25 September 2014
EMA/CHMP/S34845/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ketoconazole HRA

International non-proprietary name: KETOCONAZOLE HRA

Procedure No. EMEA/H/C/003906/0000

Note

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

ACTH  Adrenocorticotrophin Hormone
AE  Adverse events
AGT  Aminoglutethimide
AI  Adrenal insufficiency
ALT  Alanine transaminase
AP  Alkaline phosphatase
AST  Aspartate transaminase
AUC  Area under the curve
b.i.d  Twice a day
CD  Cushing’s disease
CRH  Corticotropin Releasing Hormone
CS  Cushing’s Syndrome
D  Day
DDD  Defined Daily Dose
DHEA  Dehydroepiandrosterone
DHEAS  Dehydroepiandrosterone sulfate
DOC  Deoxycorticosterone
EAS  Ectopic ACTH Syndrome
EC  European Commission
EIA  Enzyme immunoassay
EU  European Union
F  Female
GCP  Good Clinical Practice
HR  Hour
KC  Ketoconazole
M  Male
MET  Metyrapone
MTH  Month
NAH  Nodular adrenal/adrenocortical hyperplasia
NC  Not controlled
NIH  National Institute of Health
RIA  Radio immunoassay
SD  Standard deviation
SMR  Standard mortality ratio
THE  Tetrahydrocortisone
THF  Tetrahydrocortisol
TYMC  Total yeast and mold count
1. Background information on the procedure

1.1. Submission of the dossier

The applicant Laboratoire HRA Pharma submitted on 5 February 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ketoconazole HRA, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 November 2013.

Ketoconazole HRA was designated as an orphan medicinal product EU/3/12/965 on 23 April 2012. Ketoconazole HRA was designated as an orphan medicinal product in the following indication: treatment of Cushing syndrome. The applicant applied for the following indication: Treatment of Cushing’s syndrome.

The legal basis for this application refers to:

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies together with a bioequivalent study aiming at bridging the literature data with the intended marketed product.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products (Signifor).

Protocol Assistance

The applicant did not seek a Protocol Assistance at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Polfarmex S.A.
ul. Jozefow 9
99-300 Kutno
Poland
1.3. **Steps taken for the assessment of the product**

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Concepcion Prieto Yerro  
Co-Rapporteur: Patrick Salmon

- The application was received by the EMA on 5 February 2014.
- Accelerated Assessment procedure was agreed-upon by CHMP on 23 January 2014.
- The procedure started on 26 February 2014.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 May 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2014. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.

- During the meeting on 26 June 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 June 2014.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2014.

- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 August 2014 and an updated Joint assessment report on 22 September 2014.

- During the meeting on 25 September 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ketoconazole HRA.

- The CHMP adopted a report on similarity of Ketoconazole HRA with Signifor on 25 September 2014.

2. **Scientific discussion**

2.1. **Introduction**

Problem statement

Cushing Syndrome is divided into ACTH-dependent forms, either due to a corticotropic pituitary adenoma i.e. a Cushing’s disease (CD) or due to an ectopic ACTH production by a neuroendocrine tumor or an unknown source (occult ectopic ACTH syndrome), and ACTH-independent forms, due to adrenal adenoma/carcinoma or nodular adrenal hyperplasia (Boscaro, 2001; Newell-Price, 1998).

According to the Committee for Orphan Medicinal Products (COMP) (Opinion dated 23/04/12) the prevalence of the “condition” Cushing’s syndrome is approximately 0.9 in 10,000 people in the European Union (EU). This is equivalent to a total of around 46,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor. The median age at first admission was 41.4 years (range 3.6-77.7) and the female to male ratio was 3:1. Less than 10% of cases occur in pediatrics and unlike in adults no female preponderance is observed (Shah, 2011).
The clinical consequences of excess endogenous cortisol exposure are generally severe: glucose tolerance impairment or diabetes; hypertension; dyslipidemia; clotting disorders; vascular fragility; muscular weakness; osteoporosis; diminished resistance to infection; depression and psychiatric disorders; healing defects; gonadal dysfunction with hirsutism and acne (Arnaldi, 2012; Bolland, 2011; Boscaro, 2001; Cavagnini, 2001; Newell-Price, 1998). Obesity and growth arrest are the most common findings in children with CS (Shah, 2011).

