excess pituitary production of adrenocorticotropic hormone (ACTH) usually due to a pituitary adenoma.[2] Cushing's syndrome has a female preponderance with an estimated female to male ratio of 3:1.[3] Therefore, it is likely that mifepristone may be used in females of reproductive potential with Cushing's syndrome.

PRMs have various effects on the female genital tract that can be dose dependant. Mifepristone is used in low doses to treat leiomyomas and endometriosis based on its ability to block

[1] Spitz IM, Grunberg SM, Chabbert-Buffet N et al, Management of patients receiving long term treatment with mifepristone. *Fertil Steril*. 2005;84:1719-26.
[2] JUSTIN L. KAPLAN, MD, et al, eds. 2006. Merck Manual of Diagnosis and Therapy, The. Whitehouse Station, NJ. MERCK RESEARCH LABORATORIES. http://online.statref.com/document.aspx?fxid=21&docid=537. 8/15/2011 11:48:03 AM CDT (UTC -05:00).
[3] Steffensen C, Bak AM, Rubeck KZ et al. Epidemiology of Cushing's Syndrome. *Neuroendocrinology*. 2010. 92(1):1-5.

proliferation.[4] Additionally, at low doses, mifepristone delays the LH surge and inhibits ovulation.

At higher doses, some of the uterine effects of mifepristone include softening of the cervix, necrotizing the decidua, and increasing uterine contractility. Mifepristone in combination with a prostaglandin analogue is commonly used as a medical abortion regimen. [5] Long term use of mifepristone at higher doses has been shown to cause endometrial thickening and endometrial hyperplasia.

The potential effects of Mifepristone on the female reproductive tract raise the concern of whether specific precautions are necessary for the use of this medication in females.

REVIEW OF LITERATURE

Cushing's Syndrome

Cushing's syndrome results from an over abundance of cortisol levels generally due to a pituitary adenoma or adrenal adenoma. Diagnosis of this disease is challenging because several clinical features are shared with common medical diseases such as diabetes and hypertension.
In a Danish epidemiological survey, the median age at first admission was 41.4 years and female to male ratio was 3:1.

Furthermore, after transphenoidal surgery to remove a pituitary adenoma, an initial cure rate of 66.2% was achieved in the Danish study, whereas an 85.6% cure rate was seen in a US study. Late recurrences occurred in up to 20% of patients. In the subset of patients that is not cured, there is an increased rate of mortality.[6,7] Major causes of death include vascular disease, hypertension and myocardial infarction, and complications of abnormal glucose metabolism.

The mainstay for treatment of Cushing's syndrome remains surgical removal of the source of ACTH secretion. Medical management of Cushing's syndrome is used while a patient is being evaluated for the source of ACTH secretion, during preparation for surgery, following radiation to bridge the delay in efficacy, or if patients are not surgical candidates.[8]

[4] Chabbert-Buffet N, Meduri G, Bouchard P, Spitz IM. Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications. *Human Reproduction Update*. 2004. 11(3);293-307.
[5] ACOG Practice Bulletin. October 2005, Number 67. Medical Management of Abortion
[6] Steffensen C, Bak AM, Rubeck KZ et al. Epidemiology of Cushing's Syndrome. *Neuroendocrinology*. 2010. 92(1):1-5
[7] Patil CG, Prevedello DM, Lad SP et al. Late Recurrences of Cushing's Disease after Initial Successful Transphenoidal Surgery. *J Clin Endocrinol Metab*. 2008. 93:358-362.
[8] Castinetti F, Fassnacht M, Johanssen S, et al. Merits and pitfall of mifepristone in Cushing's syndrome. *European Journal of Endocrinology*. 2009. 160:1003-1010.

