26 March 2015
EMA/214194/2015
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Ketoconazole AID-SCFM

International non-proprietary name: ketoconazole

Procedure No. EMEA/H/C/003800/0000

Note

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

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List of abbreviations

Abbreviation Term

ΔΔQTcI QTc based on an individual correction

ACTH Adrenocorticotropic hormone

AE Adverse event

Afr/Am Black or African American

AIMS Abnormal Involuntary Movement Scale

ALP Alkaline phosphatase

ALT Alanine aminotransferase

AI/AN American Indian/Alaskan Native

API Active pharmaceutical ingredient

AR Assessment report

ASMF Active substance master file

AST Aspartate aminotransferase

BCRP Breast cancer resistant protein

BPRS Brief Psychiatric Rating Scale

BUN Blood urea nitrogen

cal Calories

CBC Complete blood count

CO2 Carbon dioxide

CoA Certificate of analysis

CrCl Creatinine clearance

CSR Clinical study report

CYP Cytochrome P450

DCM Dichloromethane

DIG Digoxin

DMA Dimethylacetamide

DMF Dimethylformamide

DQ Derivados Quimicos

eCcr Estimated Creatinine clearance rate

ECG Electrocardiogram

ET Early termination

F Female(s)

FDA Food and Drug Administration

FLV Fluvastatin

FSH Follicle-stimulating hormone

GFR Glomerular-filtration rate

GMP Good manufacturing practice

HDL-cholesterol High-density lipoprotein

Hisp Hispanic

HPLC High performance liquid chromatography

HS-GC Head space-Gas chromatography

ICH International Conference on Harmonisation

IDL Intermediate density lipoprotein

INR International normalized ratio

IR Infrared

IRB Institutional Review Board

IUD Intrauterine device

JP Japanese pharmacopoeia

KF Karl fischer

LDL-cholesterol Low-density lipoprotein

LDPE Low density polyethylene

LH Luteinising hormone

LOD Limit of detection

LOQ Limit of quantification

M Male(s)

MDRD Modification of Diet in Renal Disease

MedDRA Medical Dictionary for Regulatory Activities

MIFE Mifepristone

MMSE Mini-Mental State Examination

MOX Moxifloxacin

MRI Magnetic resonance imaging

MS Mass spectroscopy

NDA New Drug Application

NH/PI Native Hawaiian or Pacific Islander

NMR Nuclear Magnetic Resonance

NMT No more than

O Other medication

PAEC Progesterone modulator-associated endometrial changes

PD Psychotic depression

PE Polyethylene

PGI Potentially genotoxic impurities

Ph. Eur. European pharmacopoeia

PK Pharmacokinetic(s)

PL or PLAC Placebo

postM Postmenopausal

ppm Parts per million

preM Premenopausal

PT Prothrombin time

QC Quality control

QD Once daily

QP Qualified person

QTc Corrected QT interval

QTcF Corrected QT interval using Fridericia's method

RBC Red blood cell

RS Reference standard

SAE Serious adverse event

SD Standard deviation

SHBG Sex-hormone binding globulin

T3 Triiodothyrone

T4 Free thyroxine

TEAE Treatment-emergent adverse event

TLC Thin layer chromatography

TSH Thyroid-stimulating hormone

TVUS Trans-Vaginal Ultra Sound

UFC Urinary-free cortisol

ULN Upper limit of normal

USP United states pharmacopoeia

UV Ultraviolet

VLDL Very-low-density lipoprotein

WBC White blood cell

1. Recommendations

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Ketoconazole AID-SCFM, an orphan medicinal product in the treatment of Cushing's syndrome, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (Section VI).

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Active substance:

1. Starting materials
2. Genotoxic impurities

Drug Product:

3. Dissolution
4. Method validation

Non-clinical:

5. Insufficient quality and quantity of the non-clinical dossier
6. Lack of carcinogenicity studies/data to support the proposed chronic indication

Clinical

7. Clinical dossier insufficient in terms of quantity and quality
8. Definition of indication and evidence for proposed indication
9. Safety of use in the proposed population not addressed

Proposal for questions to be posed to additional experts

N/A

Proposal for inspection

GMP inspection(s)

None

A QP declaration from the QP at the proposed finished product manufacture and batch release site has been provided declaring that the API is manufactured in accordance with the detailed guidelines on GMP, based on an audit conducted in May 2013. This declaration may need to be revised based on the major concerns regarding the proposed starting materials.

GCP inspection(s)

N/A

New active substance status

Based on the review of the data the CHMP considers that the active substance ketoconazole contained in the medicinal product Ketoconazole AID-SCFM 200mg hard capsules is not to be

qualified as a new active substance. The concerns identified, which preclude the recommendation, are detailed in the List of Questions.

2. Executive summary

2.1. Problem statement

2.2. About the product

Ketoconazole, an imidazole derivative named *Cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1Himidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine, was originally used in the treatment of fungal infections and inhibits the synthesis of ergosterol in fungi and cholesterol in mammalian cells. In addition it interferes with cytochrome P-450 enzyme systems in several organs, namely the testis, ovary, adrenal gland, kidney and liver. Like other imidazole drugs, it appears to interact with cytochrome P-450 at the haem iron sites.

Ketoconazole has also also been demonstrated to be an adrenal-blocking drug that can be used in the treatment of endogenous hypercortisolism and it is this effect that forms the basis for this application. The proposed indication is "Treatment for Cushing's syndrome"

Ketoconazole capsules hard contain 200 mg of Ketoconazole as the active substance. The product is manufactured by dry mixing of Ketoconazole with microcrystalline cellulose, starch pregelatinised and magnesium stearate. The powder blend is then encapsulated in a size 0 white hard gelatin capsule.

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

This is well established use application, and as such, all data are provided in the form of evidence from the literature. It is unclear if protocol assistance was sought although there is mention of a possible clinical trial.

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

No comment is provided on compliance with GCP

An appropriate QP declaration has been provided in respect of the active substance manufacturer but this may need to be updated in line with the major objections raised in relation to the starting materials. A valid GMP certificate has been provided for the site of finished product manufacture, assembly and batch release.

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

Legal basis

This is a well established use application under article 10a of Directive 2001/83 as amended. The applicant notes that this is justified "by the essential similarity of Ketoconazole AID SCFM 200 mg capsules with another formulation of ketoconazole (NIZORAL 200 mg capsules, JANSSEN-CILAG LTD, UK.), already on the market in Europe for many years.

The applicant provides a separate document to show that well established use (WEU) is an acceptable route for this application. It is suggested that literature from the 1980s documents WEU but it is unclear if ketoconazole was accepted by the wider clinical community as a standard treatment and it is unclear which data support usage in the EU.

- Accelerated procedure

  N/A

- Conditional approval

  N/A

- Exceptional circumstances

  N/A

- Biosimilar application

  N/A

- 1 year data exclusivity

  N/A

- Significance of paediatric studies

  N/A

3. Scientific overview and discussion

3.1. Introduction

3.2. Quality aspects

3.2.1. Drug substance

Ketoconazole is an active substance that is currently monographed in the European Pharmacopoeia (Monograph number: 01/2008:0921). The level of detail included in the open part of the dossier regarding the active substance synthesis is not acceptable and a major concern is raised in relation to the proposed starting materials. Characterisation of the active substance is comprehensive; however, additional information is required to support the claim that there is no potential for polymorphism with the active substance. Specified impurities are in accordance with those listed in the Ph. Eur. monograph for ketoconazole. Nevertheless, another major objection is raised in relation to the lack of an overall discussion on the potential for genotoxic impurities in ketoconazole. All other impurities (e.g. solvents, inorganic impurities) have been adequately addressed. The active substance specification is generally in-line with that specified in the Ph. Eur. monograph for ketoconazole with a number of minor points for clarification being raised. All methods, apart from control of residual solvents, are in compliance with the Ph. Eur., USP and/or JP. Method validation has been satisfactorily provided for the residual solvents methods. Batch results have been provided on 3 production scale batches and the results are in compliance with the proposed specifications. A Ph. Eur. reference standard for ketoconazole is available; however, the USP reference standard is used as primary reference standard. Acceptable details are provided in relation to characterisation of the primary and working reference standards for both the active substance and the specified impurities. Appropriate data has been provided regarding the container closure system employed (inner LDPE bag in direct contact with the active substance and outer PE bag placed in a fibre drum). Adequate details on the suppliers, composition, specifications, analytical methods and a CoA have been provided for the packaging materials. Stability studies under both Long Term and Accelerated conditions have been conducted according to ICH guidelines. A 5 year retest period with no special temperature precautions is proposed. As no photostability studies have been conducted, the final active substance must be ‘protected from light’.