Because of complications such as hypertension, diabetes mellitus, cardiac abnormalities and alteration in hemostatic parameters, cortisol excess leads to an increased cardiovascular risk (Whitworth, 2005; Arnaldi, 2012) with increased frequency of arterial atherosclerosis (Neary, 2013). Inadequately treated CS is a life-threatening condition. In a Danish study (Lindholm, 2001), the mortality rate of non-malignant CS was 3.7 fold higher than in the normal population and was even worse in CD patients not cured by pituitary surgery, in which the mortality rate was 11.5 times higher than in the normal population. CD patients with persistent disease after initial surgery had a standard mortality ratio (SMR) of 3.73 (95% CI: 2.31-6.01), whereas mortality of CD patients with initial remission did not differ significantly from the general population (SMR: 1.23 (95% CI: 0.51-2.97) (Graversen, 2012). Other authors reported that in CD the mortality is significantly affected, even after apparently successful treatment. The probability of 10-year survival was 95.3% with 71.4% of the deaths attributed to cardiovascular causes or infection/sepsis (Ntali, 2013). Persistence of disease, older age at diagnosis, and presence of hypertension and diabetes were the main determinants of mortality. These results are similar to those in Spain (Etxabe, 1994) where mortality in patients with CD was significantly higher (SMR 3.8) than expected in the control population.

**About the product**

Ketoconazole is an imidazole derivative named:

\[\text{(±)-cis-1-Acetyl-4-\{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy]\}phenyl}\]

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 is an inhibitor of cortisol synthesis resulting from its ability to inhibit several cytochrome P450 enzymes in the adrenal glands. Ketoconazole inhibits primarily the activity of 17α-hydroxylase, but it also inhibits 11-hydroxylation steps, and at higher doses the cholesterol side-chain cleavage enzyme. Therefore, ketoconazole is an inhibitor of cortisol and aldosterone synthesis. Ketoconazole is also an inhibitor of androgens synthesis, inhibiting the activity of C17-20 lyase in the adrenals and also in Leydig cells.

Ketoconazole has therefore been demonstrated to be not only an inhibitor of cortisol and aldosterone synthesis but also an inhibitor of androgens synthesis. Ketoconazole could be used in the treatment of all causes of endogenous hypercortisolism, regardless of its aetiology.

Ketoconazole was subject to a referral procedure, due to public health concerns on the hepatotoxicity risk and in July 2013, the CHMP, taking into account the increased rate of liver injury, concluded that the clinical benefit of oral ketoconazole as an anti-fungal therapy is uncertain as data on its effectiveness are limited and did not meet current standards, and as alternative treatments of fungal infections were available. In addition, ketoconazole may commonly have caused an increase in liver enzyme levels and very rarely, cases of serious liver damage, including deaths, or cases requiring a liver transplant.
Ketoconazole has been available for the treatment of Cushing disease through compassionate use programs in some member states, at least until Janssen-Cilag stops the production of Nizoral 200 mg.

**Type of application and aspects of Development**

This application is based on Article 10a of Directive 2001/83/EC, as amended and relies on well established medicinal use supported by bibliographic literature. According to Article 10a of Directive 2001/83/EC, as amended it is possible to replace results of pre-clinical and clinical trials by detailed references to published scientific literature (information available in the public domain) if it can be demonstrated that the active substance of a medicinal product has been in well-established medicinal use within the EU for at least 10 years, with a recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply.

The requirements of article 10a application are discussed below:

a) Factors which have been taken into account by the CHMP in order to establish a well-established use

1- Time over which the substance has been used

Ketoconazole has been used in clinical practice for the treatment of Cushing’s syndrome since the 1980’s thus for a period of more than 30 years. In addition to its antifungal properties, ketoconazole has been shown to decrease the cortisol response to the adrenocorticotropic hormone (ACTH) stimulation in healthy subjects without any cortisol excess. In the early 1980’s ketoconazole was reported to have steroidogenesis inhibitor effects linked to a broad inhibition of cytochrome P450 enzymes.