Mifepristone Treatment of Cushing's syndrome

Mifepristone is a progesterone receptor modulator (PRM) that binds to the progesterone receptor without activating the receptor. Due to this effect on the receptor, mifepristone blocks progesterone effects. In addition, in doses exceeding 200 mg daily, mifepristone acts as a glucocorticoid receptor antagonist leading to its use as a treatment for hypercortisolism.[9] Mifepristone inhibits the central actions of cortisol by preventing its negative feedback on ACTH and corticotropic hormone (CRH) secretion, and it inhibits peripheral actions by inhibiting cortisol's effects on protein and glucose metabolism.[10] However, the mineralocorticoid effects of cortisol excess are not inhibited, resulting in hypokalemia as a common side effect of therapy.[11]

Menstrual irregularities and Cushing's syndrome

In the Endocrine Society clinical practice guidelines published in 2008, menstrual irregularity is noted as a common feature of cortisol excess in patients with Cushing's syndrome.[12] Cushing's syndrome is the cause of one percent of all cases of secondary amenorrhea.[13] Although the exact mechanism for this irregularity has not been delineated, excess circulating androgens is thought to be an etiology. Furthermore, alterations in gonadotropin release due to the effects of hypercortisolemia on the secretion of gonadotropin releasing hormone (GnRH) in the hypothalamus may be another mechanism. The ovaries from patient with Cushing's syndrome show a decrease in all phases of primordial follicles, fibrosis, and reduction in size.[14]

Lado-Abdeal et al studied forty five females diagnosed with Cushing's syndrome from 1974 to 1995. The patients were studied during their initial admission for the confirmation of Cushing's disease, and 81% gave a history of previous regular menstrual cycles. Blood samples were obtained for androgen, estradiol, LH, FSH and prolactin levels. Results of the study indicated that 80% of patients with Cushing's syndrome had irregular menstrual cycles. The majority of patients had amenorrhea as the irregularity. The measured gonadotropins were low when correlated with estradiol levels, indicating a suppression of the hypothalamic secretion. [15] Additionally, cortisol levels were inversely correlated with serum estradiol levels but not with serum androgen levels. Because of this relationship, the authors suggest that the primary

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[9] Spitz IM, Grunberg SM, Chabbert-Buffet N, et al. Management of patients receiving long-term treatment with mifepristone. *Fertility and Sterility*. 2005. 84:1719-26.

[10] Johanssen S, Allolio B. Mifepristone (RU 486) in Cushing's syndrome. *European Journal of Endocrinology.* 2007. 157;561-569.

[11] Castinetti F, Fassnacht M, Johanssen S, et al. Merits and pitfall of mifepristone in Cushing's syndrome. *European Journal of Endocrinology.* 2009. 160:1003-1010.

[12] Nieman LK, Biller BM, Findling JW et al. The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008. 93(5); 1526-1540.

[13]Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG, "Chapter 16. Amenorrhea" (Chapter). Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG: Williams Gynecology: http://www.accessmedicine.com/content.aspx?aID=3156564.

[14] Iannaccone A, Gabrilove JL, Sooval AR, Soffer LJ. The ovaries in Cushing's syndrome. N Engl J Med. 1959. 261:775-780.

[15] Lado-Abdeal J, Rodgriquez-Arnao J, Newell-Price DC, et al. Menstrual Abnormalities in Women with Cushing's Disease are correlated with hypercortisolemia rather than raised circulating androgen levels. J Clin Endocrinol Metab. 1998. 83;3083-88.

mechanism of menstrual irregularities results from hypercortisolism rather than elevated serum androgens.

Table 1: Menstrual Abnormalities in Women with Cushing's Disease			
Cycle	**Patients in Category**	**Study Definitions**	**ACOG Definitions[16]**
Normal	9 (20%)	26-30 days	21-34 days
Oligomenorrhea	14 (31%)	31-120 days	>35 days
Amenorrhea	15 (33%)	>120 days	>90days is in the 95% cycle length > 6 months- secondary amenorrhea
Polymenorrhea	4 (8.8%)	<26 days	<21 days
Irregular cycles not in other categories	4 (6.6%)		

Reviewer comments*: The menstrual abnormality that occurs most frequently in patients with elevated serum cortisol is amenorrhea. The authors' definitions of the normal menstrual cycle are inconsistent with the American College of Obstetrics and Gynecology (ACOG) definitions (see Table 1). By using different definitions, they may have increased the overall number of patients with menstrual irregularities. However, patients diagnosed with amenorrhea comprise the largest subgroup, and this subgroup most closely correlates with the ACOG definition.*