3.2.2. Drug product

The drug product is a hard gelatin capsule which contains 200 mg of Ketoconazole. According to the Ph. Eur. monograph Ketoconazole is a white or almost white powder practically insoluble in water.

The Pharmaceutical Development section of the dossier is currently not acceptable. No information is provided in relation to the physiochemical properties of the active substance. The lack of detail is of concern especially with regards to solubility as according to the Ph. Eur. monograph Ketoconazole is practically insoluble in water. Therefore control of particle size may be an important consideration in ensuring bioavailability of the drug product. The flow properties of Ketoconazole have not been discussed; the flow properties of the powder are an important factor in ensuring the even distribution of the active substance and consistent fill weight. The applicant has been asked to provide the outstanding information. All excipients contained in the capsule shell are in compliance with their respective Ph. Eur. monographs. No compatibility studies between the active substance and excipients are presented. The applicant instead refers to the results of the drug product stability studies. As the excipients are all widely used in solid dosage forms this approach is acceptable. The summary of the formulation development is lacking. Information in relation to important factors such as powder flow properties and bulk density of the final blend prior to encapsulation is required. A major objection has been raised in relation to the lack of discussion about the dissolution method used; this is of particular concern as the active substance is practically insoluble in water and no evidence is provided to show that the active substance is adequately released from the capsule. Not much detail is provided in relation to the manufacturing process development but considering the simplicity of the process which involves dry mixing and encapsulation this is acceptable. A conventional container closure system is chosen and routine microbiological testing in accordance with Ph. Eur. requirements is performed.

A simple manufacturing process is used which involves dry mixing of the active substance and excipients followed by encapsulation of the powder blend into hard gelatin capsules. The manufacturing process is described by way of a process flow diagram and narrative description. Clarification on the routine in-process controls and some of the process validation results is required before the manufacturing process can be considered to be reproducible and sufficiently controlled in order to ensure an acceptable quality finished product is reproducibly attained. A process validation scheme is provided for the alternative batch size

All excipients contained in the capsule shell comply with their respective Ph. Eur. monographs. It is confirmed that gelatin is the only material of animal origin used in the manufacture of the capsules. Valid CEPs have been provided in respect of all sources of gelatin therefore confirming compliance with the NfG on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 rev 03). The specifications applied to the hard gelatin capsules have been requested.

The specifications proposed for the finished product fulfil the requirements of the Ph. Eur. monograph for capsules. The limits applied for uniformity of mass, uniformity of dosage units and microbiological control are in line with Ph. Eur. requirements and are acceptable. The limits for related substances are tighter than the requirements of ICH Q3A and so are satisfactory. The applicant is asked to justify the limits applied for dissolution. Some amendments to the finished product specifications including addition of a second identification test are required.

In-house methods for assay by HPLC, related substance by HPLC and loss of weight are described but clarifications are required from the applicant. New validation reports in line with the requirements of ICH Q2 (R1) are requested.

No method description is provided for dissolution which is not acceptable. It will be necessary to discuss the development of the method and demonstration of its discriminatory properties in the pharmaceutical development section of the dossier. A description of the dissolution method is required as well as full validation in line with ICH Q2 (R1).

Batch analysis results for 4 commercial scale batches of the drug product are provided. Results for all batches are within specification but results for 'total unknown impurities' and 'dissolution' have been omitted and these are required.

No discussion on impurities has been presented. A discussion of the possible degradation pathways of the active substance in the drug product and a summary of degradation products observed during stability and forced degradation studies are required.

Certificates of analysis are provided for the impurity reference standards which are the same standards referenced in the ASMF. Information in relation to the Ketoconazole and loperamide reference standards is requested.

The container closure system for the finished product consists if a polypropylene bottle and a polyethylene cap. The method used for identification of the primary packaging material is required. A declaration in Italian states compliance of the packaging materials with Ph. Eur. 3.2.2. but it is not clear if the declaration refers to the bottles or caps. Certificates from the supplier also state the primary packaging material complies with EU 2002/72/EC. As this regulation has now been superseded the applicant has been asked to confirm that the bottles and caps are in compliance with EU Regulation No. 10/2011 plus amendments on plastic materials coming into contact with foodstuffs. Information on the packaging material used for bulk manufacture is required.

A shelf life of 24 months when stored below 25°C and protected from moisture is proposed based on the stability results for the primary stability batches and the supplementary batches. However the proposed shelf life is currently not acceptable (see below)

Up to 18 months real time data at ICH long term conditions is provided for 3 primary stability batches and additional stability data at later time points is provided for 3 supplementary batches. A shelf life of 24 months when stored below 25°C and protected from moisture is proposed based on the stability results. Extrapolation to a 24 month shelf life based on this data is currently not acceptable for the following reasons:

- Real time data is not supported by results from studies conducted under intermediate or accelerated conditions.
- A lack of mass balance is observed between the results for assay and related substances.
- At this time the methods used to determine assay and related substances have not been adequately validated or shown to be stability indicating. Consequently any proposals for shelf life cannot currently be accepted.
- Results for several important stability indicating parameters are missing from the primary stability batches.
- There are currently deficiencies in the supplementary stability data which was provided in order to allow extension of shelf life
- Stability batches are not manufactured according to the proposed manufacturing process. Although the change in the manufacturing process is unlikely to affect the stability of the drug product stability data for batches manufactured as per the proposed process should be provided.

Stability data to cover an appropriate in-use shelf-life of the product is requested. An acceptable stability protocol with testing points for all the required stability indicating tests has been provided for future batches. A satisfactory commitment to place one batch per year on stability at the long term storage condition is also provided

3.2.3. Discussion on chemical, pharmaceutical and biological aspects

The physicochemical and biological properties of the drug substance have not been discussed. The impact of the particle size distribution of the drug substance on the product performance or manufacturability should be discussed. Standard excipients were selected. Their function is described and they are in adequate concentration for the proposed dosage form. The origin of the pregelatinized starch should be indicated.

The aim of the development activities was to produce a drug product with solid dosage form intended for oral administration. There is very poor information on the pharmaceutical development of the drug product. Information such as products investigated during the formulation development, characterisation of development batches, results of comparative tests with the test product and the marketed similar drug products, the solubility of the drug substance, the development of the dissolution method...etc are missing. This section should be completed according to Note for Guidance on Pharmaceutical Development (ICH Topic Q8 (R2) EMEA/CHMP/167068/2004) (Major objection).

All excipients used comply with their respective European Pharmacopoeia monographs.

Name and address of facility involved in manufacture, packaging, batch control and batch release is presented.

The drug product is manufactured by use of standard pharmaceutical techniques. The proposed manufacturing process consists of mixing of the components, filling the capsules and packaging. Description and flow chart of the manufacturing method have been provided, in-process controls are specified, however there are some issues to be clarified in connection with the subbatches and IPCs. The storage time and storage conditions of the blend and the bulk capsules should be indicated. Declaration should be provided that the packaging material used for storage of the intermediates complies with the relevant monograph of the current Ph. Eur.

Validation protocol is submitted for the alternative batch size with the commitment of the Applicant to complete a full validation study on the first manufacturing campaign. The validation scheme containing flow-chart, a short description of the manufacturing process, critical process steps, finished product specification, in-process control tests with acceptance criteria and sampling plan.

Process validation data on four commercial scale batches are provided. The validation report contains the results of the in-process controls and the results of the finished product testing except dissolution test. There are several questions related to limit of uniformity of mass, sampling plan and validation results.

