21 May 2015
EMA/235012/2015
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Corluxin

International non-proprietary name: mifepristone

Procedure No. EMEA/H/C/002830/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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LIST OF ABBREVIATIONS

ΔΔQTcI QTc based on an individual correction

AAG α1-acid glycoprotein

ACTH Adrenocorticotropic hormone

ADR Adverse Drug Reactions

AE Adverse Event

ALT Alanine Aminotransferase

AST Aspartate Aminotransferase

AUC Area Under Curve

BCRP Breast cancer resistant protein

BDI-II The Beck Depression Inventory II

BfArM German Bundesinstitut für Arzneimittel und Medizinprodukte

BID Twice Daily

BMI Body Mass Index

BUN Blood Urea Nitrogen

CAR Constitutive androstane receptor

Cmax Maximum Concentration

CNS Central nervous system

CrCl Creatinine Clearance

CRH Corticotrophin-Releasing Hormone

CSR Clinical Study Report

Ctrough Trough concentration

CYP Cytochrome P450

DBP Diastolic Blood Pressure

DDI Drug-drug Interaction Study

DRB Data Review Board

DXA Dual Energy X-ray Absorptiometry

ECG Electrocardiogram

EMA European Medicines Agency

ET Early Termination

F Female(s)

GCP Good Clinical Practices

GR Glucocorticoid Receptor

HDL High-Density Lipoproteins

HOMA-IR Homeostatic Model of Insulin Resistance

HPA hypothalamic-pituitary-adrenal

HPLC High Pressure Liquid Chromatography

IC_{50} Half maximal inhibitory concentration

ICH International Conference on Harmonisation of Technical

Requirements for Registration of Pharmaceuticals for Human Use

K_i Binding affinity of the inhibitor

LOCF Last Observation Carried Forward

M Male(s)

MAA Marketing Authorisation Application

MCS Mental Component Summary

MedDRA Medical Dictionary for Regulatory Activities

MHRA British Medicines and Healthcare Products Regulatory Agency

MIFE Mifepristone

mITT Modified Intent-to-Treat

MPA Swedish Medical Products Agency

MR Mineralocorticoid Receptor

MRI Magnetic Resonance Imaging

MS/MS Tandem Quadrapole Mass Spectrometric

MTBE Methyl Tertiary Butyl Ether

NDA New Drug Application

OD Once Daily

oGTTs Oral Glucose Tolerance Tests

PAEC Progesterone Modulator-Associated Endometrial Changes

PCS Physical Component Summary

PD Pharmacodynamics

P-gp P-Glycoprotein

pH Potential of Hydrogen

PIP Paediatric Investigation Plan

PK Pharmacokinetic(s)

PsyD Psychotic depression

PT Preferred Term

PXR Pregnane X receptor

QD Once daily

QoL Quality of Life

QTc Corrected QT interval

RBC Red blood cells

SAE Serious Adverse Event

SBP Systolic Blood Pressure

SD Standard Deviation

SOC System Organ Class

T4 Free Thyroxine

TEAE Treatment-emergent adverse event

TQT Thorough QT Interval study

TSH Thyroid-stimulating Hormone

UFC Urinary Free Cortisol

WBC White Blood Cells

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Corluxin, in the treatment of signs and symptoms of endogenous Cushing's syndrome in adults is not approvable since "major objections" have been identified to which the applicant has not responded at the time of withdrawal of the application, which preclude a recommendation for marketing authorisation at the present time. The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Quality

1. Clear documentary evidence confirming inspection of the site of finished product manufacture by an EEA competent authority must be provided before a recommendation for the MA can be granted.

2. Adequate control of potentially genotoxic impurities in the active substance has not been demonstrated.

3. The discriminatory nature of the dissolution test on the finished product has not been demonstrated.

Clinical

1. The applicant is asked to comment further on efficacy, in respect of both hyperglycaemia and any other signs and symptoms of Cushing's. Please justify that efficacy can be properly quantified in the absence of a randomised control group and that other changes in patient management during the clinical trial had no important contribution to the changes from baseline observed. Please justify the external validity of the clinical trial results, in particular in the context of other medications that may improve hyperglycaemia.

2. Considering safety issues such as hypoadrenalism, electrolyte disturbance, hypertension, and endometrial hyperplasia, and the limitations to the evidence for efficacy, the applicant is asked to justify further that risk-benefit is positive.

3. Taking account of the above clinical major objections, the applicant is asked to propose an indication which will adequately reflect the study results and intended place of Corluxin in treatment of Cushing's.

Proposal for questions to be posed to additional experts

N/A

Proposal for inspection

GMP inspection(s)

A request for a GMP inspection will be adopted for a manufacturing site in order to verify its GMP compliance status. The outcome of this inspection is required for the Committee to complete its examination of the application and will be needed by Day 181.

GCP inspection(s)

None requested

2. Executive summary

2.1. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice was not obtained but advice was sought from the BfarM, MHRA, and MPA and pre-submission meetings were held with agencies of the rapporteur (IMB) and co-rapporteur (ANSM). Discussion topics included quality, pre-clinical and clinical program questions.

2.2. General comments on compliance with GMP, GLP, GCP

The CHMP has been assured that acceptable standards of GMP are in place for this product type at the sites responsible for the assembly and batch release of this product. However, such assurance has not been provided in respect of the site responsible for manufacture of the finished product; see section 1 above. A major objection is raised in relation to this point.

The CHMP has accepted a QP declaration from the site of batch release in respect of GMP compliance for the source of drug substance.

The applicant has stated that the clinical studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

2.3. Type of application and other comments on the submitted dossier

- Legal basis

This is a centralised application under Article 3(1) of Regulation (EC) No 726/2004, for an orphan designated medicinal product. Application is made under Article 8(3) for a known active substance.

- Accelerated procedure

N/A

- Conditional approval

N/A

- Exceptional circumstances
- Biosimilar application

N/A

- 1 year data exclusivity

N/A

- Significance of paediatric studies

Paediatric committee have agreed PIP, granted a deferral and granted a waiver for one or more subsets of the paediatric population.

3. Scientific overview and discussion

3.1. Quality aspects

Drug substance

The active substance is mifepristone, which has no Ph Eur monograph.

The ASMF procedure is used. The synthesis of the active substance is adequately described and controlled, although some queries exist over control of impurities. In the absence of a pharmacopoeial monograph, the in-house specification proposed by the ASMF holder is generally satisfactory, although some minor queries have been raised. A separate assessment report is provided in respect of the ASMF.

In addition to the data provided in the ASMF, the dossier contains information relating to the micronisation of the active substance . The data relating to this activity is generally satisfactory; however some queries have been raised in relation to validation of analytical methods.

Drug product

The finished product is a film-coated tablet which is formulated using commonly-used excipients; none of the excipients used are of human or animal origin and there are no novel excipients.

The manufacturing process consists entirely of standard processes; wet granulation, drying, compression and film-coating. The manufacturing process is adequately described in the dossier; validation has not yet been completed but a protocol for same has been provided.

A finished product specification is proposed; the proposed specification limits are acceptable. The dissolution test is critical to predicting the *in vivo* performance of the product, but it has not been shown to be discriminatory.

The product is packed in HDPE bottles with PP caps and silica desiccant; this is a widely used packaging system for this type of product.

A 4-year shelf-life with no special storage conditions is proposed.

3.2. Non clinical aspects

Pharmacology

The pharmacological properties of mifepristone are well studied and established in the published literature. The applicant has not performed any nonclinical pharmacodynamic studies to support this indication. The biological basis for anti-glucocorticoid therapy in this indication is established and therefore the lack of studies is acceptable.

In vitro, mifepristone binds the glucocorticoid receptor, exhibiting higher affinity and a longer half life than dexamethasone. Mifepristone also antagonized the effects of dexamethasone in rat thymocytes and pituitary cells. *In vivo*, mifepristone exhibits antagonist action in rats and dogs. The cellular mechanism of action of mifepristone is well characterised; binding to the receptor hinders the GR from releasing from the associated heat shock proteins, preventing nuclear translocation. Mifepristone has three pharmacologically active metabolites with similar affinities for the glucocorticoid receptors when compared to the parent compound. *In vivo*, only the hydroxylated and monomethylated metabolites exhibited an anti-glucocorticoid effect on the thymus, which was weaker in comparison to mifepristone. These metabolites have been measured in toxicokinetic investigations as part of the pivotal toxicology studies.

The effects of mifepristone on the progesterone, androgen, mineralocorticoid and estrogen receptors have been characterised. Mifepristone acts as a progesterone receptor antagonist in vivo, whereas binding affinity for the mineralocorticoid, androgen and estrogen receptor is minimal.

The in vitro cardiovascular studies performed for this MAA indicate a potential for QTc prolongation. The IC_{50} for hERG inhibition was not determined due to solubility limitations but was estimated to be > 10 µM (4.3 µg/mL). Moreover, QTc prolongation was noted in the chronic dog study at high doses (60/40 mg/kg) at week 52. Clinical studies have shown that high doses of mifepristone caused small prolongation of QTc interval from 3 to 7 seconds. These nonclinical findings are potentially clinically relevant, and should be reflected in the SmPC section 5.3.

It is unclear whether the CNS and respiratory studies were conducted to GLP standards, and the species used for the respiratory study is not stated. The applicant states that no respiratory effects were seen at up to 10 mg/kg; this provides no safety margin based on the proposed 1200 mg/day dosage in Cushing syndrome patients.

Pharmacokinetics

In the original studies performed with RU 146 show similar absorption profiles following oral administration to rats and monkeys. Clearance following intravenous administration was varied with plasma $t_{1/2}$ of 1 hour and 15 hours in rats and monkeys respectively. Orally administered mifepristone was rapidly absorbed in rats with C_{max} reached after 15 minutes. Absorption was more moderate in monkeys with a plasma C_{max} of 3 hours. In rats and monkeys the extent of absorption and bioavailability was consistent between species, with 75% absorption but lower systemic bioavailability of 25% and 15% in rats and monkeys respectively, which is considered to be due to intestinal or hepatic metabolism.

In Sprague Dawley rats following oral administration of 5 mg/kg ^{3}H-mifepristone, concentration was greater in most tissues than in plasma after 30 minutes with highest concentration in liver and GI tract, consistent with the route of administration and absorption profile (Deraedt *et al*, 1991). Radioactivity was decreased substantially by 24 hours. Radioactivity remained highest in the liver and GI tract, as well as kidney and in erythrocytes. The relatively high retention in erythrocytes may be reflective of globulin binding, as in human plasma, mifepristone is primarily bound to alpha-1-acid glycoprotein which reached saturation at mifepristone concentrations of 2.5 µM (Heikinheimo et al, 1987). Rat data indicates mifepristone crosses the blood brain barrier with levels roughly one third that of plasma. Mifepristone was found to cross the placental barrier in rats, with foetal exposure measurable by 24 hours post-dose.

Mifepristone was highly bound in rat monkey and human, ranging from 93% in monkey to 99% in human. With the exception of protein binding by ultracentrifugation in monkeys, protein binding was consistently ≥ 97% across species. The in vitro analysis of human plasma protein binding to the three active metabolites showed similar binding values to the parent molecule (99% for RU 42633, 98% for RU 42698 and 96% for RU 42848).

The data indicate that human metabolites are also formed in rats, dogs, and cynomolgus monkeys. Based on metabolism in rat, monkey and human liver S9 fractions, the major metabolites form in animals to a similar or greater extent than in humans. Thus the three active metabolites RU 42633 RU 42848 and RU 42698 are predicted to be present in *in vivo* toxicology studies. The data suggest that CYP3A4 is the principle metabolising enzyme involved in rats and humans. The data is supported by clinical studies which identify CYP3A4 as the principle metabolising enzyme; potential interaction with concomitant administration of CYP3A4 inhibitors is described in the SmPC.

The CYP inhibition study suggests a potential for inhibition (IC_{50} of <10 µM) of CYP3A4 and CYP2C8 by mifepristone, CYP2A6, CYP2C8/8/19 by the active metabolites. These *in vitro* studies are not described in the pharmacokinetic written or tabulated summaries. *In vitro* CYP induction studies with mifepristone indicate a potential for induction of CYP3A and CYP2B enzymes. The potential for an interaction with drugs metabolised by these enzymes are highlighted in the SmPC.

In a study of transporter interactions, mifepristone inhibited transport by MDR1, BCRP and BSEP, and uptake transporters OATP1B3, OATP1B1 and OATP2B1 at clinically relevant concentrations. Thus drug interactions with substrates for these transporters are possible. Furthermore, *in vitro* data suggest mifepristone may inhibit P-glycoprotein. The relevant potential interactions should be described in the SmPC.