Pregnancy and Cushing' Syndrome

Because of the ovulatory disturbances associated with untreated Cushing's syndrome, pregnancy occurs rarely in this population. In contrast to the general population in which most of Cushing's Syndrome results from a pituitary adenoma, adrenal tumors are found more commonly in pregnancy. [17]

Lindsay et al published a review of the Cochrane Library and Pubmed that included 136 pregnancies complicated by Cushing's syndrome resulting in 107 live births. In their study population, the majority of patients had Cushing's disease (40 patients), adrenal adenomas (46 patients), adrenal carcinoma (16 patients), and ectopic ACTH secretion (4 patients). Some of the patients had conservative therapy while others received medical therapy or had surgery during the pregnancy. Among the patients with Cushing's disease, eight women had transphenoidal surgery, one had external pituitary radiation prior to diagnosis of pregnancy, seven had medical therapy, seven had adrenalectomy, and seventeen were untreated. Of the patients with an adrenal

[16]American College of Obstetrics & Gynecology (ACOG) Committee Opinion. Number 349, November 2006. Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign

[17] Lindsay JR, Jonklaas J, Oldfield EH, Nieman LK. Cushing's Syndrome during Pregnancy: Personal experience and Review of the literature. The Journal of Clinical Endocrinology and Metabolism. 2005. 90(5):3077-3083.

source for their Cushing's syndrome, twenty four underwent unilateral adrenalectomy during pregnancy.

Significant maternal and fetal morbidity occurred in this patient population. Maternal morbidity was attributed to hypertension noted in 68% of patients, diabetes seen in 25% of patients, and preeclampsia noted in 14% of patients. Among the live births, 43% of infants were born prematurely. Eight stillbirths and six intrauterine fetal demises (IUFD) were reported. The authors noted a trend toward increased live birth rates in the group of patients treated during pregnancy in comparison to the patients that were untreated.

In this review, the authors also reported four cases of Cushing's disease diagnosed at the National Institutes of Health over a fifteen year period. These patients were diagnosed from five to 14 weeks of gestation. Three out of four patients reported regular menses prior to conception. One patient was induced for preeclampsia and delivered at 33 weeks, the second patient had an IUFD at 33 weeks, the third patient delivered a healthy infant at term, and the final patient was delivered at 24 weeks due to severe preeclampsia with the subsequent death of the baby due to complications of prematurity.

Reviewer comments: *Although the maternal and fetal implications of Cushing's disease in pregnancy are significant, the small number of patients treated at the NIH over fifteen years and the relatively small number of reports in the literature indicate that the menstrual irregularities resulting from Cushing's syndrome decrease the pregnancy rate in this population. However, because the diagnosis of Cushing's syndrome is challenging and a range of menstrual irregularities are seen among affected females, pregnancy may occur in a small subset of patients with Cushing's syndrome who are of childbearing age. This possibility should be noted in labeling.*

Effects of mifepristone on the female reproductive tract

Mifepristone, due to its actions as an antiprogestin, has various effects on the female reproductive tract. These effects appear to be dependent on the administered dose.

Impact on Ovulation

In low doses (less than 50 mg), the drug has been noted to inhibit the Luteinizing Hormone (LH) surge associated with ovulation.[18] Shoupe et al studied the effects of using mifepristone during the follicular phase in six women over three menstrual cycles. Each patient's natural menstrual cycle was studied in the initial month. During the subsequent cycle, each patient was given 50mg of mifepristone from day 10-17, and they were observed for a post treatment cycle. All patients had a normal menstrual cycle prior to the administration of mifepristone. After receiving mifepristone, the follicular phase was prolonged, and the LH surge was delayed indicating that ovulation was inhibited. In the post-treatment cycle, the patients resumed ovulation.

[18] Shoupe D, Mishell DR, Page MA, et al. Effects of the antiprogesterone RU 486 in normal women, Administration in the late follicular phase. *Am J Obstet Gynecol*. 1987. 157:1421-6.

High dose mifepristone prolongs the follicular phase by delaying the LH surge, and cessation of growth of the dominant follicle is observed. Liu et al investigated the effects of mifepristone administration at a dose of 3 mg/kg given for three consecutive days on the follicular development in six patients with regular menstrual cycles. These patients had serial ultrasounds prior to administration of mifepristone and were noted to develop a dominant follicle. Subsequent to receiving mifepristone, ultrasound examinations of these patients indicated collapse of the dominant follicle or a decrease in the size of the follicle. The patients had a prolonged follicular phase during the treatment cycle.