The product specification includes compendial methods for dissolution, uniformity of dosage units, uniformity of mass, related substances (single unknown and total impurities) and microbial purity. The finished product specifications cover appropriate parameters for this dosage form, however the dissolution test is not described in detail, it is not indicated if the uniformity of dosage units is performed by content uniformity or mass variation and the used microbial control method is not specified. The release and shelf life specifications are generally acceptable in view of the requirements of Ph Eur, however some questions with regards to the analytical methods and the specification limits proposed were raised.

The validation of the method used for identity and assay is according to ICHQ2 (R1), but the method for related substances is not satisfactorily validated. The microbiological method should also be verified for the drug product.

Batch data have been provided (except results for dissolution) and complied with the specification set by the manufacturer.

Certificates of Analysis for impurity working standards are provided, however information about the used primary and/or working reference standard of the active substance is missing from the dossier.

The specification and technical description of the proposed container closure system have been presented, however a declaration should be provided, that the plastic packaging materials contacted with the drug product are in compliance with the relevant Ph. Eur. monograph.

The conditions used in the stability studies are according to the ICH stability guideline, except the testing frequency for long term studies. Additionally, the proposed post-approval protocol should be revised to include the dissolution test at each testing point, and the shelf-life specification in 3.2.P.8.1 should be amended with the limit for dissolution and loss on drying/weight. Stability data according to the revised specification should be provided.

Stability data have been provided for six batches stored at 25°C/60%RH and 30°C/75%RH for 12/18/36 or 48 months.

In-use stability study was conducted on one batch at 25°C/60%RH for 15 days. According to the Note for Guidance on In-Use Stability Testing of Human Medicinal Products in-use stability test should be performed with one more batch towards the end of its shelf life. Moreover the lengths of the study should be extended to be in line with the posology of the product (according to SmPC 4.2), simulating the utilization of the product (opening and use on a daily basis) till the drug product is run out using the smallest dosage.

Based on the presented stability data the proposed shelf-life of 2 years with the indicated storage conditions “Do not store above 25°C. Store in the original package in order to protect from moisture.” can only be granted after the questions are satisfactorily answered.

The pharmaceutical data in the SPC, PIL and label are acceptable. However in the SPC/PIL the appearance of the product is missing, and the description of the primary packaging is not enough detailed**.**

3.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the CHMP considers that the application for Ketoconazole AID-SCFM 200 mg capsules is not approvable for the time being, since major objection has been recognised related to quality (see list of questions).

3.3. Non clinical aspects

3.3.1. Pharmacology

The imidazole derivative ketoconazole is a well known orally active broad-spectrum antifungal agent used in the treatment of superficial fungal infections. The applicant has presented a literature review describing the pharmacological aspects of ketoconazole in relation to its antifungal

activity. Given the proposed indication is for the treatment of Cushing's syndrome, a hormonal disorder associated with prolonged exposure to high levels of the hormone cortisol, the relevance of this data is considered to be limited and is not considered as part of this assessment.

In addition to its antifungal properties, ketoconazole was shown to lower cortisol and testosterone levels in mice, rats, dogs and humans via inhibition of a variety of cytochrome P450 enzymes, namely side-chain cleavage complex, C17,20-lyase, 11-µ-hydroxylase, 17-µ-hydroxylase and steroid aromatase. The applicant has provided some rationale and a potential mechanism of action for the use of ketoconazole in the treatment of Cushing's syndrome. However, direct data has not been presented examining the efficacy of ketoconazole in a Cushing's disease animal model or how the data presented adequately supports the proposed indication at the proposed dose. The applicant should provide this data or adequately justify its absence (**OC**).

Data regarding other endocrine effects of ketoconazole have not been addressed at all. For instance, some data indicate that ketoconazole may have antithyroid activity (Comby F., 1994; Caksen H.,2002) and it was also reported that it could affect cholesterol, vitamin D status and calcium metabolism (Henry HL., 1985). A discussion on other possible endocrine effects (e.g., thyroid hormone production, D-vitamin status, anterior pituitary function) is requested (**OC**).

For safety pharmacology studies, the applicant has failed to adequately discuss the potential undesirable pharmacodynamic effects of ketoconazole on the physiological functions of vital organ systems (e.g. CNS, cardiovascular and respiratory systems) as described in the ICH S7A guideline (Safety pharmacology studies for human pharmaceuticals). Some data was presented which highlighted the need to utilize the drug under restricted precautions owing to destructive impacts of ketoconazole on the adrenocortical cells (hypertrophy, pyknosis, karyorrhexis and karyolysis) thus limiting their physiological performance. The applicant is asked to provide safety pharmacology data that describes the effects of ketoconazole on vital functions at the proposed therapeutic dose or adequately justify its absence (**OC**).

The possible pharmacodynamic interactions with ketoconazole are well established and have been adequately detailed in sections 4.3 and 4.5 of the SmPC. However, no references were provided to support the information provided for the potential pharmacodynamic interactions (**OC**).

3.3.2. Pharmacokinetics

No pharmacokinetic studies have been submitted. Information on absorption, distribution, metabolism and excretion has been provided by mean of a literature review. This is considered acceptable given that the MAA has been submitted as a well-established application.

The summary for the methods of analysis is based on previously published reports (Baxter J.G. et al., J Pharm Sci 1986) which have utilised HPLC methods, which appear sufficient. The applicant's summation of the absorption data which all arose from the Baxter J.G. et al., (J Pharm Sci 1986) is considered poor. However, from the paper quoted, dogs dose with 400 mg p.o. yielded peak concentrations of 17.4 ± 16.7 µg/ml for the ketoconazole tablet and of 15.4 ±9.4 µg/ml for the ketoconazole solution. No statistical differences were observed in AUC values for all three formulations. However, analysis of individual results indicates that there was limited bioavailability in every dog with at least one of the oral formulations if not both of the oral formulations. Overall, the study presented appears to be limited as dissolution and absorption of ketoconazole is dependent on gastric pH. 9, 10. This parameter was not evaluated in the present study. However, given that that absorption of ketoconazole is variable after oral administration in humans, with large variability in peak serum concentrations and highly variable bioavailability generally, the relevance of animal data is considered to be limited.

Ketoconazole appears to be widely distributed in rats and guinea pigs with maximal levels occurring in the liver, adrenals, pituitary and connective tissue. Ketoconazole crossed the placenta membrane into fetal tissue of rats (albeit at a markedly lower level than maternal levels) and distribution into milk was also demonstrated in lactating beagle dogs dosed at 10 mg/kg (14.2 and 1.73 mcg/ml in plasma and milk, respectively). A disproportionate increase in AUC with dose was seen in rats given single intravenous doses of 10, 20 or 40 mg/kg, a finding that was considered related to the saturation of metabolizing enzymes.

The applicant has not described the metabolism of ketoconazole in sufficient detail. The applicant is asked to provide a description of pathways involved in the metabolism of ketoconazole (OC).

The major route of elimination appears to be in the faeces via the bile. The applicant has not provided a reference to support this statement and is asked to do so (OC).

3.3.3. Toxicology

No new toxicology studies have been submitted. Information on the toxicity of ketoconazole has been provided by means of a literature review. The GLP status of the quoted studies/reports cannot be confirmed. This is considered acceptable given that the MAA has been submitted as a well-established application.

A series of LD50 values for a number of different animals via oral and i.v. routes were presented for single dose toxicity studies. These studies were performed prior to the publication on the Need for revision of the guideline single dose toxicity 3BS1a, (EMEA/CHMP/SWP/302413/08) which considers that data obtained in traditional single dose toxicity studies are of limited value and on the fact that information on acute toxicity can be obtained in other types of toxicity studies.