Toxicology

The applicant has performed GLP repeat-dose studies in rat dog and monkey, in vitro genotoxicity studies and carcinogenicity studies in rat and mouse. The studies are complemented by publicly available study summaries and literature reports, largely from the prior NDA assessment of Mifegyne.

Repeat-dose toxicity studies were conducted in mice rats rabbits and dogs by the oral route. For pivotal studies rats and dogs were used. The applicant did not perform a 6 month chronic toxicity study in rats in accordance with ICH M3 (R2); however in-life and terminal observations in line with the guideline on repeated dose toxicity (CPMP/SWP/1042/99 Rev 1 Corr) were integrated into the 2 year carcinogenicity study. The approach is acceptable, however no recovery groups were included in the toxicity studies.

In mice liver, thymus, kidney and female reproductive organs were targets of toxicity. Findings in the 13 week uterine effects were consistent with the pharmacological effect associated with the anti-progesterone activity of mifepristone. Target organs for toxicity were the thymus with lymphoid necrosis in females and one high dose male, adrenal gland in females, and liver with associated hepatocellular hypertrophy. These findings were considered related to the pharmacology of mifepristone, or stress/adaptive responses**.**

In rats, mifepristone treatment identified liver, pituitary and adrenal glands were all target organs as indicated by organ weights and macroscopic and microscopic findings. In the 13 week study changes in liver weight were at doses of 125 mg/kg. The findings are in agreement with the prior studies for Mifegyne/Mifeprex. In addition to target organs seen in the 12-week study, significant ocular toxicity was identified, manifested as diffuse retinal degeneration at weeks 52 and 104 at 125 mg/kg/day, and increased incidence of cataracts in males at 125 mg/kg/day which was not statistically significant. Retinal atrophy occurred in all groups but the significance of the finding is unclear due to the high occurrence in control animals. These data should be included in the SmPC.

In dogs the main target organs of toxicity were liver, kidney, pituitary, spleen, thymus and reproductive organs and GI tract. Electrocardiograph identified a dose-related prolongation of the QT and QTc intervals at ≥ 25 mg/kg. Overall, the toxicity profile was similar across the species investigated. The effects pituitary, adrenal gland, thyroid and reproductive system can be considered related to the pharmacology of mifepristone. Effects on liver including increased AST/ALT, hepatocellular toxicity and deposition of hepatocellular pigments were treatment-related. Effects on kidney also occurred in rats, dogs and monkeys with histopathological correlates. Reversibility was not determined, and the significance is unclear.

The applicant has performed an *in vitro* bacterial mutation test and human lymphocyte chromosome aberration test which are both GLP-compliant. The *in vitro* studies do not indicate any

genotoxic potential for mifepristone. No in vivo genotoxicity study has been performed by the applicant; therefore no GLP in vivo study is available. Given the neoplastic findings in the 2 year carcinogenicity study, the applicant should further justify the absence of the in vivo study in the context of the carcinogenicity findings.

The applicant performed GLP carcinogenicity studies in mice and rats of 2 years duration. In mice there was no statistically or biologically significant increase in the incidence of neoplastic findings in males or females. Abnormal ophthalmoscopic findings were seen in all groups. The study does not indicate that mifepristone is carcinogenic in mice at up to 125 mg/kg/day. In rats mifepristone increased the incidence of spontaneous thyroid and hepatic tumours. Thyroid follicular cell adenomas were seen in males given 125 mg/kg/day and thyroid follicular cell adenomas, follicular cell carcinomas and hepatocellular adenoma occurred in females given 125 mg/kg/day, which are considered to be statistically significant and treatment-related. There is evidence that mifepristone is carcinogenic in rats when administered at 125 mg/kg/day for 2 years.

No reproductive and developmental studies have been performed for this application. A single study of treated female rats and untreated males was performed and assessed as part of the Mifegyne/Mifeprex development programme, which investigated fertility 5 weeks after cessation of treatment. The GLP status of this study is unknown. Oestrus cycle in female rats was interrupted within 10 days of administration, and was restored over 2-3 weeks. No reproductive parameters were affected after the 4 week recovery period. Studies performed in accordance with ICH S5 (R2) are not available.

Mifepristone was clearly foetotoxic in mice and rats with a marked increase in foetal loss. The abortifacient activity of mifepristone is well-characterised and is in agreement with the studies described by the applicant. In rabbits, mifepristone was associated with increased foetal loss and teratogenic effects including acephaly, exencephaly, coelosomy, torsion/flexion of a hind paw, and ossifications, were observed in two studies. As mifepristone for the treatment of Cushing syndrome is contraindicated in women who are pregnant or may become pregnant, the teratogenic effects in the nonclinical studies are addressed.

Pre- and post-natal developmental toxicity studies in line with ICH S5 (R2) have not been performed. In rats administered mifepristone from gestational day 15 to the end of weaning, treatment was not associated with developmental effects, sexual development or reproductive function. Neurological parameters were moderately affected by treatment. The studies do not indicate a potential for altered post-natal development. Considering mifepristone for the treatment of Cushing syndrome is contraindicated in women who are pregnant or may become pregnant, the effects on neurological development are considered to be adequately addressed.

Ecotoxicity / environmental risk assessment

Mifepristone is not a PBT substance as log Kow does not exceed 4.5. The calculated PECsurfacewater value is not considered appropriate. As the mifepristone PEC surface water value of 0.0156 µg/L is above the action limit of 0.01 µg/L, a phase II environmental fate and effect analysis is required.

Discussion on non-clinical aspects

The pharmacological properties of mifepristone are well studied and established in the published literature. The applicant has not performed any nonclinical pharmacodynamic studies to support this indication. Mifepristone is a synthetic steroid compound with both antiprogesterone and antiglucocorticoid properties. Antagonistic effects of mifepristone have been shown on

progesterone (mifepristone acts as an antagonist of PR with a higher affinity than progesterone itself) glucocorticoid and androgen receptors. As this application concerns the known active substance, mifepristone, and the pharmacology of the product is well established, the absence of new pharmacodynamic studies is acceptable.

In vitro cardiovascular safety pharmacology studies performed for this MAA indicate a potential for QTc prolongation which may be clinically relevant, given clinical findings, and should be described in the SmPC. Previously performed studies of CNS and respiratory safety did not indicate clinically relevant effects with mifepristone.

Absorption data are based on literature review and in a dedicated single dose PK-study conducted in dogs after single oral or s.c administration. It was found that absorption is saturated when dose is ≥ 400 mg/kg. Systemic exposure is significantly higher for females compare to males in animals. Mifepristone is rapidly and widely distributed throughout the body following oral administration to rats. It was seen that concentrations in tissues/organs were higher than in plasma and the highest levels of were detected mostly in the liver, GTI, adrenal gland, kidney. Binding studies demonstrated that mifepristone and its metabolites are highly bound to plasma proteins in the rat, monkey and human. Metabolism of mifepristone occurs via a two different mechanism demethylation or hydroxylation, both involving CYP3A4 and/or CYP2B and CYP2C. Mifepristone can also inhibit or induce CYP3A4/CYP3A and also regulate activity of CYP2A6, CYP2C8. In a study of transporter interactions, mifepristone inhibited transport by MDR1, BCRP and BSEP, and uptake transporters OATP1B3, OATP1B1 and OATP2B1 at clinically relevant concentrations. Thus drug interactions with substrates for these transporters are possible. Furthermore, *in vitro* data suggest mifepristone may inhibit P-glycoprotein.

The toxicology package consists of summaries of previous studies with mifepristone in publicly available study summaries and literature reports, largely from the prior NDA assessment of Mifegyne. New studies performed for this MAA include GLP repeat-dose studies in rat dog and monkey, in vitro genotoxicity studies and carcinogenicity studies in rat and mouse. The repeat-dose studies are acceptable in terms of duration, dose selection, and species selection. Treatment related effects have been identified in various organs such as liver, reproductive organs, endocrine organs, kidney, lungs, heart and eye (retinal effects). Liver appears to be a target organ of toxicity in mouse, rat and dog at systemic exposure lower than clinical exposure. Indeed, increased liver weight, centrilobular hypertrophy and hepatocellular toxicity were observed. Hepatocellular adenomas are consistent with rat-specific enzymatic induction in the liver and a subsequent increase in thyroid hormone metabolism that may involve neoplasia. However in the absence of further mechanistic studies the clinical relevance cannot be ascertained.

Treatment-related effects on reproductive organs were observed at low systemic exposure compare to MHRD (1200 mg/day, AUC basis) in mice, rats and dogs. These effects are attributable to the pharmacodynamic effect of mifepristone and more precisely its anti-progesterone and anti-androgenic activities. The applicant did not conduct any additional studies regarding reproductive and developmental issues. These issues have been investigated during the development of Mifeprex (Pharmacology Review(s) NDA 20-687) and the absence of studies is acceptable.

The ERA phase I PECsw determined by the applicant is not endorsed since PECsw value calculated is based on an incorrect Fpen value. A Phase II environmental fate and effect analysis should be performed.

Conclusion on non-clinical aspects

Provided that the other concerns are sufficiently resolved there are no non-clinical objections to marketing authorisation for mifepristone.

3.3. Clinical aspects

Pharmacokinetics

Mifepristone is a derivative of norethindrone. It is structurally similar to progesterone and glucocorticoids, but differs from both by the absence of the C19 methyl group and the 2 carbon side chain at C17, the 3-carbon acetylenic group at C17, the dimethylaminophenyl group at C11, and by the presence of a conjugated C9-C10 double bond.

Mifepristone is a steroid which contains 10.7% nitrogen and oxygen, and 89.3% hydrocarbon.

Absorption

The applicant considers that mifepristone is a weak base with low solubility at the near neutral pH values of the intestine and is a class II drug (i.e., low solubility/high permeability) in the Biopharmaceutics Classification System.

The effect of food on exposure and C_{max} at doses above 600 mg is considerably larger than that which can be achieved by dose increase alone for Corluxin administered in the fasted state. Based on the most recent pharmacokinetic studies, it is recommended that Corluxin should be taken with food.

Distribution

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 and distribute to other tissues, including the central nervous system (CNS). As determined in vitro by equilibrium dialysis in Study C-1073-PK-002, binding of mifepristone and its three active metabolites to human plasma proteins was only slightly concentration-dependent. Binding 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.

Metabolism

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.

Cytochrome P450 3A4 (CYP3A4) has been shown to be the only isoenzyme involved in mifepristone metabolism in human liver microsomes.

In vitro and *in vivo* studies evaluating the inhibitory effect of mifepristone on various CYP450 enzymes have been performed by the applicant and others have been reported in the literature.

Excretion

Ninety per cent of a radio-labelled dose of mifepristone is recovered in the faeces, with biliary excretion as the primary route of elimination; excretion in the urine accounts for less than 10% of the dose.

Special populations

There were no obvious indications of an association between mifepristone exposure and age, body weight and race. Some sex differences in mifepristone PK were noted however no modifications in starting doses are recommended for males and females.

The maximum recommended dose is limited to 600mg once daily in patients with renal and hepatic impairment**.**

The safety and efficacy of Corluxin in children below the age of 18 years have not yet been established.

There is limited data on use of Corluxin in the elderly however there is no evidence to suggest that dose adjustment is required in this population.

Conclusions on clinical pharmacokinetics

No formal investigations regarding elimination and excretion (mass balance study) have been done by the sponsor. However data from literature are available. Mifepristone is slowly and mainly eliminated by biliary excretion. 90% of dose of mifepristone is recovered in the feces, with biliary excretion as the primary route of elimination, excretion in the urine accounts for less than 10% of the dose.

Based on reported studies, the total clearance by oral route (CL/F) was only estimated on healthy volunteers and at 600 mg single-dose, it was estimated of 4.9 ± 2.3 L/h. The $T_{1/2}$ of the parent compound ranged from 35.9 to 90.8 hours following multiple dose administration. The terminal portions of the log concentration versus time curves show an increase in the rate of decline in concentrations at later times and are indicative of a non-linear kinetic process.

Mifepristone systemic exposure appears to evolve markedly less than proportionally to the dose in both healthy volunteers and patients after single or multiple dose administration. For instance, for Cushing's patients, doubling the dose from 300 to 600 mg resulted in only a 5% increase in C_{trough} values. Increasing the dose from 600 to 900 mg and from 900 to 1200 mg resulted in increases of C_{trough} of 21% and 5%, respectively.