The applicant refers back to more than 400 publications dating from mid 1980’s. The CHMP confirmed that the requirement of not less than one decade of medical use in in the applied indication in the EU is fulfilled. The literature provided by the applicant showed that, the clinical use of ketoconazole has been documented since at least the mid-1980 as shown by Angeli A publication dated 1985 describing long-term administration of ketoconazole in 5 women with Cushing’s disease and bilateral adrenal hyperplasia. Ketoconazole has then been increasingly used in the management of Cushing’s syndrome on an off-label basis in the EU. The therapeutic values of ketoconazole for long-term treatment of patients with Cushing’s syndrome were studied by several groups over the years. Therefore it is considered that ketoconazole has been extensively used in Cushing syndrome over the past decades and qualifies as well established-use indication.

2 - Quantitative aspects of use of the substance

Cushing’s syndrome is a rare and severe disorder. According to Orphanet 2013, the prevalence is 1/26,000. In a nationwide Danish survey from 1985-1995 (Steffensen, 2010) the annual incidence, in cases per million per year, was 1.2-1.7/million for Cushing’s disease, 0.6/million for benign adrenal adenomas, 0.2/million for adrenal cancer, and 2.3/million for non-malignant cause. A study from a defined region in Spain between 1975 and 1992 (Etxabe, 1994) reported an annual incidence of Cushing’s disease of 2.4 cases per million and a prevalence of 39.1 cases per million inhabitants at the end or 1992.

In an analysis of patient data from the Danish Civil Registration System between 1980 and 2010 (Dekkers, 2013), in collaboration with an epidemiology group from the Netherlands, the mortality rate in patients with Cushing’s syndrome (n=348) was twice as high as in age and gender matched cohorts (n=34,300). But this registry did not provide any specific data about medical therapies.
Despite the absence of official guidelines on the treatment of Cushing’s syndrome or recognized treatment algorithm, according to most authors, ketoconazole has been the most widely used medical therapy for Cushing’s syndrome because of its effectiveness (Biller, 2008; Invitti, 1999; Gross, 2007; Schteingart, 2009).

Although, it is difficult to assess the exact number of patients treated with ketoconazole for Cushing’s syndrome in the EU as this was an off-label use, some assumptions on the quantitative use for Cushing’s syndrome therapy from two official sources could be made:

- The French agency (ANSM) data on the compassionate use program initiated after the suspension of oral containing-ketoconazole products in France for providing ketoconazole (Nizoral®) to patients with Cushing’s syndrome in France. Data from ANSM indicate that about 250 patients were treated per year since 2011 in France.

- The European registry ERCUSYN: (European Registry on Cushing’s syndrome)

The ERCUSYN (European Registry on Cushing’s syndrome) study is a project funded by the European Commission Public Health Program (PHP 800200), of which the European Society of Endocrinology is one of the 41 Partners from 25 countries. The aims include obtaining prospective and follow-up data at EU level on epidemiology, mortality, outcome of therapies and a database where newly diagnosed patients -since 2005- with Cushing’s syndrome are prospectively collected at baseline and periodically after treatment, from centres of excellence throughout Europe.

1,023 patients with Cushing’s syndrome from 57 centres in 28 countries are currently included in the ERCUSYN database (up to October 2013).

In conclusion, the CHMP considers that the demonstration of the quantitative aspects of use of ketoconazole has been demonstrated.

3 - Degree of scientific interest of the use of ketoconazole

The applicant has provided detailed information supported by an adequate number of scientific publications showing that ketoconazole has been extensively studied as reported in the literature since the early 1980’s. Of the published articles supporting this application for the treatment of Cushing syndrome, Ketoconazole has been used both as sole medical therapy and in combination with other drugs (mainly with metyrapone) in more severe patients. Globally from the clinical data reviewed from the scientific literature, more than 800 patients with Cushing’s syndrome were treated by ketoconazole. These include 748 patients from 28 studies and 52 patients from individual case reports. Thus data are available from small studies/case reports as well as large retrospective chart reviews of up to 200 patients (Castinetti 2014). The usefulness of ketoconazole in the treatment of Cushing’s syndrome is well recognized among authors/ clinical experts from several countries.