A very brief overview of a number the repeat-dose toxicity studies performed with ketoconazole was provided however supportive toxicokinetic evaluation was not presented or discussed. Toxicity possibly associated with antiandrogenic effects of ketoconazole (reduction of epididymis and accessory sex organ weights, spermatid retention in the seminiferous tubules, decrease of testosterone and increases of oestradiol, luteinizing hormone (LH) and follicular stimulating hormone (FSH), prolongation of the oestrous cycle, decreases in thyroxin and triiodothyronine and increases in thyroid-stimulating hormone) were observed in male and female rats dosed oral gavage at doses of 0, 6.25, 25 or 100 mg/kg/day for 28 days. In studies up to 12 months, reduced food consumption, increased weight gain and pathological changes in the liver, kidney, adrenal and ovaries were observed in rats and dogs (20-40 mg/kg/day). In addition, female rats showed an increase in bone fragility but there was no evidence of osteoporosis. However, the principle toxicity observed was ketoconazole induced hepatotoxicity that occurred in a dose and time-dependent manner. Although the exact mechanism for this toxicity has not been fully elucidated, it is suggested that the major hepatic metabolite of ketoconazole formed by the flavin-containing monooxygenases (FMO) might be the cause of this toxicity. The non-clinical liver findings presented above support the numerous reports of hepatic injury that have lead to the withdrawal of oral ketoconazole in the EU in 2013. The applicant is asked to discuss the 18 month toxicity data referred to in Section 5.3 of the SmPC and provide the relevant references to the data quoted (**OC**).

The applicant has not presented any genotoxicity studies for this application, or provided any discussion on the genotoxic potential of ketoconozole. The applicant should submit the relevant studies or robustly justify their absence (**OC**). In Section 5.3 of the SmPC the applicant has stated "In pre-clinical studies, ketoconazole was not carcinogenic or genotoxic". The applicant is asked to provide the references that support these data quoted (**OC**).

The applicant has not presented any carcinogenicity data to support the long term use of this product. Given the proposed indication, the applicant is asked provide carcinogenicity studies/data to support its use for the proposed chronic indication or robustly justify their absence (**MO**).

In fertility studies, ketoconazole impaired male fertility in the rat and mice were significantly compared to control at 200 mg/kg/day and 40 mg/kg/day. Embryotoxic (embryonic lethality) and teratogenic (numerous skeletal anomalies e.g. oligodactylia, syndactylia cleft palate) were evident in numerous reprotoxicity reports quoted. Some of these toxicities (e.g. early pregnancy failure) are presumed related to the antiandrogenic effects of ketoconazole, however no discussion was provided on the potential teratogenicity of ketoconazole in the context of the proposed indication (**OC**). The applicant is asked provide a tabulated overview of the safety margins established for the reproductive findings seen in these studies and discuss the potential implications given that fractionated doses up to 1200 mg/day may be required to normalise urinary free cortisol as per section 4.2 of the SmPC (**OC**). The applicant is also asked provide the reference that support the data included in section 5.3 of the SmPC in relation to the reprotoxicity data quoted (**OC**).

The discussion on local tolerance is considered limited however given that the proposed route of administration is per oral route, the lack of such data is acceptable. Of the one study quoted, 1% ketoconazole ophthalmic application in rabbits was well tolerated although some histological changes in regenerating epithelium were detected.

3.3.4. Ecotoxicity / environmental risk assessment

The applicant has not performed an environmental risk assessment. The applicant argues that Ketoconazole will not result in the increase of total quantity ketoconazole released into the environment therefore will not result in increase of risk to the environment. However, in July 2013, the EMA recommended the suspension of marketing authorisation for oral ketoconazole throughout he European Union. The applicant's argument is therefore considered weak in light of this development. However, given that Ketoconazole is a potential endocrine disruptor, a Phase II ERA using a tailored risk assessment strategy should be performed in line with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (Doc. Ref. EMEA/CHMP/SWP/4447/00 corr 1*) (**OC**).

3.3.5. Discussion on non-clinical aspects

As a well established use application the data presented should facilitate the assessment of the active substance on its own merit. The current application is poorly presented with limited discussion on the various non-clinical aspects required to carry out a complete assessment on the pharmacology, pharmacokinetic and toxicity of the product.– The non-clinical data presented in the summaries and overview (which were identical) for ketoconazole fail to explain the relevance of data in terms of the current indication and posology. A number of questions are raised where the data quoted (particularly in the SmPC) are not referenced or discussed in the context of the current indication. As a result a major objection in relation to the poor quality of the non-clinical dossier has been raised (**MO**).

Another major objection has been raised, in relation to the lack of data presented for chronic use of product (carcinogenicity studies). Given that the indication and dose differ from the well established ketoconazole, the applicant is asked to provide data that support its use for the proposed chronic indication.

3.3.6. Conclusion on non-clinical aspects

The non-clinical data at this time is not considered sufficient to support the use of ketonconazole in the treatment of Cushing's syndrome.

3.4. Clinical aspects

3.4.1. Clinical pharmacology

3.4.1.1. Pharmacokinetics

Referring to a 1988 review article in Clinical Pharmacokinetics, it is noted that absorption of ketoconazole is variable after oral administration, with large variability in peak serum concentrations. Peak plasma concentrations of ketoconazole administered orally to normal human volunteers (200-mg tablet) have been reported to be 4.2 mcg/ml at 1.7 h after administration of the tablet.

It is stated that the distribution of ketoconazole varies according to the tissue sampled, the underlying disease and the dose and duration of treatment. In the presence of renal failure, ketoconazole disposition was not altered, whereas in the presence of hepatic insufficiency, an alteration in disposition was suggested.

Ketoconazole does not cross the intact blood-brain barrier, and crosses to only a limited extent in fungal meningitis. Urinary concentrations of ketoconazole are usually low. Ketoconazole is 83.7% plasma protein (mainly albumin) bound, and 15.3% is erythrocyte bound, resulting in only 1% of free drug.

The kinetics after oral administration fit a 2-compartment model. The mean elimination half-life reported ranged from 7.5 to 7.9 h. Of interest was the observation that ketoconazole serum levels and therapeutic responses did not correlate.

Ketoconazole is extensively metabolised by hepatic microsomal enzymes. Extensive metabolism to inactive metabolites occurs, the products being mainly excreted in the faeces via the bile. Saturatable hepatic first-pass metabolism is probable. The half-life of ketoconazole is dose-dependent, increases during long term treatment, suggesting auto-inhibition of metabolism.

Renal failure is associated with reduced absorption. It is stated that no change in initial dose of ketoconazole is required in renal impairment. In the presence of renal failure, ketoconazole disposition is not altered

Ketoconazole is extensively metabolised by hepatic microsomal enzymes. Extensive metabolism to inactive metabolites occurs, the products being mainly excreted in the faeces via the bile.

3.4.1.2. Pharmacodynamics

Ketoconazole, initially licensed as an antifungal agent, was observed to lower cortisol and testosterone levels via inhibition of a variety of cytochrome P450 enzymes (side-chain cleavage complex, 17,20-lyase, 11-b-hydroxylase, and 17-a-hydroxylase). Inhibition of ACTH secretion or action as a glucocorticoid receptor antagonist have been described in cell models, but there is a lack of clear evidence in humans.

Ketoconazole therefore inhibits steroid biosynthesis by inhibition of multiple P450 enzymes, including cholesterol side- chain cleavage (scc), 17,20-lyase, 11 β-hydroxylase, 17α-hydroxylase).

The most sensitive site of actions in humans appears to be 17,20-lyase explaining the greater suppressibility of testosterone secretion as compared with cortisol secretion. Therefore, owing to its different selectivity (effective blockade of cholesterol side- chain cleavage and 17 hydroxylase/C17–20 lyase activities) ketoconazole has antiandrogenic properties, which can have favourable effects on female hirsutism but m Ketoconazole interferes with cytochrome P-450 enzyme systems in several endocrine glands, namely the testis, ovary, adrenal gland, placenta, and inhibits steroid biosynthesis especially testosterone and cortisol in patients. The endocrinologic abnormalities ketoconazole-induced are partially dose-dependent and fully reversible with a recovery 8-16 hours after an oral dose. It is important to note that much higher plasma concentrations are needed to affect cytochrome P-450 enzymes in mammalian than to inhibit fungal cytochrome P-450 enzymes. This may explain why endocrine effects appear evident only at high doses of ketoconazole.

KETOCONAZOLE ACTIONS ON THE ADRENAL GLAND

The administration of Ketoconazole is able to inhibit adrenal steroidogenesis. Although plasma cortisol levels in volunteers receiving a single dose of ketoconazole were within the normal range, ACTH stimulation tests showed blunted cortisol responses for up to 8 hours after a single dose of 400 or 600 mg of the drug. In this early study, Pont et al warned the medical community that high or multiple - dose use of ketoconazole might cause hypoadrenalism in patients. Furthermore, ketoconazole can block corticosterone production by ACTH stimulated rat adrenal cells *in vitro.* However, in subjects with normal pituitary-adrenal axis, basal cortisol levels are not affected or are only slightly lower even after high- doses and long-term treatment. Substantial inhibition was achieved at concentrations of 1-5 *mcg/ml* ketoconazole, whereas peak circulating levels in patients ranged between 2 and 20 *mcg/ml* after conventional doses of 200- 400 mg/day.