In healthy volunteers, the available data shows that increasing dose from 600 mg to 1200 mg leads to negligible increase in systemic exposure. Therefore, the relevance of the claimed dosing scheme (dose escalation from 600 to 1200 mg) is not supported by the available PK data. The usefulness of the highest dose (1200 mg daily) should be substantiated based on clinical efficacy/safety data. According to the applicant, such non proportionality is linked to low solubility of mifepristone, rather than to saturation of plasma protein binding or transporters system.

Mifepristone has non-linear time- and dose-dependent kinetics driven by competing auto-inhibition and auto-induction that is largely determined by CYP3A status. After multiple dosing, these mechanistic bases define a relatively stable and uniform metabolic state. The time span to reach metabolic stability for multiple dose mifepristone would generally be a week or so, with some individual variation. Therefore a shift in mifepristone PK in the long-term use after reaching this steady-state is not expected.

A rough estimate of intra-individual variability is provided by the applicant. This estimate is not derived from cross-over studies (given the long and variable terminal half-life of mifepristone, multiple dose cross-over designs were avoided by the applicant) or PK population analysis, but from 2 studies in which bioequivalence was shown between 2 or more multiple dose profiles within a study. Based on these studies covering the dose range for mifepristone of 300 to 1200 mg, within-subject variability showed a CV% value of less than 10% for both C_{max} and AUC_{0-24}. The within-subject variability represented 13 to 34% of the between-subject variability.

Two clinical PK investigations have been performed in Cushing's patients. Based on the statistical analysis (ANOVA), conflicting results were obtained with regards to comparability between healthy volunteers and patients. According to the applicant, the absence of PK population analysis is justified by the poor documentation of PK observation in patients (food status, time sampling, concomitantly administered drugs, availability of only C_{trough} data in patients, etc…). Conclusively, the Mifepristone's PK in patients is not significantly documented. Therefore, the applicant should provide formal PK investigations in patients or indicate how the available data in Healthy subjects can be extrapolated to patients.The effect of renal insufficiency on mifipristone PKs has been investigated in severe patients. The conclusions made by the applicant could be endorsed:

In the renal impairment study C1073-19, 1200 mg mifepristone was given OD fasted for 7 days. The steady-state is not reached by day 7; and reported exposures on day 7 would most likely be higher (because of continued induction) than those at day 14. Nevertheless, under the assumption that the mifepristone CYP3A auto-induction in renal impairment patients is similar to that in healthy subjects, the comparison between normal and severe renal impaired subjects using PK data (AUC_{0-24}) at Day7 could be acceptable. The outcome of the study showed that C_{max} and AUC_{0-24h} of mifepristone increased by 30% and 31%, respectively, in subjects with severe renal impairment as compared to matched healthy volunteers. For metabolites, C_{max} and AUC_{0-24h} increased by 50% and 56% for RU 42633, 33% and 35% for RU 42698 in severely impaired subjects.

Comparison of GM terminal $t_{1/2}$ from day 7 for mifepristone and its 3 main metabolites between ESRD patients and healthy subjects do not show evidence that ESRD led to an increase in terminal $t_{1/2}$. Haemodialysis is not deemed to reduce effectively systemic drug load of mifepristone.

The effect of hepatic insufficiency on mifepristone PKs has been investigated in moderate hepatic impaired subjects (Child-Pugh B). Similar pharmacokinetic parameters were observed following single and multiple dose (7 day) administration in subject with moderate liver insufficiency and matched healthy volunteers. Considering that metabolism is the main route of elimination (90%) of mifepristone, the outcome of the study is almost unexpected. The conclusions made by the applicant from this investigation could not be endorsed. Additionally, the comparison of systemic exposure in normal and moderate liver impaired subjects was mainly made upon AUC24 at day 7 after repeated dose administration, while steady-state is not reached on day 7. The reported exposures on day 7 would most likely be higher (because of continued induction) than those at day 14 and no evidence that mifepristone CYP3A auto-induction in hepatic impairment patients is similar to that in healthy subjects. Therefore, PK conclusions (similar mifepristone PK parameters between the two groups) from such results could not be endorsed. The recommendation in patients with mild-to-moderate hepatic impairment to not exceed 600 mg OD administered with food, could be endorsed. The contra-indication of mifepristone in patients with severe hepatic impairment could be endorsed.

No formal investigations, neither PK population analysis have been performed in order to characterize the effect of intrinsic factors (age, weight, sex, smoking status and race/ethnicity) on the PKs of mifepristone under the claimed conditions of use. However, taking into account the importance role of the metabolic balance between inhibition and induction that defines, after multiple dosing, a relatively stable and uniform metabolic state that is largely determined by CYP3A status, only intrinsic factors that have such metabolic effects will be of clinical significance. Therefore, the effects of usual covariates such as sex, age and body parameters are expected to be small. Exploratory and univariate analyses provided by the applicant could be accepted.

The claimed indication implies the use of mifepristone in adult's patients only. The safety and efficacy of Mifepristone in children below the age of 18 have not yet been established.

There are a few pharmacokinetic issues which require clarification by the applicant. Further drug-drug interaction studies are required.

Pharmacodynamics

Mifepristone is competitive antagonist of the progesterone receptor at low doses and also competitively antagonises the glucocorticoid receptor (GR) at higher doses. Mifepristone has high affinity for the GR but little or no affinity for the mineralocorticoid receptor (MR). In addition, mifepristone appears to have little or no affinity for oestrogen, muscarinic, histaminic, or monoamine receptors.

There are 6 known metabolites: RU 42633, RU 42848, RU 42698, M4, M5 and M6. It is reported in the literature that 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%).

Results of studies submitted in healthy subjects indicate that mifepristone did not indicate a meaningful effect on the QTcF interval.

In vitro and *in vivo* studies evaluating the effect of mifepristone on various CP450 enzymes have been performed and evaluated in the literature. Based on known metabolism of mifepristone and the drug-drug interaction studies conducted, the drug-drug contraindications and precautions are proposed in the SmPC.

Conclusions on clinical pharmacodynamics

There is already information in the literature on the pharmacodynamics of mifepristone. Data from the literature and new data are presented in this application. Some pharmacodynamic drug interaction issues require clarification in the SmPC by the applicant.

Clinical efficacy

Dose-response studies and main clinical studies

Two uncontrolled studies have been submitted to support efficacy. The pivotal study and an extension of the pivotal study which is regarded as a supportive study.

No dose response/dose finding studies were submitted. The sponsor justifies the dosing on the basis that subjects could present with a wide range of cortisol levels at study entry and therefore optimal dosing might differ from patient to patient. Literature reports of dosing in Cushing's syndrome quote doses ranging from 200mg to 2,000 mg per day of 5 to 30mg/kg/day.

Because the study used a 300-mg mifepristone tablet, fixed daily doses (QD) were increased in a stepwise fashion in 300-mg increments. Dosing started with 300 mg/day (one tablet). Because the optimal dose of mifepristone for each subject was not known, dose escalation was undertaken cautiously with careful observation of clinical status. Dose escalations beyond 300 mg were made under the following conditions:

- If no clinical improvement had been seen,
- If the drug had been well tolerated, and
- Based on the subject's weight at the escalation visit.

After 14 days treatment at a dose of 300mg, the dose of mifepristone would be increased as outlined in Table 1.

Table 1. Mifepristone Dosing Regimen

Subject Weight	Day 1	Day 14	Week 6	Week 10[a]
< 60 kg	300 mg	600 mg	900 mg	900 mg
≥ 60 kg	300 mg	600 mg	900 mg	1200 mg

a Dose escalation stopped at Week 6 for subjects weighing < 60 kg.

Summary of main efficacy results

The pivotal study for this application is Study C1073-400. This is an open label uncontrolled Phase 111 study.

The sponsor justifies the lack of a control on the basis of a lack of an approved comparator drug.

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table: Summary of efficacy for trial C1073-400

Title: 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		
Study identifier	C1073-400	
Design	An open label uncontrolled study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase: Extension phase was a separate study An Open-label Extension Study of the Efficacy and Safety of CORLUX® (mifepristone) in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome C1073-415	24 weeks not applicable A series of 6 month modules up to a total of 36 months
Hypothesis	DM Population Null hypothesis Ho: π 25% reduction in the glucose AUC at 24 weeks $\leq$ 0.2 HT only population Ho:п 5 mmHg reduction in the diastolic blood pressure at 24 weeks ≤ 0.2	
Treatments groups	group descriptor	Not applicable

Endpoints and definitions	Co-Primary endpoints	<label>	Primary endpoint for DM population 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/end of treatment in subjects with diabetes/impaired glucose tolerance with or without hypertension at screening. A responder analysis using the modified Intent-to-Treat (mITT) population was used to measure success on this primary efficacy endpoint. A responder was defined as a subject who experienced at least a 25% decrease in AUCglucose from baseline to Week 24. This efficacy measurement was to be declared successful if the lower limit of the exact 95% binomial confidence interval for the responder rate was ≥ 20%. Primary endpoint for hypertension only population: Change in diastolic blood pressure from baseline to Week 24/end of treatment. A responder analysis of the reduction in diastolic blood pressure from baseline to Week 24 was performed for the efficacy population. A responder was defined as a subject who experienced a ≥ 5 mmHg decline in diastolic blood pressure from baseline to Week 24. This efficacy measurement was to be declared successful if the lower limit of the exact 95% binomial confidence interval for the responder rate was ≥ 20%.

	Secondary endpoints	label	*Clinical improvement as determined by the Data Review Board*: a responder analysis was used to determine clinical improvement in all subjects. The DRB performed a review of eight categories of clinical parameters to evaluate whether a subject's signs and symptoms of Cushing's syndrome had changed. For this secondary efficacy endpoint, a responder was defined as a subject whose median reviewer score was +1 (of possible ratings of -1, 0, or +1) at any reviewed visit after baseline through Week 24/ET. This efficacy measurement was to be declared successful if the lower limit of the exact 95% binomial confidence interval for the responder rate was ≥ 30%. *AUCglucose or decrease in anti-diabetic medications responder analysis:* a responder was defined the same way as in the primary analysis for C-DM, with the addition of any subject who, at the final visit as compared to the baseline visit, was prescribed a) at least one fewer anti-diabetic drug, or b) a reduction in the total daily dose of an anti-diabetic drug using descriptive statistics (95% binomial confidence interval [CI]) • *Body weight:* percent change from baseline in body weight as measured at the last visit (Week 24/ET) in the combined C-DM and C-HT subjects using descriptive statistics (95% CI) • *Diastolic blood pressure or change in antihypertensive medications responder analysis*: a responder was defined the same way as in the primary analysis for C-HT, with the addition of any subject who, at the final visit as compared to the baseline visit, was prescribed a) at least one fewer antihypertensive drug, or b) had and maintained a reduction in the total daily dose of an antihypertensive drug. This analysis was conducted in C-HT subjects and C-DM subjects who had a diagnosis of hypertension at baseline using descriptive statistics (95% binomial CI). • *HbA1c:* percent change from baseline in HbA1c as measured at the last visit (Week 24/ET) in the C-DM subjects using descriptive statistics (95% CI) • *Systolic blood pressure:* change from baseline in systolic blood pressure as measured at the last visit (Week 24/ET) in the C-HT subjects and C-DM subjects who had a diagnosis of hypertension at baseline using descriptive statistics (95% CI)
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Modified intent to treat (subjects who had received at least 30 days treatment with Corluxin) Intent to treat (subjects who had received at least one dose of Corluxin)			
Descriptive statistics and estimate variability	Treatment group	DM population	HT only population	DM +HT population
	Number of subject	29 (ITT)	21 (ITT)	50 (ITT)
	AUC glucose responder rate	52%		N/A
	variability statistic	35.2% (lower bound 1-sided 95% Exact binomial CI)		
	DBP responder rate		38.1%	
			20.57% (lower bound 1-sided 95% Exact binomial CI)	

Primary efficacy analysis

Subjects with diabetes mellitus and impaired glucose tolerance (DM)

A response in AUCglucose was observed in 60% of the subjects (95% CI lower bound, 42%) in the mITT population. Because the lower bound of the 95% CI was greater than 20%, according to the sponsor this response rate of 60% was statistically significant. Note the 95% confidence intervals were calculated using a one sided rather than two sided test.

The results of the responder analysis for the ITT population were similar to those for the mITT population and were also statistically significant (52% response rate and 35% lower bound 95% CI for the ITT population.