4 - Coherence of scientific assessments

Despite limitations observed in most of the studies evaluated (retrospective analysis with lack of uniformity in the frequency of assessments within and across studies), they provide consistent results on the efficacy and safety profiles of ketoconazole when used as a treatment for Cushing syndrome. Most of these articles analyzed were peer-reviewed therefore the coherence of the scientific assessment has been shown.

Overall, this application is based on a comprehensive and updated literature review of non-clinical and clinical data, supported by more than thirty years of clinical practice with the use of ketoconazole in the proposed indication. The CHMP therefore concludes that within the recognised limitation of a rare and life threatening condition, ketoconazole has been a well-established medicinal use within the EU for more than 10 years.
The conclusion on systematic use takes into consideration the relevant proportion of patients covered by the presented data compared to the overall population affected by this condition, the consistency amongst the publications, the representativeness of the patients, as well as the duration over which such use has occurred. Therefore, it is the view of the CHMP that they are a reflection of the overall population, in which the applied product has systematically been used; hence the use of ketoconazole can therefore be considered as well-established in the claimed indication.

b) The CHMP considers that the documentation submitted by the Applicant has covered all aspects of the quality, safety and efficacy and includes review of the relevant literature. The documentation, both favourable and unfavourable has been communicated.

c) Due to the rarity of the disease, attention has been paid to any missing information and the CHMP considers that adequate justifications have been provided by the applicant which demonstrates that an acceptable level of safety and efficacy can be supported.

d) The Applicant explained the relevance of data submitted concerning the product reviewed in the literature being different from the product intended for marketing and the PK study performed by the applicant to bridge the scientific data with the product intended for marketing and was considered acceptable. It is noted that the formulations used are not always stated in the publications.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as uncoated tablets containing 200 mg of ketoconazole as active substance. Other ingredients are: maize starch, lactose monohydrate, povidone, microcrystalline cellulose, colloidal silica and magnesium stearate.

The product is available in PVC/Alu blisters.

2.2.2. Active Substance

**General information**

The chemical name of ketoconazole is 1-acetyl-4-[4-[[2RS,4SR]-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)1,3-dioxolan-4-yl]methoxy]phenyl]piperazine and has the following structure:

![Chemical structure of ketoconazole](image)

The active substance is a white or almost white powder, which is practically insoluble in water, freely soluble in methylene chloride, soluble in methanol, sparingly soluble in ethanol (96 per cent).
Ketoconazole exhibits stereoisomerism due to the presence of two chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation. Polymorphism has not been observed for ketoconazole.

As there is a monograph of ketoconazole in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application.

**Manufacture, characterisation and process controls**
The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

**Specification**
The active substance specification includes tests for: appearance (visual), identification (IR, melting point, reaction of chlorides), appearance of solution (Ph. Eur), optical rotation (Ph. Eur), assay (Ph. Eur), related substances (HPLC), heavy metals (Ph. Eur), loss on drying (Ph. Eur), sulfated ash (Ph. Eur), residual solvents (GC) and particle size (Ph. Eur).

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for methanol (included in the CEP) and particle size (not included in the CEP and tested only by the drug product manufacturer). The analytical method for particle size has been adequately validated and described according to ICH Q2 (R1).

Batch analysis data on two batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

**Stability**
Stability data on six commercial scale batches (two different batch sizes) of active substance from the proposed manufacturer stored in the intended commercial package for 36 months (pilot scale batches) or 72 months (commercial scale batches) under long term conditions at 25 ºC / 60% RH and, for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines have been provided.

The following parameters were tested: appearance, loss on drying, assay and related substances. The analytical methods used were the same as for release and were stability indicating.

No trends were observed for any of the parameters tested under long term or accelerated conditions, and all the batches complied with the proposed specification.