In the 1983 Loose *et al* demonstrated that Ketoconazole blocks adrenal steroidogenesis by inhibiting several cytochrome P450-dependent enzymes. The most sensitive site of action in humans appears to be the C17-20 lyase explaining the greater suppressibility of testosterone as compared with cortisol secretion. Cholesterol side-chain-cleavage blockade by ketoconazole has been demonstrated in both testicular and adrenal tissue preparations. Adrenocortical steroid biosynthesis is also inhibited at the 11β-hydroxylation and 18-hydroxylation steps.

KETOCONAZOLE ACTIONS ON THE TESTIS

Ketoconazole inhibits C17-20 desmolase, the enzyme responsible for androstenedione biosynthesis, and this can lead to stronger inhibition of testosterone biosynthesis compared with its inhibition of cholesterol side-chain cleavage, 11β-hydroxylation, and 18-hydroxylation. Total and free testosterone and androstenedione levels decrease in normal men two hours after 200 mg of ketoconazole. The nadir is reached 6 h after drug administration. This effect is transient and recovery of normal levels begins at 8 hours and is complete by 24 hours. There is a compensatory increase of LH and no change n cortisol levels confirming that there is a selective inhibition of C17-20 lyases at low dose of ketoconazole. Higher doses of ketoconazole (800-1200

mg/day), even once daily, cause more pronounced and more prolonged androgen blockade, and in some men testosterone levels are depressed throughout the day. Prolonged treatment with high doses cause hypogonadism with in some cases reduced sperm counts, azospermia, decreased libido, impotence and gynaecomastia. This hypogonadism appear to be reversible.

3.4.2. Discussion on clinical pharmacology

Pharmacokinetics in special populations are either poorly characterised or ignored. The applicant should discuss pharmacokinetics in hepatic impairment, renal impairment, older people and in

children and propose appropriate statements for section 4.2 of the SmPC. Interactions have been listed and appropriate inclusions for the sections 4.3 and 4.5 of the SmPC have been provided. The applicant should indicate which references support the information on interactions. (The two references cited deal in general with treatment of Cushing's and don't deal specifically with interactions).

Ketoconazole inhibits steroid biosynthesis by inhibition of multiple P450 enzymes, including cholesterol side- chain cleavage (scc), 17,20-lyase, 11 β-hydroxylase, 17α-hydroxylase). The most sensitive site of actions in humans appears to be 17,20-lyase explaining the greater suppressibility of testosterone secretion as compared with cortisol secretion.

The discussion of mechanism of action and pharmacodynamics is not acceptable, and the applicant needs to provide further justification.(MO)

3.4.3. Conclusions on clinical pharmacology

Basic pharmacokinetics have been addressed but PK in special populations has not been dealt with. Mechanism of action has been characterised.

3.4.4. Clinical efficacy

3.4.4.1. Dose-response studies and main clinical studies

The clinical summary provides a review of recent publications but the clinical expert does not discuss or justify the choice of dosing regimen as proposed in the SmPC. "Treatment for Cushing's syndrome is usually started at a dose of 200 mg twice daily but the daily doses of Ketoconazole may be increased. Fractionated doses of 600–800 mg/day (but in some cases up to 1200 mg/day) are usually required to normalise urinary free cortisol".

Ketoconazole was first used in Cushing's syndrome in 1983 when repeated oral doses of ketoconazole (200 mg every 5 h over a period of 48 h) have been able to induce a reproducible clear-cut fall of serum cortisol in a patient with a cortisol secreting adenoma. Later studies and case reports described its effects in various patients including patients with Cushing's disease. Because most reports included both preoperative, naïve patients and patients previously treated with surgery and/or radiotherapy, results are difficult to interpret.

In 1985, in the study of **Sonino et al**, 5 patients with CD were treated by ketoconazole at a dose of 600- 800 mg/day. Urinary free cortisol markedly decreased in all patients immediately after the beginning of treatment with ketoconazole. All patients rapidly improved clinically, all had regained their normal appearance, with regression of symptoms such as diabetes, hypertension, and muscle weakness. Normal menstrual cycles resumed in a patient after a long period of amenorrhea. No patient developed Addisonian crisis or hyperpigmentatiori, or required replacement steroids for symptoms of adrenal insufficiency.

Similar effective results were noted in the report of **Angeli and Frairia** in which 5 patients with Cushing's disease were effectively managed with 600-800 mg/ day ketoconazole.

In 1987, **Loli et al** treated with 600-800 mg/day of ketoconazole for 3-13 months seven patients with Cushing's disease and one with an adrenal adenoma. Rapid and persistent clinical improvement occurred in all patients; plasma dehydroepiandrosterone sulphate and urinary 17-ketosteroid and cortisol excretion decreased soon after the initiation of treatment, subsequently remaining normal or nearly so throughout the treatment period. Plasma ACTH levels did not

change, and individual plasma ACTH and cortisol increments in response to CRH were comparable before and during treatment.. There were no adverse reactions in this study.

Similarly, **McCance et al** showed in 19871987 that after treatment with ketoconazole 400 mg twice daily for 7 days, urinary cortisol levels rapidly fell to within the normal level in five of the six patients with Cushing's disease but acute hypoadrenalism occurred in one patient and nausea and pyrexia in three. Three patients developed abnormal liver function tests which returned to normal after the drug had been stopped.

In 1989, **Cerdas et al** (study in French) evaluated the effects of Ketoconazole (600 mg/day) in 10 patients with Cushing's syndrome during a mean period of 4.5 weeks (range 1-12). The urinary free cortisol excretion decreased by 21 +/- 15% (mean +/- SEM) (p less than 0.01) on day 1; 54 +/- 8% (p less than 0.0001) on day 2; 60 +/- 15% (p less than 0.0001) on day 3 and 87 +/- 3% (p less than 0.0001) on day 8 compared to baseline. On day 3, 7 patients showed normal UFC values and on day 8, only 1 patient, with the ectopic ACTH syndrome, had persistent hypercortisolism. No significant variations were observed in ACTH.

Sonino et al in 1991 confirmed their previous data treating 34 patients with CS (28 females/six males; age range 14-67 years) due to different causes. During treatment, urinary cortisol decreased from 1296 +/- 176 to 270 +/- 69 nmol/d (P less than 0.001); plasma cortisol decreased from 672 +/- 31 to 549 +/- 35 nmol/l (P less than 0.001). For patients with Cushing's disease, urinary cortisol decreased from 1073 +/- 126 to 200 +/- 21 nmol/d (n = 28; P less than 0.001) while plasma ACTH changed from 12.5 +/- 1.3 to 11.3 +/- 0.8 pmol/l (n= 26; not significant).

Twelve patients were treated for more than 6 months, and those with Cushing disease all received pituitary radiation therapy except the two who eventually escaped pharmacological control. One additional patient with adrenal carcinoma and one with ectopic ACTH syndrome showed lack of control of urinary cortisol levels.

A rapid clinical improvement was observed together with the normalisation of urinary cortisol levels, with regression of symptoms such as diabetes mellitus, hypertension, hypokalaemia, and restoration of well being. Ketoconazole was withdrawn within the first week in two patients for allergic reaction and acute liver toxicity. Other side-effects included: asymptomatic liver function abnormalities, gastrointestinal symptoms and worsening of gynaecomastia.

In 1991, **Tabarin** et al successfully treated four patients with Cushing's disease with 400-1200 mg ketoconazole per day. All had full clinical and biochemical regression of the disease for more than 6 months.

Similar data were obtained by **Mortiner** et al in 1991 treating eight patients (six female, two male) with Cushing's disease with 200 mg ketoconazole orally four times daily.