Reviewer comment: *The above studies indicate that by inhibiting progesterone effect during the menstrual cycle, mifepristone can disrupt follicular maturation and potentially inhibit the LH surge preventing ovulation.*

Impact on the Endometrium

Effects on the endometrium are detected with intermittent mifepristone use, in both low and high doses. These effects of mifepristone on the endometrium may contribute to its ability to inhibit implantation.[19] In patients treated with mifepristone from 50-800 mg in a single dose, bleeding was noted within three days of mifepristone administration. Shoupe[20] et al treated thirty-one women from age 22 to 35 years old with 50 to 800 mg of mifepristone six to eight days after the LH surge. In 33% of the patients, a single bleeding episode occurred, and these patients had an abbreviated cycle during the treatment cycle. In the majority of patients, two bleeding episodes occurred, with the first one occurring within three days of administration of mifepristone, and the second one occurring after a prolonged luteal phase. This group of patients did not have any changes in the LH, estradiol, or progesterone levels indicating that the first bleeding episode was a result of the direct effects of mifepristone on the endometrium.

Additionally, in 2005, Spitz et al reported a study of twenty-five patients, including five premenopausal and eleven postmenopausal women, who were treated chronically with 200 mg mifepristone daily for the management of unresectable meningiomas.[21] Patients in the study were treated with mifepristone for durations ranging from 4 months up to 13 years. Cessation of menses occurred in all of the premenopausal women and resumed after discontinuation of mifepristone. In this study, any female with unexplained vaginal bleeding had sonographic evaluation of the pelvis and an endometrial biopsy as indicated. Two premenopausal patients experienced irregular bleeding after 18 months of treatment. One patient had endometrial hyperplasia, which following hysterectomy was diagnosed as persistent adenomatous hyperplasia. Two postmenopausal patients were evaluated because one had bleeding and the other had endometrial thickening on ultrasound examination. The patient with bleeding had an endometrial polyp and endometrial hyperplasia diagnosed by endometrial biopsy. The patient with endometrial thickening did not have hyperplasia.

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[19] Spitz IM, Croxatto HB, Robbins A. Antiprogestins:Mechanism of action and contraceptive potential. *Annu Rev Pharmacol Toxicol*. 1996. 36:47-81.

[20] Shoupe D, Mishell DR, Lahteenmakki, et al. Effects of the antiprogesterone RU 486 in normal women, Single dose administration in the midluteal phase. *Am J Obstet Gynecol*. 1987. 157: 1415-20.

[21] Spitz IM, Grunberg SM, Chabbert-Buffet N, et al. Management of patients receiving long-term treatment with mifepristone. *Fertility and Sterility.* 2005. 84:1719-26.

Histological Changes of the Endometrium

Endometrial cells are regulated by both estrogen and progesterone during normal menstrual cycles. Estrogen effects, such as increased mitotic activity, are noted in the follicular phase of the menstrual cycle. At the time of ovulation until the end of the luteal phase, progesterone suppresses the mitotic activity and secretory changes are seen in the endometrium. In a normal cycle, these changes in the endometrium are sequential and distinct in each phase of the cycle. The effects of mifepristone are novel because of mixed features attributed to hormone depletion coexist with features of stimulation by estrogens or progesterone. Prominent cystically dilated glands with admixed estrogen (mitotic) and progesterone (secretory) features are noted.[22] However, these changes are seen only in a subset of the exposed population. The etiology of this effect of mifepristone used in high doses on the endometrium is unknown.[23] Aromatization of increased adrenal androgens androstenedione and testosterone, produced due to elevated adrenalcorticotrophic hormone (ACTH) and cortisol levels at these doses of mifepristone, may be associated with these endometrial changes. The aromatization of these androgens could result in increased local estrogen effects.