In the ITT population the baseline mean value for HbA1c decreased from 7.37±1.52% to 6.25±0.963% at week 24/ET. The 95% CI for the mean change from baseline to Week24/ET was (-1.54%, -0.61%). In addition fasting plasma glucose values declined from 149.0 ± 74.72 mg/dL at baseline to 104.7 ± 37.50 mg/dL at Week 24/ET and the 2 hour post-prandial glucose declined from Baseline at 296.2 ± 89.19 mg/dL to 197.7 ± 91.01 mg/dL at Week 24/ET (Table 14.2.1). Insulin levels also declined over the course of the study.

Subjects with hypertension

A response for diastolic blood pressure was observed in 38% of the subjects (95% CI lower bound, 21%). Because the lower bound 95% CI was greater than 20%, according to the applicant this response rate of 38% was statistically significant (Table 16). However a one sided rather than a two sided 95% CI was used to estimate the lower bound for the percentage of responders. Confidence intervals will need to be recalculated using a two sided test. A two sided test is unlikely

to give a lower bound above 20% given that the one sided test estimated a lower bound of 20.57%. Therefore the results are unlikely to demonstrate statistical significance. The ITT and the mITT populations were the same for the C-HT cohort.

Weight loss

76% of subjects experienced weight loss with a mean percentage loss in the ITT population of -5.17% (-6.63, -3.17) +and there was a decrease from baseline to ET/Week 24 in waist circumference and body fat.

Clinical studies in special populations

No studies were carried out in special populations

Analysis performed across trials (pooled analyses AND meta-analysis)

N/A

Supportive study(ies)

An open label extension study of C1073-400 was conducted and included subjects who had completed the week 24 and 6 week follow up visit and who in the opinion of the investigator were expected to maintain clinical benefit from mifepristone. Patients had a 6 week break from taking mifepristone prior to entering the extension study. Doses were similar to those in Study C1073-400. The primary objective of the study was to evaluate the long-term safety of mifepristone. The secondary objective was exploratory and examined the long-term benefit of mifepristone in Cushing's syndrome as measures by the Physician's Global Assessment of disease Severity and Subject Related Disease Severity Scores. Thirty subjects entered the study and 21 completed. Endpoints included The Physician's Global Assessment of Disease Severity and the Subject Rated Disease Severity Scores. In the view of both patient and physicians patients would have appeared to have demonstrated some improvement in their signs and symptoms of Cushing's syndrome. Unfortunately no evaluation was undertaken on whether improvements in AUCglucose and other parameters related to glycaemic control were maintained in the extension study.

Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has submitted one pivotal study and an extension study to support their application for marketing authorisation. This study was conducted at a number of sites in the US. According to the applicant the study was conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki.

The study was an uncontrolled open label study. At the time of initiation of the study no medical treatments were authorised for Cushing's syndrome. Given the mode of action of mifepristone (glucocorticoid receptor blockade) it would still not be possible to compare it with an authorised product such as pasireotide which has a lowering effect on cortisol levels. The study is a before and after study. In general these studies have weaknesses as it is in the nature for some conditions to improve over time even without treatment. However Cushing's syndrome of the severity described in the study population is most unlikely to improve or remit spontaneously. No new treatments or increases doses of current therapy for diabetes were allowed in the DM population. Therefore any positive changes observed over the course of this study in terms of glycaemic control are likely to be due to mifepristone.

The sample size in this study was small (n = 50). In effect the sample size was even smaller given that this study was really two smaller studies (n=29 for DM population and n=21 for HT population). A sample size was not calculated and was chosen by clinical judgement.

This was due to the fact that there have been no prospective clinical trials from which to estimate a treatment effect or standard deviation of treatment effect in subjects with Cushing's syndrome.

However it is recognised that endogenous Cushing's syndrome is a rare condition with an estimated prevalence of approximately 0.6 in 10,000 people in the European Union (EU). This is equivalent to a total of around 30,000 people.

Efficacy data and additional analyses

The pivotal study had two co-primary endpoints, one for each sub-population. The study was considered to have had a positive outcome and to have achieved the primary endpoint if either of the two primary measures described above were positive.

The primary endpoint for subjects with Cushing's syndrome and diabetes mellitus (or impaired glucose tolerance) (C-DM cohort) was the 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 in subjects with diabetes/impaired glucose tolerance with or without hypertension at screening. A responder was defined as a subject who experienced at least a 25% decrease in AUCglucose from baseline to Week 24 or end of treatment. This efficacy measurement was to be declared successful if the lower limit of the exact 95% binomial confidence interval for the responder rate was ≥ 20%.

In the mITT population 60% were classified as responders (51.7% in the ITT population) The lower bound of the one sided 95% exact binomial confidence interval was 41.68% in the mITT population and 35.2% in the ITT population. It is likely that a 2 sided test would show a lower bound > 20% in both the ITT and MITT populations given the size of the lower bound in the one sided confidence interval.

A decrease in mean AUC glucose was seen as early as week 6 with a mean decrease of 21.8% from baseline. Overall there was a decrease of 27% mean AUC glucose from baseline to Week 24/ET . There was a slight increase in mean AUC glucose between Week 16 and Week 24/ET.

There were a number of secondary endpoints relating to glycaemia control and an exploratory endpoint relating to insulin levels

18 subjects in the DM group had at least a 25% decrease in AUC from baseline to Week24/ET or a reduction in antidiabetic medication (72% in the mITT population and 62% in the ITT population). Changes from baseline to week 24/ET in mean HbA1C reflect changes seen in AUC glucose. The mean change from baseline to week 24/ET in the ITT population was -1.19% (95% CI -1.54, -0.61). In addition reductions in fasting blood glucose, 2 hour post prandial glucose and insulin reflect the changes in AUC and are strongly supportive of the efficacy of Corluxin in managing hyperglycaemia in those with Cushing's syndrome with DM or impaired glucose tolerance.

The applicant has recalculated response rates for the primary endpoint in the DM population using the ITT population and two sided 95% confidence intervals. The lower bound for the 95% CI in the ITT population is 32.5% which is above the pre-defined threshold of 20% for determining efficacy.

The primary endpoint for the hypertension only sub-population was a decrease in diastolic blood pressure of ≥ 5 mmHg in diastolic blood pressure from baseline to Week 24/ET. This efficacy measurement was to be declared successful if the lower limit of the exact 95% binomial confidence interval for the responder rate was ≥ 20%.

The pre-specified primary endpoint was not met for this population. A one sided rather than a two sided 95% CI was used to estimate the lower bound for the percentage of responders. Confidence intervals were recalculated using a two sided test. The lower bound of the two sided 95% CI was 18.1%, which is below the threshold set for defining efficacy, demonstrating that the primary endpoint for efficacy in the HT population was not met.

The failure to demonstrate an effect in the HT population population may be due to patient selection criteria i.e. increased SBP > 140mmHG and/OR increased DBP > 90mmHg or pharmacological therapy for hypertension due to or aggravated by hypercortisolaemia. Therefore a number of subjects were recruited to the study with a 'normal' DBP. In this population it would be anticipated that a further decrease would be unlikely and it is also questionable whether a further reduction would be of benefit. No reduction was noted from baseline to week 24/ET in mean systolic blood pressure.

A Data Review Board of three independent endocrinologists reviewed data on eight parameters for study subjects at the end of the study. Subjects were categorised at each visit as either improved (score +1), unchanged (score 0) or disimproved (score -1) compared to baseline. A responder was defined as a subject who had a median score of +1 at any review. As an endpoint it would have been more meaningful to assess sustained response and a response at any review is likely to exaggerate the overall response.

The evaluation of change based on the eight parameters does not appear to be based on any particular criteria and no weighting seems to have been ascribed to any particular parameter. No guidance has been given on whether improvement would need to have occurred in all parameters or some of the parameters in which the subject was adversely affected at baseline. Overall it is difficult to assess the significance of this efficacy analysis given its subjectivity.

Overall 76% of subjects experienced weight loss over the course of the study. Reductions in waist circumference and body fat were also seen.

Conclusions on clinical efficacy

Efficacy was demonstrated in those with DM and impaired glucose tolerance when two sided 95% confidence intervals are calculated for responders with a reduction in AUC glucose of 25% or more. Reduction in AUC glucose, HbA1C, fasting blood glucose and 2 hour postprandial glucose and insulin were impressive. However it is unclear whether this improvement is sustained. Unfortunately the applicant did not investigate whether the effects on glucose control were maintained in the extension study.

Efficacy in the hypertensive population (in terms of impact on blood pressure) was not shown. This may be due to the population chosen or may be an actual effect. It is possible that the mineralocorticoid effects of cortisol could cause an increase in blood pressure.

Clinical safety

Patient exposure

The safety of mifepristone has been examined in 34 Corcept-sponsored studies, including the **two studies in Cushing's syndrome**, 13 studies in other indications, and 19 studies in healthy volunteers.

A total of approximately 1470 subjects received at least one dose of mifepristone.

Subjects received doses of 300 to 1800 mg daily, with one trial having a loading dose of 3600 mg within 24 hours. Most studies evaluated short courses of mifepristone.

Most subjects in the Cushing's studies have been exposed for 6 months, and some for as long as 42 months. At entry into study C-1073-415, most patients (46.7%) received 600 mg; the mean (±SD) dose in the 30 subjects enrolled was 705.0 mg (± 327.57).

Table 14: Number of Patients/Subjects Exposed in Mifepristone Clinical Studies

Study No.	# Patients treated with mifepristone	Dose [mg]	Duration of treatment
Cushing's syndrome			
C-1073-400	50	300 - 1200	24 weeks
C-1073-415	30	300 - 1200	up to 36.6 months
Other indications			
Major psychotic depression			
C-1073-99-01	33	50, 600, 1200	7 days
C-1073-02	99	600	7 days
C-1073-03	105	600	7 days
C-1073-04	28[a]	600	7 days
C-1073-06	332	300, 600, 1200	7 days
C-1073-07	132	600	7 days
C-1073-09	124	600	7 days
C-1073-10	22[b]	600	7 days
C-1073-13	9[c]	600	7 days
Alzheimer's disease			
C-1073-71	39	300	16 weeks
Induced weight gain			
C-1073-200	7	600	3 weeks
C-1073-200-I	35	600	2 weeks
C-1073-205	46	600	28 days
Studies in healthy volunteers			
C-1073-05	20	600	single dose/7 days
C-1073-12	50	600	single dose
C-1073-16	19	1200	7 days
C-1073-19	18	1200	7 days
C-1073-20	24	300, 600, 1200	single dose
C-1073-22	15	300	single dose
C-1073-23	22	1200	10 days
C-1073-24	16	1200	single dose/12 days
C-1073-25	20	1200	10 days
C-1073-26	20	300	14 days
C-1073-27	24	1200	7 days/8 days
C-1073-28	20	1200	3 doses (every 12 h)
C-1073-29	28	300	14 days
C-1073-30	12	300	single dose
C-1073-31	12	300, 600	8 days
C-1073-300	105	600, 1800	14 days
C-1073-301	5[d]	600	7 days
C-1073-425	20	600	6 weeks
C-108297-102 (Cohort 3)	10	600	14 days

A total of **50 subjects entered** the 6 month pivotal study C-1073-400, and **34 completed the study**.

Of the 16 subjects (32%) who withdrew from the study, seven withdrew because of AEs and two subjects withdrew because of death due to underlying malignancy while participating in the study. Two additional subjects withdrew due to progression of their cancer and died subsequently. Five subjects withdrew consent, one subject was too ill to travel and one subject was withdrawn due to non-compliance with study procedures. Discontinuations were evenly distributed between the C-DM and C-HT study groups.

Of the 34 subjects completing study C-1073-400, 33 were eligible to enrol in the extension study (one subject was not eligible due to non-compliance with study procedures and study medication). **Thirty of these 33 entered the C-1073-415 extension study**. To enter study C-1073-415, subjects had to have completed the C-1073-400 Week 24 and 6-week follow-up study visits; during the interval between those two visits, mifepristone was not administered.

The initial dose of mifepristone in the extension study was the same dose that was administered at the Week 24 visit in study C-1073-400. As a result, dose levels were specific to each subject.

However, dosages were titrated according to the needs of the individual patient in compliance with the protocol.

In study C-1073-400, subjects received 24 weeks of mifepristone treatment, followed by a 6-week observation period during which no treatment was administered. Most subjects in this study have been exposed for 6 months; the median duration of exposure was 166 days (range: 14 – 179 days).

Overall, the dose level with the longest mean number of days of administration was the 1200 mg dose, with a mean of 68.91 days, followed by the 600 mg dose (45.36 days), the 900 mg dose (41.09 days), and the 300 mg dose (27.60 days).