In the 1993 **Miller and Crapo**, meta-analysis of 12 studies treating 85 Cushing's disease patients reported 81 % (range 25–93%) normalisation of urinary steroids with clinical improvement. In particular, it was effective in lowering cortisol in eight of 12 studies with Cushing's disease patients. Of three groups of investigators reporting treatment failures, only one used maximal doses of 1200 mg/day. The longest reported period of treatment in Cushing's disease was 38 months. Effective doses have ranged from 200-1200 mg/day, with most studies reporting biochemical response at 600- 800 mg/day, administered twice daily. Some patients required increased doses during long-term therapy. ACTH levels did not override steroidogenic blockade by ketoconazole in Cushing's disease. Of eight studies that measured plasma ACTH values, six reported no significant increase. One study of five patients reported a mean decrease in ACTH values of 60% after 3 months of therapy. Two studies of ACTH responses to chronic ketoconazole therapy in Cushing's disease demonstrated no significant increase in basal ACTH values.

In 2008, **Castinetti et al**, retrospectively studied 38 patients treated with ketoconazole for two years. The drug was begun at 200–400 mg/day and titrated up to 1200 mg/day until biochemical remission. With a mean follow-up of **22.6 months** (6-72), 17 patients were controlled (51.5% of those treated long term); doses of ketoconazole varied from 200 to 1000 mg/day (mean 529 mg/day). On an intention to treat basis, **44.7% of cases had thus normalised their urinary cortisol**. Control of the disease was observed during the first month in eight patients and at 3 months after dose titration in nine patients. The controlled patients also presented clinical regression of signs of hypercortisolism including lowering of blood pressure and loss of weight (mean loss: 1–2 kg 3 months after initiation of treatment, 5 kg 1 year after initiation of treatment). Blood pressure was normal in all controlled patients 3–6 months after initiation of ketoconazole. However, anti-hypertensive drugs were not stopped despite blood pressure control in most of the patients, and *none of the five patients in whom anti-hypertensive treatment was stopped had normalised blood pressure* (anti-hypertensive drugs were re-introduced at the same dose).

In the five diabetic patients also metabolic control was improved with a reduction in insulin requirements in two patients and a decrease in HbA1C in three patients (without a change in dose of oral hypoglycaemic). Ketoconazole was stopped in the first week of treatment in five patients (13%) because of clinical or biological intolerance (nausea and diarrhoea in 5 patients, and 5 fold increase in gamma GT in one patient). The treatment was safe and no adrenal insufficiency was observed.

In contrast, 16 patients (42.3% of the total cohort, 48.5% of those treated long term), treated for a mean period of 10 months with a mean dose of 890 mg/day (varying from 600 to 1200 mg/day), were uncontrolled at the end of the follow-up: five of them had initially been controlled, for a period of 3 months (two patients), 2 years (two patients), and 3 years (one patient), at doses varying from 600 to 1000 mg/day.

Of the 16 uncontrolled patients, 8 presented a significant decrease in UFC: 5 of them normalised high blood pressure without modification of their antihypertensive therapy. From the other eight patients with unchanged UFC, the blood pressure status was not modified including three patients with normal blood pressure at initiation of ketoconazole treatment. Half of the 16 uncontrolled patients also displayed clinical regression of signs of hypercortisolism with mean loss of weight similar to that of controlled patients.

Three patients had a moderate increase of g-GT at initiation of therapy (not exceeding two- to threefold the upper limit of normal), spontaneously regressive at 3 months; two uncontrolled patients presented clinical intolerance (nausea, diarrhoea) when increasing dose to 1200 mg/day; and one uncontrolled patient presented biological intolerance (eightfold the upper limit of normal of ASAT and ALAT) when increasing dose to 1200 mg/day. The symptoms subsided after dose was decreased to 1000 mg/day. The authors suggest that intolerance is more likely to appear initially or at dose increase than during prolonged treatment at a stable dose. Close clinical and biological follow-up is necessary at titration steps on a weekly/monthly basis, while follow-up during long-term treatment with unchanged dose requires much less frequent controls.

Feelders et al in a 2010 review of medical treatment of Cushing's syndrome note that no prospective studies with ketoconazole monotherapy have been performed, so that efficacy data are only available from retrospective studies, mostly with small patient numbers. They mention the Castinetti study but conclude that taking all studies together, ketoconazole has an efficacy of approximately 70%, noting again that studies are, however, difficult to compare with respect to patient selection, treatment duration, pre-treatment with radiotherapy,etc.

A 2012 retrospective review of pre-operative medical therapy in 62 Cushing's syndrome by **Valassi** et al. 17 of the 62 patients were treated with ketaconazole alone. The patients' Initial daily dose of ketoconazole ranged from 200 to 600 mg and was increased by 200 mg at a time based on patient's drug tolerance, clinical status and treatment efficacy. There were abnormal LFTs in 3 patients: in one patient, there was a four-fold elevation after 1 week which led to the discontinuation of KTZ. In the other two patients, the elevation was mild and KTZ was reduced in one case and temporarily suspended in the other.

Summary of main efficacy results

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).

Efficacy of ketoconazole in published studies including more than five patients.

Author	Patients number	Mean follow up (months)	Controlled patients (%)	Side effects (%)
Sonino (26)	28a	7	93	29
Loli (30)	6	8	100	0
Cerdas (33)	6	1	100	40
Mortimer (35)	8	0.5	100	25
McCance (32)	6	0.5	83	50
Engelhardt (23)	7	0.5	14	0
Castinetti (25)	38	22.6	51.5	29
All studies	99	5.7	74	25

aSome of the studies included patients previously treated by conventional radiotherapy

Clinical studies in special populations

As would be expected, there were no specific studies in special populations. Discussion on special population is limited to a discussion on pregnancy

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

N/A

Supportive study(ies)

N/A

3.4.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

There were no controlled studies. The papers refer to retrospective reviews of case studies or case series.

Efficacy data and additional analyses

Feelder 2013 states that pituitary surgery is the first-line treatment of Cushing's disease (CD), and remission rates vary between 60 and 90%. However, the true remission rate is considerably lower because up to 25% of patients develop a recurrent adenoma. In addition, transsphenoidal surgery is less successful in patients with non-visible adenomas and macro-adenomas. Second surgery is an option in patients with persistent or recurrent CD, but the remission rates are lower, also with a considerable risk on hypopituitarism. Radiotherapy can be applied in patients with persistent hypercortisolism after surgery, but it has the disadvantage of having a slow onset of action with a mean period of 2 years, after which remission is induced. In this period, patients remain exposed to the deleterious effects of cortisol excess. In addition, radiotherapy can induce hypopituitarism, and it was shown that quality of life is most impaired in those CD patients with pituitary dysfunction after treatment, despite replacement therapy. Bilateral adrenalectomy is an effective but rigorous treatment for CD necessitating lifelong gluco- and mineralocorticoid replacement therapy with a permanent risk on acute adrenal insufficiency in case of physical stress.

Ketoconazole is one of the most widely used (off label) adrenal-blocking drugs. A major side effect includes hepatotoxicity. Liver function should therefore be carefully monitored during treatment. Other adverse events of ketoconazole treatment include hypogonadism in men and gastrointestinal complaints. In a retrospective study, Castinetti et al (93) reported biochemical cure in 51% of patients with CD (median follow-up, 23 months), with a treatment dose starting at 200–400 mg/d and up titration to 1200 mg/d until biochemical remission. The normalisation of cortisol production was paralleled by regression of clinical features, a decrease in blood pressure

3.4.4.3. Conclusions on clinical efficacy

This well established use application is based on the literature and the papers provided reflect case series of varying sizes and with Cushing's with different aetiologies.

The applicant notes that all studies evaluating efficacy of ketoconazole therapy in Cushing's syndrome are small and differ in patient's characteristics, previous treatment, medication type and doses, length of follow-up, and criteria used to define disease control.

The applicant also notes that the clinical indication of ketoconazole encompasses a variety of different conditions. Ketoconazole treatment may represent a second-line treatment option in patients with Cushing's syndrome undergoing surgery (especially in the presence of diabetes, hypertension and marked coagulation abnormalities). This drug is also indicated in patients who have persistent or recurrent disease after unsuccessful surgery and/or in the interim before the effects of pituitary radiotherapy are observed, and in patients in whom definitive treatment is delayed prior to adrenalectomy. Finally, this drug is a therapeutic option for all patients who are not suitable for surgery or who have decreased chances of a surgical cure considering adenoma localisation, size and growth pattern.