In addition, a forced degradation study under acid, base, UV radiation, thermal and oxidation conditions was conducted and showed that the analytical method used to determine related substances is stability indicating.

The stability results indicate that the drug substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

**2.2.3. Finished Medicinal Product**

**Description of the product and pharmaceutical development**
The aim of the pharmaceutical development was to obtain a generic product of the reference product Nizoral tablets 200 mg, marketed by Janssen-Cilag, with the same pharmaceutical form (uncoated immediate release tablets for oral administration) and the same qualitative composition.

Therefore, the excipients selected for the formulation of the product are the same as those contained in the reference product. They are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur
standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The development started with the evaluation of the physicochemical properties of the drug substance which could potentially influence the performance of the drug product and its manufacturability: solubility at different pH, particle size distribution, flow properties and polymorphism. The results of these studies showed that ketoconazole being a weak dibasic agent (pKa = 2.94; 6.51) requires an acidic environment for dissolution, its particle size distribution (within the limits included in the active substance specification) does not influence dissolution, its flow properties do not have an impact on the homogeneity of the final dosage form and, according to the Ph. Eur. ketoconazole does not exhibit polymorphism.

Although no specific studies were conducted to evaluate the hygroscopicity of the active substance, water content is controlled by the active substance specification (loss on drying) and the stability results provided demonstrate that it remains constant during storage.

Due to the high content of the active substance in the tablet formula (about 65%), wet granulation was selected for the manufacture of the tablets. During development of the manufacturing process it was determined that the granulate moisture content, the proportion of lubricant and glidant influenced the compression process and tablet quality. Therefore, these parameters were further studied in order to determine their optimal values.

In addition, parameters that can affect the bulk density (weight, hardness and uniformity of content of the tablets) are controlled through specifications and demonstrated to be reproducible.

In line with the "Guidance on the investigation of bioequivalence" (CPMP/EWP/QWP/1401/98 rev.1 corr.) comparative dissolution profiles at different pH values (1, 4.5 and 6.8) were provided. They demonstrated that test and reference product show similar dissolution profiles. Specifically, more than 85% of ketoconazole was dissolved in 15 minutes at pH 1; and although at pH 4.5 and 6.8 dissolution was incomplete, due to the limited solubility of the active substance at those pH, the $f_2$ values were higher than 50. No differences on the impurity profile of the test and reference product were observed.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is PVC/Alu blister. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: wet granulation (mixing of ketoconazole with the excipients, granulation, drying and calibration), lubrication, compression and packaging. The process is considered to be a standard manufacturing process.

Adequate in-process controls have been established.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), disintegration time (Ph. Eur.), identification (UV-Vis, HPLC), assay (UV-Vis), purity (HPLC), dissolution
(UV-Vis), uniformity of dosage units (Ph. Eur.), water content (KF), microbiological purity (TAMC, TYMC and 
*E.coli*) (Ph. Eur.).

The finished product is released on the market based on the above release specifications, through traditional 
final product release testing.

Non-compendial analytical methods have been described and validated in accordance with ICH Q2 (R1).

According to the data available at the time of opinion, the proposed HPLC method for determination of purity 
does not ensure mass balance between levels of ketoconazole and degradation product. However, this can be 
accepted at the time of opinion due to the proved stability of the active substance and the finished product, the 
use of a standard manufacturing process, and the therapeutic indication of the product. Nevertheless, the 
applicant is recommended to revalidate this method for mass-balance, accuracy and specificity and has 
committed to doing so by the end of 2014.

Additionally, although the suitability of the microbiological method on TYMC has been performed using dilution, 
with additional rinsing and membrane filtration to neutralize the antimicrobial activity of ketoconazole, the use 
of neutralizing agents was not tested. The applicant commits to complete the suitability of the microbiological 
method on TYMC by using neutralising agents to counteract the antimicrobial activity of ketoconazole by the end 
of 2014.

Batch analysis results on 2 commercial scale batches (analyzed with the proposed product specification) and 3 
commercial scale batches (analyzed with a preliminary product specification used during development - which 
used other methods for identification, purity and uniformity of dosage units-) confirmed the consistency of the 
manufacturing process and its ability to manufacture to the intended product specification have been provided.