The 30 patients enrolled in the extension study C-1073- 415 took study drug for a median of 22.5 months (range 0.8 – 36.6 months), in addition to the 6 months exposure during study C-1073-400. Two patients took mifepristone for a total of 42 months

Table 15: Exposure to Mifepristone in the Primary Safety and Efficacy Studies

Study Number - Description	Number of Subjects by Mifepristone Dose (mg/day)	Total Number Subjects Dosed
C-1073-400: Phase 3, open-label, dose-escalation study in patients with Cushing's syndrome	Beginning with a dose of 300 mg mifepristone, dosing was escalated and titrated during the study as needed depending upon clinical response and adverse events. Number of subjects who reached each dose level: 300 mg = 50 600 mg = 45 900 mg = 34 1200 mg = 22	50
C-1073-415: Phase 3, open-label, dose-escalation extension study in patients with Cushing's syndrome	Dosing was started with the same dose the subject had taken at the end of study C-1073-400 and escalated and titrated as needed depending upon adverse events. Visit / N / Median daily dose (mg)* Entry 30 600 Month 1 28 600 Month 3 29 900 Month 6 25 900 Month 9 25 600 Month 12 25 600 Month 15 20 750 Month 18 19 600 Month 21 14 900 Month 24 14 900 Month 27 9 600 Month 30 11 900 Month 36 2 900 Last dose 30 600	30

* Prescribed dose.
Source: Table 14.1.3.3 in C-1073-400 CSR and Table 14.1.3 in C-1073-415 CSR.

Adverse events

In study C-1074-400 safety was assessed by adverse events (AEs), vital signs (heart rate, respiratory rate, and temperature), clinical laboratory tests (haematology, serum chemistry, and urinalysis) and electrocardiograms (ECGs). Thyroid status was evaluated by thyroid stimulating hormone (TSH) and free thyroxine (T4). ACTH, serum cortisol, nocturnal salivary cortisol, and 24-hour urinary free cortisol (UFC) were measured throughout the study. Subjects with pituitary-based disease had magnetic resonance imaging (MRI) to monitor for the development of pituitary enlargement. Women with an intact uterus underwent transvaginal ultrasound and endometrial biopsies (biopsies initiated after protocol amendment in late 2009). Following implementation of a protocol amendment in late 2010, patients were scheduled for detailed eye examinations including slit-lamp examination and retinal evaluation WHY. All subjects were monitored for signs and

symptoms of adrenal insufficiency. Any vaginal bleeding in a postmenopausal woman was to result in discontinuation of mifepristone treatment and subjects were to undergo transvaginal ultrasound as soon as feasible.

In the extension study C-1073-415, safety variables included an assessment of AEs, vital signs (blood pressure, heart rate, respiratory rate, and body temperature), physical examination, clinical laboratory tests (haematology, serum chemistry, and urinalysis), and 12-lead electrocardiograms (ECG). Thyroid function tests and lipid panels were also examined.

As noted, women with an intact uterus underwent periodic transvaginal ultrasounds to examine endometrial thickness. Endometrial biopsies were performed in women with an intact uterus at study entry and after 12 months of treatment (or early termination [ET]). ACTH, serum cortisol, and 24-hour UFC were measured at various time points during the study. Subjects with Cushing's disease underwent periodic MRI imaging of the pituitary gland to monitor for increased pituitary size.

All 50 subjects who participated in study C-1073-400 and all subjects who participated in study C-1073-415 experienced a treatment-emergent adverse event (TEAE) at some time during the study. The majority of TEAEs in both studies were treatment related.

Four subjects died during study C-1073-400 and 2 during study C-1073-415. None of the deaths was considered related to mifepristone treatment. Twenty-eight subjects (93.3%) in study C-1073-415 had AEs that were ongoing from study C-1073-400.

Table 18: Summary of Adverse Events in the Primary Safety and Efficacy Studies

Event	Number of patients (%)	
	C-1073-400 N = 50	C-1073-415* N = 30
At least 1 TEAE	50 (100.0)	30 (100)
Deaths	4 (8.0)	2 (6.7)
Serious TEAEs	16 (32.0)	18 (60.0)
TEAE leading to discontinuation	7 (14.0)	3 (10.0)
TEAE related to study medication	44 (88.0)	29 (96.7)

*AEs are those that began in Study C-1073-415. An AE was classified as treatment emergent if it had an onset date greater than or equal to the first dose date of study treatment in C-1073-415. If the event occurred prior to enrollment and worsened during study treatment it was also considered treatment emergent.
Source: Table 14.3.1.1 in C-1073-400 CSR and Table 14.3.1.1 in C-1073-415 CSR

The most frequently reported TEAEs in study C-1073-400 (occurring in 10 or more subjects [20%]) were nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral oedema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy (endometrial thickening).

The majority of TEAEs were considered mild or moderate in severity. The only severe TEAEs that occurred in more than two subjects each were fatigue (four subjects), and nausea and vomiting (three subjects each).

All of the 30 patients enrolled in the extension study experienced TEAEs. The most frequent TEAEs (i.e., those occurring in six or more subjects [20%]) in study C-1073- 415 included nausea, decreased blood potassium, fatigue, headache, endometrial hypertrophy, hypertension, vomiting, peripheral oedema, dizziness, nasopharyngitis, upper respiratory tract infection, and abnormal thyroid function test.

Overall, 88.0% of subjects (44/50) in study C-1073-400 and 96.7% of subjects (29/30) in study C-1073-415 experienced TEAEs that were considered by the investigator to be related to study drug.

Table 19: Comparison of Treatment-Emergent Adverse Events (Occurring in >15% of Patients in at least one group) in Study 400 and Study 415

System Organ Class Preferred Term	TEAE in Study 400 N = 50 n (%)	TEAE Starting in Study 415 N = 30 n (%)	TEAE Ongoing from Study 400 N = 30 n (%)
Patients with at least 1 TEAE	50 (100.0)	30 (100.0)	28 (93.3)
Endocrine disorders			
Adrenal insufficiency	2 (4.0)	5 (16.7)	0 (0.0)
Gastrointestinal disorders			
Abdominal pain upper	3 (6.0)	5 (16.7)	0 (0.0)
Diarrhea	6 (12.0)	3 (10.0)	1 (3.3)
Dry mouth	9 (18.0)	1 (3.3)	3 (10.0)
Nausea	24 (48.0)	15 (50.0)	2 (6.7)
Vomiting	13 (26.0)	7 (23.3)	0 (0.0)
General disorders and administration site conditions			
Fatigue	24 (48.0)	12 (40.0)	7 (23.3)
Edema peripheral	13 (26.0)	7 (23.3)	1 (3.3)
Infections and infestations			
Nasopharyngitis	6 (12.0)	6 (20.0)	1 (3.3)
Sinusitis	7 (14.0)	2 (6.7)	0 (0.0)
Upper respiratory tract infection	3 (6.0)	6 (20.0)	0 (0.0)
Investigations			
Blood potassium decreased	17 (34.0)	15 (50.0)	2 (6.7)
Thyroid function test abnormal	9 (18.0)	6 (20.0)	2 (6.7)
Metabolism and nutrition disorders			
Decreased appetite	10 (20.0)	3 (10.0)	2 (6.7)
Musculoskeletal and connective tissue disorders			
Arthralgia	15 (30.0)	2 (6.7)	5 (16.7)
Back pain	8 (16.0)	5 (16.7)	1 (3.3)
Myalgia	7 (14.0)	2 (6.7)	2 (6.7)
Nervous system disorders			
Dizziness	11 (22.0)	7 (23.3)	2 (6.7)
Headache	22 (44.0)	11 (36.7)	5 (16.7)
Reproductive system and breast disorders			
Endometrial hypertrophy	10 (20.0)	10 (33.3)	4 (13.3)
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	8 (16.0)	3 (10.0)	1 (3.3)
Vascular disorders			
Hypertension	12 (24.0)	9 (30.0)	3 (10.0)

All patients experienced some adverse reactions.

The most frequently reported TEAEs in study C-1073-400 (occurring in 10 or more subjects [20%]) were **nausea, fatigue**, headache, **decreased blood potassium**, arthralgia, **vomiting**, peripheral oedema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy (endometrial thickening).

All of the 30 patients enrolled in the extension study C-1073-415 experienced TEAEs. The most frequent TEAEs (i.e., those occurring in six or more subjects [20%]) in study C-1073- 415 included **nausea, decreased blood potassium, fatigue**, and headache, endometrial hypertrophy, hypertension, **vomiting**, peripheral oedema, dizziness, nasopharyngitis, upper respiratory tract infection, and abnormal thyroid function test.

Serious adverse events and deaths

Sixteen subjects experienced SAEs after receiving mifepristone in study C-1073-400. Most SAEs were isolated occurrences, occurring in individual patients only. Only respiratory failure and adrenal carcinoma occurred in more than one subject (two and three subjects, respectively). Seven SAEs were considered possibly or probably related to study treatment: orthostatic hypotension, respiratory failure, confusional state and blood potassium decreased (1 patient), vomiting, asthenia, and adrenal insufficiency.

Eighteen patients experienced SAEs in study C-1073-415, 8 of which were considered by the investigator to be related to the study drug: adrenal insufficiency (2 cases), hypokalaemia (4 cases), hypertensive crisis (1 case), hip fracture (1 case).

Four of the 16 subjects with SAEs died during study C-1073-400: three subjects died of metastatic adrenal carcinoma, and one subject died of metastatic neuro-endocrine carcinoma. All deaths were considered not related to study drug.

Two of the subjects with SAEs died in study C-1073-415. One patient experienced a TEAE of amyloidosis that led to death; this event was not considered related to study drug but was thought to be caused by multiple myeloma. One patient experienced a TEAE of respiratory failure that occurred post-operatively (adrenalectomy) and led to death; TEAE onset was 21 days after discontinuation of mifepristone. The event was also considered unrelated to mifepristone treatment.

In study C-1073-400, seven subjects (14.0%) were discontinued from study drug because of a TEAE; the only TEAE leading to discontinuation of study drug occurring in more than one subject was fatigue.

In study C-1073-415, three patients were discontinued from the study because of a TEAE (moderate endometrial hypertrophy, endometrial disorder, adrenal insufficiency).

Deaths were not related to administration of mifepristone, but rather to progression of underlying disease. Withdrawals were due to underlying disease or, in several cases, a multitude of symptoms including fatigue. SAEs were either related to the underlying disease or were related to the expected effects of the drug (considering the mechanism of action).

Laboratory findings

In both, studies C-1073-400 and C-1073-415 there was no evidence for an effect of mifepristone on clinical haematology or most biochemistry values. Changes from baseline were generally small and without clinical relevance.

In study C-1073-400, as expected with mifepristone and this subject population, potassium values decreased throughout the study but it was generally mild to moderate and was often associated with alkalosis (elevated CO2) and variably associated with oedema. Four subjects had potassium values that met the definition of severe hypokalaemia. The hypokalaemia responded to treatment with potassium supplementation.

Mean potassium values also decreased in study C-1073-415. In general, mean changes from baseline in potassium remained < -0.25 until Month 21, when the mean change from baseline was -0.31. After that time point, all other mean changes from baseline were >-0.31 mmol/L, except for the 6-week follow-up when mean potassium increased slightly (0.23 mmol/L).

Severe hypokalaemia was defined as a serum potassium of <2.5 mEq/L; no subject had a measured potassium level in the database that met this criterion. However, four subjects had a

potassium level <2.5 mEq/L found in reports of SAEs. Potassium and mineralocorticoid antagonist drugs (spironolactone or eplerenone) were frequently used to treat or prevent hypokalaemia.

There were reductions in total cholesterol and HDL-cholesterol throughout the study. Decreases in HDL-cholesterol were common but returned to baseline levels on cessation of mifepristone treatment.

Mean ACTH and serum cortisol values were increasing until Week 10 and stabilised afterwards. At the 6-week follow-up, all values returned to or were approaching baseline levels.

Mild increases in TSH were common and reversible on cessation of mifepristone. The changes in these measures did not progress during study C-1073- 415. Changes from baseline in TSH and free T4 values were small and not considered clinically significant.

Overall, mean ACTH and serum cortisol levels increased from baseline until Month 12 and fluctuated afterwards.

Safety in special populations

Age, Sex, Race

Safety data for mifepristone studies in Cushing's syndrome were analysed by **age and sex**. These results did not indicate a difference between gender and age groups with respect to safety. However, there are known reproductive side effects of mifepristone in women, including vaginal bleeding and endometrial thickening as well as termination of pregnancy.

Safety with respect to race and ethnicity was not analysed because of the small sample sizes.