Because of the unique endometrial architecture, the National Institutes of Child Health and Human Development (NICHD) held a workshop in 2006 to discuss the effects of PRM on the endometrium. Furthermore, an expert panel of pathologists examined eighty-four endometrial specimens prior to the conference and presented their consensus observations at the meeting. The panel noted that PRM-affected endometrium has cystically dilated glands as the background for unusual changes that include both inactivity and mitosis. These endometrial changes differ from those seen with exposure to unopposed estrogen, because these glands are only weakly mitotic, have various levels of epithelial secretory changes, show occasional stromal pseudodecidual changes, and lack fibrin thrombi or stromal breakdown. Additionally, unlike progesterone effect seen with delayed ovulation or progestin treated anovulation, patients with PRM exposure, both estrogen and progestational changes occur concomitantly rather than sequentially. The panel did not diagnose atypical hyperplasia or endometrial neoplasia in any of the specimens.[24] The panel classified these unique changes in PRM treated women as PRM-associated endometrial changes (PAEC).

Reviewer comments*: Prior to this classification of PRM associated endometrial changes by the panel convened by NICHD, there were no recommendations regarding pathological interpretation of the unusual changes associated with PRM use. Therefore, in the studies done prior to this time, potential overdiagnosis of endometrial hyperplasia in patients using PRM such as mifepristone could have occurred. However, the long term implications of these changes have not been established.*

[22] Spitz IM, Mifepristone:where do we come from and where are we going? Clinical development over a quarter of a century. *Contraception*. 2010. 82;442-452.
[23] Chabbert-Buffet N, Meduri G, Bouchard G, et al. Selective progesterone receptor modulators and progesterone antagonists: mechanism of action and clinical applications. *Human Reproduction Update*. 2005. 11 (3);293-307.
[24] Mutter GL, Bergeron C, Deligdisch L, et al. The Spectrum of Endometrial Pathology induced by progesterone receptor modulators. *Modern Pathology*. 2008. 21.591-598.

Mifepristone exposure in Pregnancy

Administration of mifepristone followed by a prostaglandin, usually misoprostol, is a common medical abortion regimen throughout the world.[25] The US Food and Drug Administration (FDA) approved a protocol of 600 mg mifepristone orally to be followed in forty eight hours by misoprostol 400 µg orally until 49 days of gestation. Patients are evaluated fourteen days after administration of medications, and if a gestational sac is seen, suction dilation and curettage is performed. This drug regimen is 92% successful in pregnancies up to 49 days, and from 43-49 days is 91-95% effective.

However, in clinical practice, an alternative evidence-based regimen has been implemented to reduce side effects and cost of medical abortion. Per this regimen, patients are given a 200 mg dose of mifepristone orally followed by 800 µg of misoprostol vaginally. A 95-99% success rate is seen for pregnancies up to 63 days with this regimen. In a survey of abortion providers published in 2003, they noted that 83% of providers used the 200 mg regimen for medical abortions.

An ACOG practice bulletin regarding medical abortion states that there is no evidence that mifepristone is teratogenic. Bjornsson[26] et al reported three cases in which patients were given mifepristone for pregnancy termination and then decided to continue pregnancy. Each patient received mifepristone at eight to nine weeks gestation and then prior to prostaglandin administration did not wish to proceed with pregnancy termination. All three patients had live births of normally developed infants.

In the Mifeprex labeling, 82 cases of patients who received mifepristone or mifepristone in combination with misoprostol and had on-going pregnancies were reported as of May 2000. Of the 42 patients treated with Mifepristone alone, three patients had surgical abortions and one fetus had a diagnosis of sirenomelia and cleft palate. Among the 13 patients with live births, no abnormalities were detected in the infants at birth. [27]

REMS Considerations

The Division of Metabolic and Endocrine Products requested that the PMHS-MHT consider whether risk mitigation strategies are needed to ensure the safe and effective use of (b) (4) among patients with Cushing's Syndrome. The REMS established by the Food and Drug Administration (FDA) for Mifeprex (mifepristone) addressed risk issues specific to use of the drug as part of an effective regimen for medical abortion at and before 49 days gestation. While sharing the same active ingredient, Mifeprex and (b) (4) would be indicated for different patient populations and for the treatment of different medical conditions. This section will provide an overview of the Mifeprex REMS, explore the risk mitigation issues for Corcept, and discuss whether the Mifeprex REMS provides an appropriate model for a potential REMS for Corcept.