**Stability of the product**

Stability data of three commercial scale batches of finished product stored under long term conditions for 24 
months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to 
the ICH guidelines have been provided. The batches of ketoconazole tablets are identical to those proposed for 
marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, disintegration time, uniformity of mass, purity, dissolution, assay and 
microbiological purity. The analytical procedures used are stability indicating. All the results met the 
specifications and no trends were observed for any of the parameters tested.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug 
Substances and Products. The photostability study showed that the product is not sensitive to light.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

**Adventitious agents**

It is confirmed that magnesium stearate is of vegetable origin and the lactose is produced from milk from 
healthy animals in the same condition as those used to collect milk for human consumption and that the lactose 
has been prepared without the use of ruminant material other than calf rennet according to the Note for 
Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and 
veterinary medicinal products.
2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, see 2.2.6.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant is recommended to revalidate for accuracy and mass balance the HPLC method for determination of purity of the finished product and has committed to do so by the end of 2014.

The applicant is recommended to complete the suitability testing of the microbiological method on TYMC by using neutralising agents to counteract the antimicrobial activity of ketoconazole and has committed to do so by the end of 2014.

2.3. Non-clinical aspects

2.3.1. Introduction

No pharmacology studies have been submitted. The pharmacological profile of ketoconazole is well known, and the applicant presented literature data on the effectiveness of ketoconazole as a potent inhibitor of cortisol and deoxycortisol synthesis through its ability to interfere with different cytochrome P450 enzymes in the adrenals. This activity is considered as the likely mechanism of action for the proposed indication.

Primary pharmacology

The applicant has provided literature in vitro data that supports that the inhibition of cortisol synthesis results from its ability to interfere with different cytochrome P450 enzymes in the adrenals: CYP17, acting primarily on the 17-20 lyase component of CYP17, but also on the 17α-hydroxylase, 11β-hydroxylase (CYP11B1), P450 side chain cleavage (CYP450ssc) and 21-hydroxylase. High variability in the IC₅₀ values for the same enzyme was reported depending on the study. The cause of the differences may be the systems were the ketoconazole effects were measured. Available published data do not allow to compare the ketoconazole potency on each enzyme among the different species and to estimate the individual contribution of each enzyme to the clinical treatment of patients with Cushing’s Syndrome. Despite variability in the results, in humans IC₅₀ values of ketoconazole for inhibition of 17, 20 lyase and 11β-hydroxylase enzymes were in the low μM range, while the
study performed in dog adrenal cells suggests ketoconazole mainly acts on 17α-hydroxylase activity in this species. Thus, the pattern of steroids may be modified by ketoconazole in different ways depending on the species.

The Applicant has provided several reports that examined the in vivo effects of ketoconazole on both basal and ACTH induced cortisol levels in healthy dogs and dogs with hyperadrenocorticism. Ketoconazole led to reductions in cortisol levels in dogs treated with 10 and 30 mg/kg/day and significantly reduced cortisol response to ACTH challenge with a once daily oral dose regimen and with 10 mg/kg dose administered every 8 hours for 5 days.

In dogs with hyperadrenocorticism as a result of adrenocorticol tumours and pituitary-dependent disease, ketoconazole reduced both resting and ACTH-stimulated increased cortisol in both groups with dose in the range of 5-25 mg/kg. Improvements in clinical parameters were also seen in dogs with remission of polydipsia, polyuria, polyphagia and other signs of hyperadrenocorticism.

In addition to its primary activity in inhibiting adrenal synthesis of cortisol, ketoconazole inhibited the production of aldosterone in vitro and in vivo in both rats and dogs. This activity was mediated primarily through the inhibition of 11β-hydroxylase and to a lesser extent via the enzymes involved in the transformation at C17 and C21. Moreover, ketoconazole decreased androgen production in male and female gonads.