The proposed indication is simply treatment of Cushing's syndrome. The indication should be amended to reflect the place of medical treatment and the specific situations where treatment with ketoconazole has been shown to be effective.

The experience in the papers cited relates to mostly retrospective reviews of cases of approximately 100 patients. The mechanism of action of ketoconazole is known and the studies are in accord with an effect that would be expected taking account of the known effects of the drug. However, overall, efficacy has not been adequately documented.

The applicant should provide a discussion on experience with long term treatment with ketoconazole and should summarise experience from available cases in the literature (as there are isolated cases with long term use)

3.4.5. Clinical safety

Patient exposure

Patient exposure is not addressed specifically. There is a body of experience on use of ketoconazole in the treatment of fungal infections, which is reflected in the SmPC which was available, but patient exposure in the proposed indication is not discussed.

Adverse events

The applicant suggests that ketoconazole shows a favourable safety profile and notes the following approved product information (which seems to taken from a patient information leaflet):

The following common (affects less than 1 in 10 people) adverse effects have been reported:

Stomach pain, feeling sick (nausea) or being sick (vomiting)

Itching (pruritus)

Increased transaminases and/or alkaline phosphatase;

The following un common (affects less than 1 in 100 people) adverse effects have been reported:

Headache

Diarrhoea

Skin rash or reddening

Sleepiness

Dizziness

The following side effects have been reported, however the precise frequency cannot be identified and therefore how often they occur is classed as unknown:

lower number of blood platelets that can cause abnormal bleeding

Insufficiency of the adrenal gland has occurred (see below)

Increased pressure in the brain (in infants, the fontanelle may bulge),

Tingling sensation in the hands or feet

Increased sensitivity to strong sunlight.

Hair loss

Heartburn

Impotence

Menstrual disorders may be experienced in women, and in men a short-term decrease in testosterone levels can also be experienced and, at higher doses lower sperm count

Men may get swelling of the breasts.

The main adverse effects associated with the use of ketoconazole are liver enzymes elevations which are more common at the higher dosages.

Generally, there are mild elevations in liver enzymes (up to3-fold normal). These can be transient, and are not a contraindication to medical therapy with ketoconazole, but liver function should be monitored carefully because of the rare complication of liver failure.

Intolerance is more likely to appear initially or at dose increase than during prolonged treatment at a stable dose so it is necessary a strict follow-up at each titration steps

Monitoring of liver function is recommended prior to starting treatment with Ketoconazole and after one, two, four, eight weeks during treatment. Thereafter, liver function should be monitored as clinically indicated. Therapy with Ketoconazole should be discontinued if the patient develops jaundice or other signs suggestive of clinically significant liver dysfunction, in the event of a sustained increase in AST (aspartate aminotransferase) or ALT of 5 xULN or greater, or if ALT or AST elevations greater than 3 x ULN occur within bilirubin elevations greater than 2xULN. Following discontinuation of treatment with ketoconazole, patients should be monitored until resolution.

Although rarely, another adverse effect that has been reported with the use of ketoconazole is adrenal insufficiency. Treatment with Ketoconazole inhibits adrenal steroidogenesis which results in diminished cortisol production with consequent decrease in circulating levels of cortisol and potentially hypocortisolism. As the consequence of this effect, symptomatic adrenal insufficiency may occur.

Special attention should be placed to signs and symptoms associated with hypocortisolism such as weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyponatraemia, hyperkalaemia or hypoglycaemia. Patients should be educated to these symptoms.

If hypocortisolism occurs, consider temporary dose reduction or interruption of treatment with Ketoconazole, as well as temporary, exogenous glucocorticoid replacement therapy.

The information from the PIL reflects marketed experience with Nizoral and although this is relevant, the proposed indications for this application and the associated doses must be considered. Safety in the bibliographic information is not specifically addressed, but as would be expected, safety from papers is limited. The applicant should summarise available safety data from the publications and should in particular summarise and discuss experience of hepatic adverse reactions in the proposed indications (also considering the likely doses).

Serious adverse events and deaths

These are not specifically addressed.

Laboratory findings

There is no specific discussion or provision of data on laboratory changes. It is noted that “Generally, there are mild elevations in liver enzymes (up to3-fold normal). These can be transient, and are not a contraindication to medical therapy with ketoconazole, but liver function should be monitored carefully because of the rare complication of liver failure”. It is unclear if this information reflects experience in the proposed indication or in the treatment of fungal disease.

Safety in special populations

There is no discussion on safety in special populations other than use in pregnancy

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

The applicant notes that Ketoconazole may interfere with the effects of several drugs widely used in humans for long term therapy.

Concomitant administration of drugs which reduce gastric acid output or increase gastric pH may decrease absorption of ketoconazole because gastric acidity is necessary for its dissolution and absorption.

Ketoconazole can cause severe liver toxicity so the concomitant administration with other potentially hepatotoxic drugs should be carefully monitored.

Like other imidazole derivatives, ketoconazole may enhance the anticoagulant effect of coumarin anticoagulants. When ketoconazole is used concomitantly with these drugs, the anticoagulant effect should be carefully monitored and dosage of the anticoagulant adjusted accordingly.

Ketoconazole is structurally related to miconazole, so there is the possibility that severe hypoglycaemia could occur with ketoconazole in concomitant with an oral sulphonylurea anti-diabetic agent. Prolongation of the QT interval and QT interval corrected for rate (QTc), and rarely, serious cardiovascular effects, including arrhythmias (e.g., ventricular tachycardia, atypical ventricular tachycardia [torsades de pointes, ventricular fibrillation]), cardiac arrest, palpitations, hypotension, dizziness, syncope, and death, have been reported with ketoconazole concomitantly with terfenadine or astemizole. Ketoconazole markedly inhibits the metabolism of these drugs, probably via inhibition of the cytochrome P-450 microsomal enzyme system, resulting in increased plasma concentrations of unchanged drug (to measurable levels) and reduced clearance of the active desmethyl or carboxylic acid metabolite, respectively. Such alterations in the pharmacokinetics of these antihistamines may have been associated with prolongation of the QT and QTc intervals.

Concomitant administration of ketoconazole and rifampin has resulted in decreased serum concentrations of ketoconazole, and the drugs not be administered concomitantly.

Pharmacokinetic interactions are likely if ketoconazole is used with protease inhibitors. Concomitant use may result in altered serum concentrations of the protease inhibitors and/or the antifungal. In addition, concomitant use of ketoconazole and delavirdine may result in increased trough plasma concentrations of delavirdine.

Concomitant administration of ketoconazole affects the pharmacokinetics of midazolam or triazolam resulting in increased peak plasma concentrations and prolongation of the plasma half-life of these benzodiazepines.

Concomitant administration of ketoconazole and cisapride is contraindicated. Ketoconazole appears to inhibit metabolism of cisapride. Concomitant use of ketoconazole and cisapride has resulted in markedly elevated cisapride plasma concentrations and a prolonged QT interval and has rarely resulted in serious cardiovascular effects, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Concomitant administration of ketoconazole and methylprednisolone or prednisolone may result in increased plasma concentrations of the corticosteroid. Ketoconazole may enhance the adrenal suppressive effects of corticosteroids.

Concomitant administration of ketoconazole and cyclosporine increases the plasma concentrations of cyclosporine and serum creatinine concentrations.

Elevated plasma concentrations of digoxin have been reported with the concomitant administration of ketoconazole.

In vitro studies indicate that ketoconazole can inhibit the metabolism of paclitaxel. Concomitant administration of ketoconazole and phenytoin reportedly may alter metabolism of one or both of the drugs, and serum concentrations of both drugs should be monitored if they are used concomitantly.

Ketoconazole is a potent inhibitor of the CYP3A4, and concomitant use of a phosphodiesterase inhibitor can substantially increase plasma concentrations of the PDE inhibitor.

Concomitant use of ketoconazole and tadalafil results in a increase in the tadalafil AUC and a increase in peak tadalafil plasma concentrations.