[25] ACOG Practice Bulletin, Medical Management of Abortion. Number 67, October 2005.
[26] Bjornsson S, Lunan CB, Cohn MR et al. Normal development after mifepristone exposure in early pregnancy. Lancet. 1990. 336 (8709). 257-258.
[27] Mifeprex labeling, last revised 7/9/2005, page 10

The Mifeprex REMS includes a medication guide to educate patients, provides a system to certify providers and ensure that providers can monitor patients and treat complications of medical abortions, and establishes the restricted distribution of Mifeprex to certain providers. The following concerns regarding the use of Mifeprex likely contributed to the current framework of the REMS:

- exposure of a healthy patient population for an elective procedure
- the need to use a prostaglandin (such as misoprostol) subsequently for increased efficacy
- follow up after treatment to confirm completed pregnancy termination or the need for surgical intervention.

However, several key differences exist between of use of mifepristone as an abortifacient and for the treatment of Cushing's syndrome. These include the different prescriber population, the underlying medical condition that the drug is treating, the need for chronic management rather than an individual treatment cycle, and the concern for inadvertent exposure during a pregnancy.

The prescribers of Mifeprex differ from those healthcare practitioners who may prescribe (b) (4) for patients with Cushing's syndrome. The chronic nature of Cushing's syndrome necessitates management of the Cushing's patient by a healthcare provider who has a long term relationship with the patient. In contrast, because many of the providers of medical abortion do not have general obstetrics and gynecology practices, and loss to follow up after medical abortion is a concern. Because of the risk of bleeding and infection associated with incomplete abortion, the need for a post-treatment evaluation verifying completed abortion, which is specified in the REMS, is essential to the safe use of Mifeprex.

Furthermore, a goal of the Mifeprex REMS is to ensure that the prescribers are able to manage appropriately the complications of incomplete abortion. Because patients with Cushing's syndrome need medication to treat an ongoing and serious medical condition, they are more likely to have a healthcare provider who will monitor the use of this drug on a regular basis as part of an extended treatment plan. Furthermore, in the subset of Cushing's patients that the Sponsor is proposing for the use of mifepristone therapy, other treatment options are limited.

Another consideration when using mifepristone (Corcept) for the treatment of Cushing's syndrome is the potential for inadvertent pregnancy termination. However, both the disease state itself and the effects of long term use of mifepristone upon the menstrual cycle and endometrium mitigate this risk and make pregnancy highly unlikely. Pregnancy is a rare occurrence in patients with uncontrolled Cushing's disease, such as the patient population proposed by the Sponsor. In the review of literature by Lindsay et al published in 2005, only 136 pregnancies were identified in patients diagnosed with Cushing's disease. In the case studies from the NIH experience, only four patients with Cushing's syndrome were diagnosed with pregnancy in a fifteen year interval. Additionally, unlike patients presenting for a medical abortion, patients with Cushing's syndrome would receive continuous, not intermittent, dosing of mifepristone. As seen in the Spitz et al study, most female patients taking mifepristone long term and in the doses proposed for the treatment of Cushing's syndrome experience delayed ovulation and prolonged amenorrhea. Furthermore, in order to prevent exposure in the first trimester to minimize the risk

of pregnancy termination, females of reproductive potential with Cushing's syndrome could be screened prior to administration of this drug with a pregnancy test.

From a pregnancy planning and prevention perspective, especially in the first trimester, a goal of REMS would be to prevent fetal exposures to a known or suspected human teratogen in females of reproductive potential through labeling, education, required or recommended use of contraception, and pregnancy testing. For mifepristone, existing data indicate that exposure in the first trimester is not teratogenic. Therefore, REMS elements to minimize the risk of pregnancy such as requirements for contraception or periodic pregnancy testing may be too burdensome in the patient population being treated with (b) (4). Therefore, dissimilarities in the patient population, the healthcare providers, the disease state, and the effect of the drug itself between (b) (4) and Mifeprex indicate that a REMS may not be needed for safe and effective (b) (4) use.