Renal Insufficiency (Study C-1073-19)

This study was conducted to evaluate the effect of severe renal impairment (glomerular filtration rate [GFR] <30 mL/min/1.73 m2 but not on dialysis) as compared to normal renal function (creatinine clearance [CrCl] ≥ 90 mL/min/1.73 m2) on the pharmacokinetics of mifepristone and its metabolites following multiple doses of mifepristone. Mean exposure to mifepristone increased 31%, with similar or smaller increase in metabolite exposure. No change in the initial dose is required in renal impairment. The maximum dose should be limited to 600 mg.

Hepatic Insufficiency (Study C-1073-05)

This study was conducted in subjects with moderate hepatic impairment (Child-Pugh Class B) to evaluate the pharmacokinetics of mifepristone. Similar pharmacokinetics was seen in hepatically-impaired subjects and those with normal hepatic function. No change in the initial dose is required in mild to moderate hepatic impairment. The applicant proposes that the maximum dose should be limited to 600 mg. Corluxin should not be used in severe hepatic impairment.

Paediatric Populations

The safety and efficacy of Corluxin in children below the age of 18 have not yet been established.

Drug-Disease Interactions

Hypokalaemia occurs in patients with Cushing's syndrome and can be increased in patients receiving mifepristone. Hypokalaemia can occur at any time during Corluxin treatment.

Use in Pregnancy and Lactation

Mifepristone is a potent antagonist of progesterone via the progesterone and glucocorticoid (GR-II) receptors. The antiprogestational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with mifepristone 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 sterilisation, in which case no additional contraception is needed.

Mifepristone is excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Corluxin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

Discontinuation due to AES

A total of 50 subjects entered the pivotal study C-1073-400, and 34 completed the study. Of the 16 subjects who withdrew from the study, seven withdrew because of AEs and two subjects withdrew due to death due to underlying malignancy while still participating in the study. Two additional subjects withdrew due to progression of their cancer and died subsequently. Five subjects withdrew consent, one subject was too ill to travel and one subject was withdrawn due to non-compliance with study procedures. Discontinuations were evenly distributed between the C-DM and C-HT study groups.

Discussion on clinical safety

Morbidity associated with Cushing's syndrome is significant.

All patients treated with Corluxin experienced some adverse reactions.

The most frequently reported TEAEs in study C-1073-400 (occurring in 10 or more subjects [20%]) were **nausea, fatigue**, headache, **decreased blood potassium**, arthralgia, **vomiting**, peripheral oedema, hypertension, dizziness, decreased appetite, and endometrial hypertrophy (endometrial thickening).

All of the 30 patients enrolled in the extension study C-1073-415 experienced TEAEs. The most frequent TEAEs (i.e., those occurring in six or more subjects [20%]) in study C-1073- 415 included **nausea, decreased blood potassium, fatigue**, and headache, endometrial hypertrophy, hypertension, **vomiting**, peripheral oedema, dizziness, nasopharyngitis, upper respiratory tract infection, and abnormal thyroid function test.

There were a number of adverse events which were of particular interest:

Hypokalaemia

Hypokalaemia as a mineralocorticoid effect is not unexpected.

In the two studies of mifepristone in subjects with Cushing's syndrome, hypokalaemia (defined as a potassium value ≤3.4 mEq/L) was commonly observed and probably represents this mineralocorticoid effect. **Seventeen subjects in study C-1073-400 had reported TEAEs of decreased blood potassium**, and for one subject the event was reported as serious. Three subjects had reported TEAEs of hypokalaemia 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 hypokalaemia** (≤2.5 mEq/L).

Decreased blood potassium was reported as a TEAE for 15 subjects in study C-1073-415, for **four of them the hypokalaemia was reported as SAE**. Most often, hypokalaemia was mild to moderate and treatable with supplemental potassium and mineralocorticoid antagonist medications. All cases of serious decreased blood potassium were resolved.

In the C-1073-400 study, 22 of the 50 subjects (44%) enrolled had low potassium values at some point during the study. In the C-1073-415 trial thirteen subjects had at least one episode of hypokalaemia (≤ 3.4 mEq/L) based on laboratory testing. Of note, 15 subjects had reported TEAEs of decreased blood potassium.

Study participants were often treated with potassium supplementation and mineralocorticoid receptor antagonist medications which were effective in managing hypokalaemia, although large doses of these agents were sometimes required. The applicant should list all cases which required either spironolactone or potassium supplementation, indicating how frequently either treatment was required.

“Mineral supplements” are recorded in 36/50 (72%) in the pivotal study: 20% on potassium; 44% on potassium chloride and 6% on other potassium; 60% on furosemide, spironolactone, and hydrochlorothiazide diuretics; 60% on drugs affecting the renin angiotensin system; 32% corticosteroids for systemic use.

The applicant should elaborate on corticosteroid use indicating why they were required and what specifically they were used for.

Because hypokalaemia is a known side effect of treatment with mifepristone, spironolactone use was permitted by study protocol to treat hypokalaemia not responsive to potassium supplementation alone and it is unclear when hypokalaemia is recorded, if this is on the context of pre-dose hypokalaemia, supplementation with potassium, or treatment with other medicines which affect potassium levels. It is however clear that hypokalaemia was frequent. The applicant should list all subjects being treated with medication that would be associated with decreased potassium.

The frequency and degree of hypokalaemia in the Cushing’s studies was greater than other studies because the high cortisol levels did contribute to hypokalaemia and this can be exacerbated by mifepristone.

The Corluxin SmPC recommend correcting hypokalaemia prior to initiating Corluxin, and to measure serum potassium 1 to 2 weeks after starting or increasing the dose of Corluxin and periodically thereafter. Mifepristone-induced hypokalaemia should be treated with potassium supplementation based on event severity. If hypokalaemia persists in spite of potassium supplementation, adding a mineralocorticoid antagonist should be considered. All patients will therefore require pre-dose potassium measurement and a specific requirement to correct potassium levels before dosing. Because of the possibility of hypokalaemia and the problems associated with this, routine measurement of potassium levels should be specified.

Adrenal Insufficiency

The mode of action of mifepristone is antagonism of the glucocorticoid receptor (GR) and cortisol levels are not decreased during mifepristone treatment. The applicant considers that the description of this situation as adrenal insufficiency is misleading and the term “excess GR antagonism” is more physiologically accurate.

Signs and symptoms of hypoadrenalism include hypoglycaemia, hyperkalaemia, dehydration, weight loss, disorientation, weakness, tiredness, dizziness, orthostatic hypotension nausea, vomiting and diarrhoea which can develop gradually. Adverse effects associated with Corluxin include nausea, vomiting, fatigue and dizziness.

Excess GR antagonism may result in similar signs and symptoms as adrenal insufficiency, however because mineralocorticoid activity is preserved or increased, hypotension may be uncommon. With concomitant use of anti-diabetic and antihypertensive medications the risk of hypoglycaemia and hypotension, respectively, may be increased.

Only **two subjects reported AEs of adrenal insufficiency during study C-1073-400**, but only one required glucocorticoid treatment. For one subject, the event was documented as moderate intensity SAE after 5 months of mifepristone treatment, with 1200 mg as current dose. The event resolved with hydration, dexamethasone and discontinuation of mifepristone. The subject later resumed mifepristone in Study C-1073- 415. The second subject was reported to have an episode of adrenal insufficiency while being treated with mifepristone 600 mg QD. The event resolved without supplemental glucocorticoids or other treatments. Both events were assessed as probably related to study medication treatment. Hypotension or hypoglycaemia was not associated with either of these events.

In study C-1073-415, five patients (16.7% patients) were reported to have an episode of adrenal insufficiency, including 2 SAEs and one patient who was withdrawn from study medication (not an SAE). Two episodes were associated with hypotension: one in the setting of concomitant antihypertensive therapy and one with a TEAE of mild hypotension (no available documentation of low blood pressure at time of the event) with no concomitant use of antihypertensive medication. Cases of reported adrenal insufficiency resolved with mifepristone dose reduction or interruption and the use of supplemental glucocorticoids.

Biochemical diagnosis of adrenal insufficiency is not possible in subjects taking mifepristone as cortisol levels are not decreased and in this patient population is likely to be increased. Therefore, a diagnosis is only possible relying on clinical findings alone. In study 400 there is a table providing a list of **7 subjects who were administered systemic glucocorticoids** coincident with two or more of the following symptoms that can be associated with adrenal insufficiency: dizziness/dizzy, fatigue, weakness, hypoglycaemia, hypotension, fatigue, lethargy, malaise, nausea, orthostatic hypotension, syncope, and vomiting. Systemic glucocorticoids were also administered during study drug administration for a number of reasons including the following indications: pneumonia; breathing difficulties, shortness of breath, and chronic obstructive pulmonary disease; contrast agent reaction, stress of acute illness; **prophylaxis secondary adrenal insufficiency**, acute renal insufficiency and Cushing's syndrome; prophylaxis to decrease brain swelling as a result of routine pituitary gamma knife procedure; sinus infection; and pre-chemo treatment. It is unclear from the report on the extension study if dexamethasone was required in any patients other than those 5 listed as having adrenal insufficiency

The applicant suggests that physicians must maintain a high index of suspicion in cases where suggestive symptoms and signs are present but mifepristone may produce symptoms similar to symptoms of adrenal insufficiency. Since mifepristone does not reduce cortisol concentrations and mineralocorticoid receptor activity is preserved or increased, hyperkalaemia is not expected and hypotension is uncommon. It is recommended that in cases of excessive glucocorticoid receptor blockade, physicians must withhold mifepristone and provide supplemental glucocorticoid.

It is however unclear as to what exactly constitutes excess GR antagonism and even what from a clinical point of view this will be. Considering the mineralocorticoid effects of mifepristone and the fact that cortisol levels cannot be used to diagnose hypoadrenalism, it is unclear how

hypoadrenalism is to be confidently and reliably diagnosed. In particular it is difficult to see what particularly is to be monitored to make the diagnosis.The applicant is asked to elaborate on and define what is meant by *excess* glucocorticoid antagonism (since GR antagonism may result in similar signs and symptoms as adrenal insufficiency, and some of the frequent adverse reactions associated with mifepristone can be associated with hypoadrenalism).

In accordance with mifepristone's risk for excess GR antagonism, the Corluxin SmPC appropriately recommends that patients should be closely monitored while being treated with Corluxin and reduction in antihypertensive and/or antidiabetic medications may be necessary. Patients should also be evaluated for events such as infection, surgery or trauma that may increase the likelihood of signs and symptoms of excess GR antagonism. If excess GR antagonism is suspected, treatment with Corluxin should be discontinued and glucocorticoids administered without delay although it may be difficult to define this suspicion. In some patients high doses of supplemental glucocorticoids may be useful to increase GR activity. Treatment with Corluxin can be resumed at a lower dose when the physician has determined that excess GR antagonism is resolved. The applicant is requested to provide further guidance on stopping and starting the Corluxin (considering in particular the need for a 1 week delay in restarting)

Vaginal Bleeding

In studies C-1073-400 and C-1073-415, 15 TEAEs of bleeding occurred in 9 pre-menopausal and 2 post-menopausal patients. Of these cases, minor bleeding occurred at the start of dosing in 2 pre-menopausal patients in study C-1073-400. Clinically relevant bleeding occurred at 14 to 24 weeks of treatment in 4 pre-menopausal patients with endometrial thickness >20 mm (median 38 [25-55] mm). Endometrial thickening was not uniformly accompanied by bleeding; there was no bleeding beyond 6 months of treatment in 3 patients with endometrial thickness >20mm.

Three pre-menopausal subjects who had experienced several vaginal bleeding episodes throughout both studies underwent elective hysterectomy to be able to continue mifepristone treatment. Pathology results showed benign endometrium for all three subjects.

In accordance with potential events of vaginal bleeding, the following precautions are included in the Corluxin SmPC: Because it is an antagonist of the progesterone receptor, mifepristone may result in thickening of the endometrium, cystic dilatation of endometrial glands, and vaginal bleeding. Corluxin should be used with caution in women who have haemorrhagic disorders or are receiving concurrent anticoagulant therapy. Women who experience abnormal vaginal bleeding during Corluxin treatment should be referred to a gynaecologist for further evaluation. Corluxin is contraindicated in women with unexplained vaginal bleeding, endometrial hyperplasia with atypia, or endometrial carcinoma. The applicant is asked to comment further on how patients should be assessed for diagnosis of endometrial hyperplasia, in the context of contraindicating such use in these patients.

Endometrial Thickness

Twenty-six pre-menopausal and 9 post-menopausal women enrolled in studies 400 and 415.