Concomitant use of ketoconazole and vardenafil results in an increase in the AUC of vardenafil and an increase in peak plasma concentrations of vardenafil.

Norfloxacin may enhance the antifungal activity of antifungal agents.

Because ketoconazole is a potent inhibitor of CYP3A4 concomitant use with trazodone may result in substantially increased plasma trazodone concentrations.

As a CYP inhibitor, ketoconazole can affect the metabolism of doxorubicin and other anthracyclines,

etoposide, the taxanes, and the vinca alkaloids, and it can increase drug toxicity. When using these drugs it is best to avoid co-administration of ketoconazole. However, if ketoconazole is an integral component of the management of hormonal excess, it should be discontinued 24 to 48 hours before giving the chemotherapy drugs and may be resumed 24 to 48 hours after the administration of these drugs.

However, there is no discussion on interactions in general and it is unclear which papers reflect and support these interactions.

Discontinuation due to AES

This is not specifically addressed. Discontinuation of individual subjects is mentioned in some of the reports

3.4.5.1. Discussion on clinical safety

The EMA's recommendations following an Article 31 referral (opinion dated 25/7/13) ,based on a review by the Committee for Medicinal Products for Human Use (CHMP), which looked at available data on the benefits of oral ketoconazole and the risk of hepatotoxicity from preclinical and clinical studies, post-marketing spontaneous case reports, epidemiological studies and the scientific literature, advised the following:

Although the potential for hepatotoxicity is a class effect with azole antifungals, the data assessed show that the incidence and seriousness of hepatotoxicity is higher with ketoconazole than with other antifungal agents. Reported cases of hepatotoxicity included hepatitis, cirrhosis and liver failure with fatal outcomes or requiring liver transplantation.

The onset of hepatotoxicity occurred generally between one and six months after starting treatment, but has also been reported earlier than one month after starting treatment, and at the recommended daily dose of 200 mg.

The efficacy studies on oral ketoconazole are limited and have not been carried out in line with the most recently agreed guidelines. There are also inadequate data to support the efficacy of

ketoconazole when other treatments have failed or are not tolerated, or resistance has been detected.

The risk-minimisation measures proposed, such as limiting the treatment duration or restricting the use to patients refractory or intolerant to alternative treatments and to physicians experienced in treating rare fungal infections, were not considered sufficient to reduce the risk of hepatotoxicity to an acceptable level.

CHMP recommended that the marketing authorisations of oral ketoconazole-containing medicines should be suspended throughout the European Union (EU). The CHMP concluded that the risk of liver injury is greater than the benefits in treating fungal infections."

Because of this issue, oral ketaconazole has been taken off the market in all EU member states.

This is not mentioned by the applicant.

The applicant summarised safety by stating that "the most common side effects are gastrointestinal reactions and liver function alterations. Reversible elevation of hepatic serum transaminases occurs in approximately 5–10% of patients. But serious liver injury is much less frequent, occurring in ~1 of 15,000 patients. For this reason, it is recommended to monitor liver function tests weekly at the beginning of treatment rather than monthly. In general, periodic liver function tests during long term treatment with ketoconazole is advised."

This application considers use in Cushing's Syndrome, but as noted in the clinical summary, this can cover a significant number of indications such as Cushing's disease, ectopic ACTH syndrome, and adrenal Cushing's. Ketoconazole treatment may be a second-line treatment option in patients with Cushing's syndrome undergoing surgery (especially in the presence of diabetes, hypertension and marked coagulation abnormalities), or for patients who have persistent or recurrent disease after unsuccessful surgery and/or in the interim before the effects of pituitary radiotherapy are observed, or in patients in whom definitive treatment is delayed prior to adrenalectomy. It could also be used in patients who are not suitable for surgery or who have decreased chances of successful surgery.

In the 1993 review by Miller and Crapo of 12 studies, they note that most published reports of ketoconazole treatment of Cushing's syndrome have not systematically assessed the incidence of side effects. In four studies including 52 patients, elevated transaminases were seen in 15%, gynaecomastia in 13% of males, gastrointestinal upset in 8%, oedema in 6%, and skin rash in 2%. Side effects are not dose-dependent.

Safety of use in the proposed population is not addressed. The applicant should discuss safety in the context of the proposed indication and the proposed dose regimen: starting dose is 200mg twice daily with 600-800mg/day usually required and doses of up to 1200mg possible. (If 600mg how is this taken); proposed indications is broad.. is benefit risk positive in all cases.

It is agreed that monitoring of liver function is appropriate (and supported in a number of papers). However, it is assumed that the figures quoted related to ketoconazole use as an anti-fungal rather than in the proposed indications.

3.4.5.2. Conclusions on clinical safety

There are inadequate data and inadequate discussion provided on safety in the target population treated with the proposed drug regimen. In particular, there is no mention or discussion of the safety issues associated with ketoconazole, or of the reasons for withdrawal from EU markets and the applicant should discuss the benefit risk of ketoconazole in the context of use in the proposed indications.

The applicant should provide a review and discussion of safety in long term use

Hypoadrenalism is mentioned in the SmPC but not in the overview or summary. The applicant should review the occurrence of hypoadrenalism in patients treated with ketoconazole taking account of the dose and duration of treatment. Therapeutic manoeuvres in patients experiencing hypoadrenalism should be discussed and justified.

3.5. Pharmacovigilance system

The applicant has provided a summary of their pharmacovigilance system, including a statement signed by the applicant and the qualified person for pharmacovigilance to confirm that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX. The address at which the Qualified Person for Pharmacovigilance carries out their tasks has been provided, however the Member State in which they reside has not, in line with Directive 2001/83/EC as amended by Directive 2010/84/EU.

An updated summary of the Pharmacovigilance system should be provided to include details of the Member State in which the QPPV resides. Furthermore, a copy of the PSMF should be submitted.

4. Orphan medicinal products

At the time of designation, Cushing's syndrome affected approximately 0.9 in 10,000 people in the European Union (from COMP report).

5. Benefit risk assessment

Benefits

Beneficial effects

From the data provided it appears that ketoconazole may be effective in suppressing cortisol and this effect is manifest in reductions to urinary free cortisol.

Uncertainty in the knowledge about the beneficial effects

Documentation provided is based on case series from a variety of patients with Cushing's disease. No randomised controlled studies are available. In most cases efficacy is shown by demonstrating an effect on urinary free cortisol which is taken as a marker of response to treatment of Cushings There is little discussion on associated clinical effects such as improvement in glucose tolerance (reduction in glycosylated haemoglobin); hypertension; or hypokalaemia.

Risks

Unfavourable effects

Ketoconazole was removed from the EU market because of concerns that benefit risk in the treatment of infection was negative and the main concerns related to hepatotoxicity.

Uncertainty in the knowledge about the unfavourable effects

No discussion or evidence is provided on the safety of ketoconazole in the proposed indications and in particular with the higher doses that might be required to treat.

Balance

Importance of favourable and unfavourable effects

Cushing's syndrome has a number of different aetiologies but surgery is usually first line treatment. Ketoconazole treatment may represent a second-line treatment option in patients with

Cushing's syndrome undergoing surgery (especially in the presence of diabetes, hypertension and marked coagulation abnormalities). This drug could also be indicated in patients who have persistent or recurrent disease after unsuccessful surgery and/or in the interim before the effects of pituitary radiotherapy are observed, or in patients in whom definitive treatment is delayed prior to adrenalectomy. Finally, this drug could be a therapeutic option for all patients who are not suitable for surgery or who have decreased chances of a surgical cure considering adenoma localisation, size and growth pattern.

Ketoconazole appears to reduce cortisol levels in a proportion of patients and hopefully has associated effects on blood pressure, and blood sugar. However, ketoconazole is associated with hepatotoxicity, which can be severe and even fatal and has a negative benefit risk balance in treatment of infection.

Benefit-risk balance

Discussion on the benefit-risk assessment

Efficacy has not been adequately characterised. Safety in the proposed indication and with the associated doses has not been addressed, and in these circumstances, it is not possible to provide an adequate assessment of benefit risk balance.

6. Conclusions

The overall B/R of ketoconazole is, for the present, negative.