In females, ketoconazole also reduced the ovarian production of estradiol and progesterone. This resulted mainly from inhibition of the activity of CYP17 in Leydig cells and of 17-20 lyase and aromatase in rat ovaries. The doses of ketoconazole required to lower testosterone and estradiol levels in rats and dogs were in the same range as those inhibiting corticosterone and cortisol production in these species. In vitro ketoconazole binds to the glucocorticoid receptor and antagonized the activity of dexamethasone in functional assays. However this did not translate in vivo in rats co-administered with ketoconazole and methylprednisolone and does not seem clinically relevant for Cushing’s patients treated with the recommended doses of ketoconazole.

In vitro Ketoconazole has been shown to inhibit cholesterol synthesis in cultures of human fibroblasts, while in vivo, no significant reductions in cholesterol was seen in rats dosed up to 100 mg/kg/day. A slight reduction of cholesterol was seen in dogs dosed at 30 mg/kg/day but not at lower doses. Reductions in plasma cholesterol have been reported in patients with prostate carcinoma receiving ketoconazole (400 mg every 8 hours) or in patients with familial hypercholesterolemia.

Finally, ketoconazole is a well-known orally active broad-spectrum antifungal agent and has been recently suspended but remains authorised as topical agent for the treatment of superficial fungal infections. Ketoconazole inhibits the synthesis of ergosterol in fungi resulting in accumulation of C-14 methylsterols and permeability changes in the fungal cell membrane.

Ketoconazole is a racemic mixture of the cis-(2S,4R) and the cis–(2R,4S) enantiomers. The cis-(2S,4R) isomer was more potent in inhibiting progesterone 17α,20-lyase than its cis-enantiomer, (IC50 values of 0.05 and 2.38 μM, respectively) and in inhibiting 11β-hydroxylase (IC50 values of 0.152 and 0.608 μM, respectively). In contrast, isomer 4 was more potent than isomer 2 in inhibiting cholesterol 7α-hydroxylase (IC50 values of 0.195
and 2.40 μM, respectively). Both isomers were relatively weak inhibitors of human placental aromatase with IC\textsubscript{50} values of 40 and 110 μM for isomers 4 and 2, respectively.

**Secondary pharmacology**

With regards to the cardiovascular system, ketoconazole blocked hERG and voltage-gated K\textsuperscript{+} (Kv1.5) channels expressed in Xenopus oocytes with IC\textsubscript{50} values of 49±13 and 107±5 μM (26.5 and 56.8 μg/mL) respectively. In cardiac myocytes isolated from neonate rats, ketoconazole blocked inward rectifying K\textsuperscript{+} currents (IK\textsubscript{ir}), the delayed rectifier K\textsuperscript{+} currents (IK\textsubscript{dr}) and voltage-gated L-type Ca\textsuperscript{2+} currents (IC\textsubscript{aL}) with IC\textsubscript{50} values of 3.2, 20.8 and 3.5 μM, respectively. The relevance of these results to humans was considered limited given the relatively high IC\textsubscript{50} values obtained and the effect of high protein binding of ketoconazole. Furthermore, ketonazole had little effect on in vivo ventricular repolarization or associated arrhythmias in guinea pigs (200 mg/kg) and dogs dosed for up to 40 mg/kg for one year. Prolonged RR and QT intervals were reported in animals coadministered ketoconazole and terfenadine, but this is likely the result of a pharmacokinetic interaction affecting the metabolism of terfenadine. Despite a clear signal from pre-clinical studies, QT prolongation and Torsade de Pointes have been observed in the clinical setting with ketoconazole. This is further discussed in the clinical part of this report and appropriate warnings have been mentioned in the SmPC under sections 4.3, 4.4 and 4.5 and 5.3.

An increased frequency of pentylenetetrazol-induced seizures was observed in mice that have been treated with ketoconazole. It could be a consequence of the pharmacological action of the drug on progesterone synthesis. However, since signals of neurotoxicity have not been identified in humans treated with doses of ketoconazole equivalent to those planned for treatment of endogenous Cushing’s syndrome (up to 1200 mg/day); there is no known concern about the safety of ketoconazole on the central nervous system.