Endometrial biopsies were obtained in 11 pre- and 4 post-menopausal patients. The median and range of endometrial thicknesses for pre- and post-menopausal patients were 5.0 mm [1.0-13.0 mm] and 3.0 mm [2.0-3.4 mm] at baseline, and 11.0 mm [4.8-55.0 mm] and 6.4 mm [1.0-17.0 mm] at Week 24/ET in study C-1073-400, respectively. Endometrial thickness increases of >5mm occurred in 9 patients, 8 pre-menopausal and 1 postmenopausal, of whom 4 pre-menopausal patients and 1 post-menopausal patient had increases >10 mm.

During extended follow-up for 18 female patients in Study C-1073-415 (median of 26.9 [13.7-43] months), there were continued increases in endometrial thickness, with a median maximal thickness in pre-menopausal women (N=12) of 14.0 mm [3-38 mm].

In post-menopausal patients (N=6), the maximal thickness was 9.0 mm [5-18 mm].

Biopsies showed progesterone modulator-associated endometrial changes (PAEC) with benign endometrium in variable patterns (inactive, atrophic, and disordered). One patient was reported to have simple hyperplasia that was not confirmed on a repeat sample. Complex atypical endometrial hyperplasia that was believed by the pathologist to have existed prior to study entry was noted in a second patient due to the lack of co-existing histological changes consistent with mifepristone exposure. None had endometrial carcinoma.

To facilitate continued treatment with mifepristone, three women with Cushing's underwent elective hysterectomy during chronic mifepristone therapy due to persistent endometrial thickening with vaginal bleeding. One woman underwent hysterectomy due to chronic fibroids; pathological examination of the uterine specimens showed benign endometrium without evidence of atypia or carcinoma.

The applicant should comment further on long term use of Corluxin in female patients in the context of increased endometrial thickness.

Thyroid Function

In the C-1073-400 study, eight subjects had undetectable TSH at baseline. Of these, only one subject had an increase in TSH during the study, which resolved with a dose reduction in laevothyroxine replacement therapy. The TSH levels remained very low in the other seven subjects. Six of those subjects had Cushing's disease and may have had central hypothyroidism due to previous pituitary surgery and/or radiation as the reason for the low TSH; one subject did not have pituitary-based Cushing's disease.

Of the other study subjects with detectable TSH at baseline, eight had increases in TSH above the normal range (three subjects with TSH > 10 µ/L, including one subject with a TSH of 32.8 µ/L). At the 6-week follow-up visit, the elevated TSH levels had returned to normal.

In study C-1073-415, eight subjects had at least one TSH or Free T4 value below the lower limit of the normal range. Of these eight, four had undetectable TSH levels at study entry, and five had a medical history of hypothyroidism (as recorded in the initial study, C-1073-400). One subject had a TSH value above the upper limit of normal range (7.83 mU/L at Month 6, increased from 1.73 mU/L at baseline; normal range, 0.4-5.5 mU/L) with a stable Free T4 value. This subject also experienced elevation of TSH in study C-1073-400. Three patients experienced a TEAE of hypothyroidism during study C-1073-415, of these, one patient had a medical history of hypothyroidism and for a second patient, the event was ongoing from the C1073- 400 trial. Only one patient experienced a new onset of hypothyroidism which was assessed as unrelated to the study drug and responded to laevothyroxine with normalisation of both TSH and free T4. Additionally the other two patients responded well to laevothyroxine, too and TSH and free T4 were found to be normal again.

Concomitant use of laevothyroxine was common in these studies. **These changes in TSH and Free T4 values were clinically mild and are confounded by pre-existing pituitary-thyroid axis dysfunction due to pituitary surgery and radiation.**

Vital Signs

Blood pressure-related TEAEs included two subjects with hypotension and 12 subjects with hypertension. In **five of these 12 subjects, the hypertension was considered possibly or probably related to the study drug**; several of these subjects had evidence of increased mineralocorticoid receptor activation, due to excess circulating cortisol, suggested by the presence of hypokalaemia, oedema and alkalosis. The applicant is asked to indicate if these patients with hypertension had associated hypokalaemia.

Twelve subjects in the overall population had TEAEs of hypertension. All of the TEAEs of hypertension were considered mild or moderate in severity. Five subjects experienced hypertension during the study that was considered possibly or probably related to the study drug and these subjects also had hypokalaemia (either as a reported TEAE or as evidenced by potassium values) and some had oedema and biochemical evidence of alkalosis suggesting apparent mineralocorticoid excess. All but one subject were treated for their hypertension and one subject had the dose of mifepristone reduced because of the TEAE of hypertension. At the completion of the study, the TEAEs of hypertension had resolved in six of the 12 subjects; the hypertension was ongoing in the other six subjects. Three of these seven subjects enrolled in the mifepristone extension study (C1043-415). Two had their TEAEs of hypertension resolve during that study. The outcome of the TEAE of hypertension for the other subject (Subject 24-001) is unknown.

In the extension study (C-1073-415), no trends in blood pressure (both systolic and diastolic), heart rate, or body temperature were noted.

Ophthalmologic events

In November 2010, following a request from the FDA to provide ophthalmologic safety data, the C-1073-415 protocol was amended to include complete eye exams.

All of the subjects had been treated with mifepristone for over 6 months so it was not possible to obtain pre-treatment baseline readings. After ethics committee approval of this amendment, subjects were to have the complete eye exams at entry into the extension study and again every 6 months. For those subjects who had already entered the study, investigative site staff was encouraged to arrange for the subject to have the exam as soon as possible.

Seven subjects had entered the study prior to the amendment but these subjects have completed the eye exams. Aside from one diabetic subject who had changes consistent with diabetic retinopathy and one hypertensive subject who had changes consistent with hypertensive retinopathy, results of these exams showed no abnormal findings beyond a scattering of mild changes due to aging that would be expected in this cohort of patients. There was **no evidence to suggest that any of these changes are related to treatment with mifepristone**.

Skin Rashes

Findings of skin rash on physical examination were common and might not be unexpected in subjects with Cushing's syndrome.

Ten subjects experienced a TEAE of rash, three of which were related to study drug. The rash in one subject was an exacerbation of a lupus rash, but was considered related to study drug.

Rashes were mild to moderate in severity, were most often described as papular or erythematous and tended to be localised and not generally distributed. There were no reports of exfoliation or associated systemic signs or symptoms. Five subjects received no treatment for their rashes, four subjects were treated with medication for their rashes, and one subject had the dose of mifepristone reduced (Subject 03-004) because of the rash. By the end of the study, the majority

of the rash events had resolved (in seven of the 10 subjects); the rash events in the other three subjects were ongoing.

Conclusions on clinical safety

Overall, use of mifepristone is associated with signs and symptoms which in many cases reflect the mechanism of action of the drug. Adverse effects including nausea, fatigue, headache, decreased blood potassium, vomiting, peripheral oedema, hypertension, dizziness, and decreased appetite occur frequently, but are for the most part, mild to moderate.

Hypokaemia is associated with Cushing's disease and syndrome and is exacerbated by treatment with mifepristone. It is difficult to separate the effects on potassium and many patients need potassium supplementation and/or potassium sparing treatments. Hypokalaemia has also to be considered in the context of it's likely effect on the heart and in the context of a possible effect on QTc from mifepristone.

A major concern is the issue of mifepristone induced hypoadrenalism and there is some difficulty with regard to diagnosis, in the context of preserved mineralocorticoid effects, and not being able to use cortisol levels to predict hypoadrenalism. Considering the adverse events associated with mifepristone, it is difficult to clearly state what confidently how excess GR antagonism can be diagnosed clinically

Endometrial thickening and vaginal bleeding also occur in female patients treated with mifepristone and although there is no evidence of significant endometrial change, long term treatment could constitute a risk.

Pharmacovigilance system

A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC has been provided per Co-Rapp request.

Risk management plan

Please refer to PRAC RMP Assessment Report.

4. Orphan medicinal products

On 27 October 2011, orphan designation (EU/3/11/925) was granted by the European Commission to Voisin Consulting S.A.R.L., France, for mifepristone for the treatment of hypercortisolism (Cushing's syndrome) of endogenous origin. At the time of designation, hypercortisolism (Cushing's syndrome) of endogenous origin affected approximately 0.6 in 10,000 people in the European Union (EU). This was equivalent to a total of around 30,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000.

The sponsorship was transferred to Dr Ulrich Granzer, Germany, in December 2012 and subsequently to FGK Representative Service GmbH, Germany, in October 2013.

5. Benefit risk assessment

Benefits

Endogenous Cushing's syndrome is a rare syndrome with significant mortality and morbidity. First line treatment particularly for those with pituitary adenomas is usually surgery. However a

proportion of patients do not respond to surgery (10 – 35%) or relapse (5 – 36%)1. A proportion will be treated with radiotherapy after surgical failure and again some will not respond. Control of hypercortisolism following radiotherapy can take from between 8 months and five years to achieve. Therefore there is a need for medical therapies for those who have failed surgical or radiotherapy or those who are awaiting control of hypercortisolism with radiotherapy. Currently three medicinal products: pasireotide; ketaconazole and metyrapone are licensed in the EU.

Beneficial effects

The applicant submitted one small uncontrolled open label study conducted in two subpopulations of patients with Cushing's syndrome to support their application (Study C1073-400).

At the time of initiation of the study no medical treatments were authorised for Cushing's syndrome. Given the mode of action of mifepristone (glucocorticoid receptor blockade) it would still not be possible to compare it with an authorised product such as pasireotide which has a lowering effect on cortisol levels. The study is a before and after study. In general these studies have weaknesses as it is in the nature for some conditions to improve over time even without treatment. However Cushing's syndrome of the severity described in the study population is most unlikely to improve or remit spontaneously. No new treatments or increased doses of current therapy for diabetes were allowed in the DM population. Therefore any positive changes observed over the course of this study in terms of glycaemic control are likely to be due to mifepristone.

The primary endpoint endpoint for subjects with Cushing's syndrome and diabetes mellitus (or impaired glucose tolerance) (C-DM cohort) was the 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 in subjects with diabetes/impaired glucose tolerance with or without hypertension at screening. A responder was defined as a subject who experienced at least a 25% decrease in AUCglucose from baseline to Week 24. The endpoint was to be declared successful if the lower limit of the exact 95% binomial confidence interval for the responder rate was ≥ 20%.

Overall, the effect of mifepristone on glycaemic control has been observed in **25** Cushing's syndrome subjects suffering from type 2 diabetes or impaired glucose tolerance. 15 subjects were taking antidiabetic medicines (insulin, sulfonylurea, metformin, DPP IV inhibitors, incretin mimetics). A 25% reduction in AUC glucose after oGTT has been observed at Week 24 in 60% of the Cushing's syndrome subjects suffering from type 2 diabetes or impaired glucose tolerance. Effects of mifepristone on other parameters associated with glycaemic control, studied as secondary endpoints, support the use of mifepristone in Cushing's syndrome subjects with type 2 diabetes or impaired glucose tolerance:

- mean HbA1c reduction from baseline of 1.14% (nine subjects achieved an HbA1c ≤ 7% a the end of the study);

- reduction in antidiabetic medications from baseline (5 showed a > 50% reduction in insulin daily dose, including 2 who also showed a > 50% reduction in sulfonylurea).

In addition there were positive effects on weight loss, waist circumference and body fat composition. Seventy six percent of the ITT population experienced weight loss. The mean percent change form baseline bodyweight at week24/ET was -5.2% (-6.6, -3.7%).

Considering that the mode of action of mifepristone is blockade of glucocorticoid receptors and efficacy has been demonstrated in a DM sub-population with Cushing's syndrome it is likely that the effects of glucocorticoid blockade will be equally relevant in other symptoms and signs of Cushing's syndrome.

Uncertainties in the knowledge about the beneficial effects

1) On the clinical relevance of the beneficial effects:

- a beneficial effect of mifepristone on hypertension associated with Cushing's syndrome has not been demonstrated. Although diastolic blood pressure (DBP) improved in 38% of the subjects in the C-HT cohort, the mean DBP at baseline was already below the threshold of 90 mmHg and was not further reduced at Week 24. Furthermore, confounding effect with spironolactone use to treat hypokalaemia cannot be excluded. In addition, when including the C-DM cohort, DBP worsened in 30% of the subjects (14/46 subjects), Systolic Blood Pressure (SBP) also worsened in the same proportion of subjects. Overall 20% of the subjects with no hypertension at baseline developed hypertension (C-HT and C-DM cohorts).