Internal discussions have occurred about the potential need for a restricted distribution program for (b) (4) based on concerns about potential off label use for medical abortion resulting from increased access to mifepristone. Currently, Mifeprex distribution is through certified providers only. While the FDA approved regimen for medical abortion is a 600mg of mifepristone followed by 400 µg of misoprostol, the evidence based off–label regimen that is used most frequently in clinical practice is 200 mg of mifepristone followed by 800 µg of misoprostol. (b) (4) will be marketed as 300 mg tablets. Use of (b) (4) for the evidence based regimen (200 mg mifepristone) would be difficult, but potentially it could be used for the FDA approved regimen (two 300 mg tablets). However, providers would be departing from the current standard regimen to a regimen is potentially more costly in order to use (b) (4).

DISCUSSION

Mifepristone (Corcept) is a progesterone receptor modulator (PRM) that acts as an antiprogestin. In higher doses, mifepristone's mechanism of action includes antagonism of the glucocortoid receptor. The Sponsor is seeking approval for the use of (b) (4) (mifepristone) for the treatment of patients with Cushing's disease who have not adequately responded to or have relapsed after surgery, who are not candidates for surgery, (b) (4). The proposed dose is 300mg daily, which may be increased up to 1200mg daily.

Cushing's syndrome is a relatively rare disease but is associated with significant morbidity and increased mortality. Cushing's syndrome affects females with a greater preponderance than males. The major cause of death is cardiovascular disease. The challenges in diagnosis of the disease remain because of similarities to other more common diseases such as diabetes and hypertension. Even after primary therapy, which is generally surgical removal of a tumor, there is a significant relapse rate.

Because female patients with Cushing's syndrome often have ovulatory dysfunction and irregular menses causing them to have decreased fertility, spontaneous pregnancy is rare in this population. Furthermore, given continuously in the doses proposed by the Sponsor, mifepristone

causes amenorrhea. Based on the effects of the underlying medical condition and the effects of mifepristone, pregnancy is unlikely in female patients with Cushing's syndrome, However, given mifepristone's abortifacient effects, it would be prudent to test females of reproductive potential for pregnancy prior to starting (b) (4) treatment for Cushing's syndrome.

Mifepristone (Mifeprex) has an approved indication for medical abortion. However, the Food and Drug Administration (FDA) approved regimen using 600 mg mifepristone followed by 400µg of misoprostol is not used often in clinical practice. The evidence-based regimen of 200 mg mifepristone followed by 800 µg of misoprostol is predominantly used. A REMS was created for Mifeprex in order to ensure safe use of this product. The REMS provides education through a medication guide, ensures that the providers could adequately follow up and treat complications of medical abortion, and restricts distribution to sites that were supervised by certified prescribers.

When considering whether REMS would be appropriate for Corcept, the chronic nature of Cushing's syndrome and the patient population being treated with (b) (4) must be considered. Medical management of Cushing's syndrome requires frequent monitoring. Therefore, patients given (b) (4) will be followed on a regular basis to ensure that therapy is efficacious. Furthermore, the healthcare providers prescribing (b) (4) will be a subset of providers well acquainted with Cushing's syndrome. These patients could be informed about the risks and benefits of (b) (4) treatment through a Medication Guide. Finally, DMEP and its consultants discussed the potential use of specialty pharmacies to distribute (b) (4). Because Cushing's syndrome is a relatively rare disease, the population that needs access to (b) (4) is limited, and use of specialty pharmacies may give the patients that need (b) (4) the most convenient access to the medication while discouraging off label use.

RECOMMENDATIONS

1. The Pediatric and Maternal Health Staff's Maternal Health Team (PMHS-MHT) recommends the use of a Medication Guide to educate patients about the safe and effective use of (b) (4) to manage Cushing's syndrome.

2. Distribution of (b) (4) through specialty pharmacies could give access to patients being managed for Cushing's syndrome and would address concerns about off-label prescribing.

3. The need to evaluate females of reproductive potential with an initial serum pregnancy test should be addressed through labeling for (b) (4). Additionally, contraceptive requirements for (b) (4) would be excessively burdensome in the Cushing's population since spontaneous pregnancy occurs rarely.

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/s/

UPASANA BHATNAGAR
09/09/2011

Karen B FEIBUS
09/09/2011
I concur with the information presented and recommendations provided in this review.

LISA L MATHIS
09/15/2011