2) On the proposed indication which is too broad:

i. The applicant has amended the indication to take account of the included population (Cushing's syndrome patients who had not responded adequately to surgical and/or radiation treatment for Cushing's disease or subjects with non pituitary based ACTH-dependent and ACTH-independent disorders, with type 2 diabetes or impaired glucose tolerance and/or hypertension);

ii. two primary endpoints were chosen (glycaemic control and blood pressure in a subset of the Cushing's syndrome population suffering from diabetes, impaired glucose tolerance or hypertension) but it is considered that an effect has only been documented in glycaemic control.

3) On the claimed maximum dose:

The SmPC recommends a starting dose of 300mg daily that may be increased in 300mg increments to a maximum of 1200mg daily. In the pivotal study Study C1073-400 the maximum dose was 900mg for those weighing under 60 kg and 1200mg for those weighing 60 kg or more. In Cushing's syndrome patients treated with multiple doses of mifepristone doubling the dose from 300mg to 600mg resulted in a 6% increase in Ctrough values. Increasing the dose from 600mg to 900mg and from 900mg to 1200mg increased Ctrough by 21% and 5% respectively but the 1200mg dose has been justified.

4) On long term efficacy:

The evidence of efficacy for long term use of mifepristone is only available for a maximum of 24 weeks in the pivotal study. The emergence of serious potential adverse events with longer-term use and the difficulties to monitor therapy from an efficacy point of view (via cortisol levels) and from a safety point of view (hypokalaemia, adrenal insufficiency) will limit a long-term use of the product, except in a minority of patients. This underlines the need to careful monitor patients and to discontinue the drug in patients who fail to show any improvements in Cushing's symptoms

Risks

Unfavourable effects

The safety assessment is mainly based on the pivotal study 400 and extension 415 made in Cushing syndrome, and secondary from the other studies in non-Cushing syndrome (Alzheimer, psychotic depression and healthy patients' studies). Except one study of 16 weeks duration for Alzheimer disease, the other studies submitted are single dose studies or studies of short duration. The safety data were not pooled taking into account the various indications, dose and duration of studies.

The most frequently reported TEAEs in the pivotal study C-1073-400 (occurring in 10 or more subjects [20%]) were nausea, fatigue, headache, decreased blood potassium, arthralgia, vomiting, peripheral oedema, hypertension, dizziness, decreased appetite and endometrial hypertrophy (endometrial thickening). The majority of TEAEs were considered mild or moderate in severity. The severe TEAEs that occurred in more than two subjects each were fatigue (four subjects) and nausea and vomiting (three subjects each). These adverse events occurred with a similar frequency in the extension study 415. Some adverse events, relying to the mechanism of action of mifepristone, seem to be exacerbated in the extension study, notably adrenal insufficiency (4 to 16.7%), hypokalaemia (30 to 50%), endometrial hypertrophy (20 to 33.3%) and infection as pneumonia and upper respiratory tract infections.

Hypokalaemia may become a treatment limiting side-effect of mifepristone. Hypokalaemia was observed in 30 and 50% of patients in study 1073-400 and 1073-415 respectively and severe hypokalaemia (4 patients) was observed even with the use of spironolactone and potassium supplementation. Hypokalaemia do not appear predictable based on baseline level prior to treatment and can occur at any time during mifepristone treatment.

A major concern is the issue of mifepristone induced hypoadrenalism /excess GR antagonism and there is some difficulty with regard to diagnosis, in the context of preserved mineralocorticoid effects, and not being able to use cortisol levels to predict hypoadrenalism. Considering the adverse events associated with mifepristone, it is difficult to clearly state confidently how excess GR antagonism can be diagnosed clinically. During mifepristone treatment, adrenal insufficiency can only be assessed by clinical observations, as cortisol and ACTH concentrations are elevated. Two subjects developed adrenal insufficiency in study 400 and 5 subjects in study 415 (among them, two patients had already reported this adverse event in study 1073-400). It could be not excluded that other adverse events, notably when dexamethasone was used, could be attributed to adrenal insufficiency. Furthermore, nausea and vomiting being associated with treatment with mifepristone could be misleadingly taken into account as adrenal insufficiency or conversely adrenal insufficiency could be under diagnosed.

Hypoadrenalism is a serious medical condition and diagnosis of hypoadrenalism in patients being treated with mifepristone is difficult in the context of side effects of mifepristone. In the clinical studies such diagnosis was described as being clinical. Considering the mineralocorticoid effects of mifepristone and the fact that cortisol levels cannot be used to diagnose hypoadrenalism, hypoadrenalism is difficult to diagnose. The applicant has elaborated on the issues but has not clearly defined what is meant by *excess* glucocorticoid antagonism (since GR antagonism may result in similar signs and symptoms as adrenal insufficiency, and some of the frequent adverse reactions such as fatigue, nausea or dizziness associated with mifepristone can be associated with hypoadrenalism).

There is a definite risk of hypoadrenalism and this has to be diagnosed by careful and frequent monitoring and SmPC warnings provide advice and warning.

Vaginal bleeding and endometrial changes observed during chronic mifepristone treatment in women appear to be mainly driven by the drug's antiprogestin activity. There were 10 TEAEs of endometrial thickening in trial C-1073-400, four of them were ongoing when patients were enrolled in trial C-1073-415. During conduct of trial C-1073-415 another 10 cases of endometrial thickening were reported as TEAEs. The effect of mifepristone on the endometrium could be monitored with ultrasound and the drug-induced thickening of the endometrium generally decreased with cessation of the drug. Clinically problematic bleeding occurred in some premenopausal women with large degrees of endometrial thickening.

Hypertension occurs in 24 and 30% respectively in studies 400 and 415, whereas many patients were well-controlled before treatment. This could be problematic notably considering the target population including diabetics and patients with cardiovascular history. In the mITT population, DBP worsened in 30% of the subjects (14/46 subjects), Systolic Blood Pressure (SBP) also worsened in the same proportion of subjects. Overall 20% of the subjects with no hypertension at baseline developed hypertension (C-HT and C-DM cohorts).

There were reductions in total cholesterol and HDL-cholesterol throughout the study. Decreases in HDL-cholesterol were common and the applicant is asked to comment on the likely long term implications of these changes.

Moreover, many other adverse events will reduce the useful of the product in clinical practice, as the abortive effect of mifepristone, the drug-drug interactions notably with ketoconazole and the precautions of use due to potential QT interval prolongation.

Uncertainty in the knowledge about the unfavourable effects

Because of the combination of potassium supplementation, potassium sparing and potassium losing diuretics, during treatment of patients who were hypokalaemic on screening, it is difficult to quantify the issue of hypokalaemia (although it is clear that there is an issue with hypokalaemia).

Considering that hypoadrenalism/ excess GR antagonism has to rely on clinical signs and symptoms (some of which are effects of the drug itself), it is difficult to get a clear picture on the diagnosis and treatment of these serious and life threatening drug effects.

Effects on HDL, taken in the context of other cardiovascular effects (hypertension, hypokalaemia) could in the longer term have a deleterious effect on the cardiovascular system.

Although no eye changes were seen in the studies, long term effects on the eye cannot be excluded.

The long-term effect of increases in TSH and T4 although reversible on cessation of therapy are unknown and annual assessment is suggested in the SmPC.

Balance

Importance of favourable and unfavourable effects

There is substantial unmet need for medical therapy for Cushing's syndrome in those who have failed surgical or radiotherapy. Currently medicinal products licensed for the Cushing's syndrome indication include pasireotide which can give rise to hyperglycaemia and might not be the most suitable treatment for those with DM/ITT related to Cushing's syndrome.

At this stage, the benefit of mifepristone in the indication *Corluxin is indicated for the treatment of adult patients with Diabetes Mellitus associated with endogenous Cushing's syndrome for whom surgery or radiotherapy is not an option or for whom these treatments have failed and in whom other pharmacological therapies have given inadequate control.* is considered demonstrated for the following reasons:

a) This indication would be acceptable, taking into account:

the included population (Cushing's syndrome patients who had not responded adequately to surgical and/or radiation treatment for Cushing's disease or subjects with non pituitary based ACTH-dependent and ACTH-independent disorders, with type 2 diabetes or impaired glucose tolerance) ;

the primary endpoints where benefit was shown (glycaemic control in a subset of the Cushing's syndrome population suffering from diabetes, impaired glucose tolerance).

b) The only demonstrated effect of Corluxin is an improvement of glycaemic control in subjects with type 2 diabetes/impaired glucose tolerance. .

c) a beneficial effect of mifepristone on hypertension associated with Cushing's syndrome has not been demonstrated. Although diastolic blood pressure (DBP) improved in 38% of the subjects in the C-HT cohort, the mean DBP at baseline was already below the threshold of 90 mmHg and was not further reduced at Week 24. Furthermore, confounding effect with spironolactone use to treat hypokalaemia cannot be excluded. In addition, when including the C-DM cohort, DBP worsened in 30% of the subjects (14/46 subjects), Systolic Blood Pressure (SBP) also worsened in the same proportion of subjects. Overall 20% of the subjects with no hypertension at baseline developed hypertension (C-HT and C-DM cohorts).

From a safety point of view, there are very limited data with respect to long term safety of the use of mifepristone in patients with Cushing syndrome:

a) The long-term cardiovascular consequences of mifepristone in the target population known to be prone to many CV risks factors (diabetics, hypertension, history of CV events, cardiac failure) considering the consequences (e.g. hypertension, hypokalaemia, aldosterone-like effect on the myocardium) due to the stimulation of mineralocorticoid receptors by high level of circulating cortisol in serum.

b) The potential long-term impact of mifepristone at endometrial and mammary levels (warning in SmPC, keys elements in risk management plan).

c) The relevant treatment duration considering the uncertainties mentioned above as well as the expected duration of use in the target population.

Lastly, the risk of hypoadrenalism/adrenal insufficiency raised concern. Hypoadrenalism is a serious medical condition and diagnosis of hypoadrenalism in patients being treated with mifepristone is difficult in the context of side effects of mifepristone. In the clinical studies such diagnosis was described as being clinical. Considering the mineralocorticoid effects of mifepristone and the fact that cortisol levels cannot be used to diagnose hypoadrenalism, it is unclear how hypoadrenalism is to be confidently and reliably diagnosed. In particular it is difficult to see what particularly is to be monitored to make the diagnosis. The applicant has not defined what is meant by *excess* glucocorticoid antagonism (since GR antagonism may result in similar signs and symptoms as adrenal insufficiency, and some of the frequent adverse reactions such as fatigue, nausea or dizziness associated with mifepristone can be associated with hypoadrenalism) but it is clear that hypoadrenalism will be a clinical diagnosis, and frequent careful monitoring will be required.

Benefit-risk balance

Overall, a benefit has been observed in improvement of glycaemic control and the safety issues driven by long term cardiovascular effects, long term impact of endometrial and mammary effects, and hypoadrenalism are known and can be managed by SmPC guidance and warnings. There are still concerns about the definition of the treatment population (which patients respond best to Corluxin) and therefore benefit risk has to be considered as negative.

Discussion on the benefit-risk assessment

The clinical development program relies on a single, small, open-label and uncontrolled trial. Although spontaneous improvement of untreated hypercortisolism in Cushing's syndrome is not

expected, confounders and biases cannot be excluded due to the open-label nature of the trial, in particular for evaluation of subjective endpoints.

The only demonstrated effect of Corluxin is an improvement of glycaemic control in subjects with type 2 diabetes/impaired glucose tolerance. A beneficial effect of mifepristone on hypertension associated with Cushing's syndrome has not been demonstrated, although blood pressure improved in 38% of the subjects in the C-HT cohort (primary analysis), overall 20% of the subjects with no hypertension at baseline developed hypertension (C-HT and C-DM cohorts).

Efficacy of mifepristone in the treatment of other signs and symptoms of Cushing's is not considered demonstrated, as it has only been studied through secondary endpoints and the responses to treatment are heterogeneous, depending on the signs/symptoms and on the patients.

From a safety point of view, this medication requires a close monitoring of patients by specialist physicians experienced in the management of Cushing syndrome and patient education in order to recognize potential toxicities of the product

Three major safety issues have been raised: long term cardiovascular effects, long-term impact of mifepristone at endometrial and mammary levels, hypoadrenalism and the relevant treatment duration considering the uncertainties mentioned above. Lastly, hypokalaemia, although expected taking into account the mechanism of action, does not appear predictable and can occur at any time during mifepristone treatment

Conclusions

The overall B/R of Corluxin from the clinical point of view is negative until section 4.1 of the SmPC is agreed and outstanding quality issues also mean that overall B/R is negative.