Although non-clinical safety studies investigating effects of ketoconazole on the respiratory system are not available, it is considered acceptable by the CHMP since evidence of toxicity at respiratory level have not been reported in patients during decades of clinical experience with ketoconazole.

### 2.3.2. Pharmacokinetics

No new pharmacokinetic studies have been submitted to support the Marketing Authorisation Application. The summary for the methods of analysis is based on previously published reports which have utilised HPLC /UV, HPLC/fluorescence and LC/MS methods. While the majority of these reports do not include information on the validation methods, the methods are considered adequate given the type of application.

Two studies reported have demonstrated linearity in the range of 0.015-10 μg/mL and 62.5-5000 ng/mL for ketoconazole and ketoconazole enantiomers, respectively. While, lower limits of quantification quoted for ketoconazole and ketoconazole enantiomers were 5 ng/ml and 62.5-5000 ng/ml.

**Absorption and Distribution**

The bioavailability of ketoconazole following oral doses was 35.8%, 50%, 22% and 81.2 % in rats, dogs, monkeys and humans, respectively. Pharmacokinetic in these species showed a high degree of inter-animal
variability. Studies in rats showed non-linear pharmacokinetic of ketoconazole with plasma levels increasing with the dose, indicative of saturation of metabolising enzymes and of tissue binding sites. Pharmacokinetic studies in rabbits, dogs, pigs and monkeys only assayed a dose and thus the dose-dependency of pharmacokinetic parameters cannot be evaluated in these species. In dogs, exposure to ketoconazole increased following repeated administration. Given that absorption of ketoconazole is variable after oral administration in humans, with large variability in peak serum concentrations and highly variable bioavailability, the relevance of animal absorption data is potentially limited.

**Metabolism**

Differences in pharmacokinetics between male and female rats were observed, with higher plasma levels and a longer half-life in female than in male rats. An analysis of the pharmacokinetics parameters of ketoconazole administered to castrated males and to females supplemented with testosterone showed that metabolizing enzymes are under androgenic control in rats. This observation explains because higher plasma levels and longer half-life were reported in female than in male rats. It is unknown if gender differences exist in exposure to ketoconazole in other non clinical species, but they have not been observed in humans.

Half-life of ketoconazole after oral dosing is lower in rats (1.08-1.83 hours), followed by dogs (2.76-3.61 hours) and humans (3-10 hours). It was independent of dose in rats, but dose-dependent in humans. Both data (low and dose-independent half-life) together with the low bioavailability of ketoconazole observed in rats support the extensive first pass hepatic metabolism in rats.

Ketoconazole is highly bound (99%) to human plasma proteins and appears to be widely distributed in rats and guinea pigs with maximal levels occurring in the liver, adrenals and pituitary. Ketoconazole crossed the placenta membrane into fetal tissue of rats and guinea pigs (albeit at a markedly lower level than maternal levels) which suggested that the placenta provides some levels of protection against the passage of ketoconazole to the foetus.

Ketoconazole appears to be extensively metabolized by the liver to a large number of inactive metabolites. Oxidation and subsequent scission and degradation of the imidazole ring, scission and degradation of the piperazine ring, scission of the dioxolene ring and oxidative O-dealkylation were reported as the major metabolic pathways. The predominant metabolite seen was the N-deacetyl ketoconazole (DAK) which accumulated upon repeat ketoconazole dosing. All available data support that the metabolic pathways of ketoconazole are very similar across species in both human and animals, particularly rodents and canines.

**Excretion**

The major route of excretion appears to be in the feces via the bile. Excretion of ketoconazole in milk was also reported. Therefore, the administration of ketoconazole to breast-feeding women is contraindicated and this is adequately mentioned in the SmPC (Section 4.3).

**Pharmacokinetic interactions**

The possible pharmacokinetic interactions with ketoconazole are well established. Ketoconazole is considered a universal inhibitor of CYP450 dependent monoxygenases. In vitro studies have shown that ketoconazole is a
very potent inhibitor of CYP3A4, but inhibition of CYP1A, CYP3A5, CYP2B6, CYP2C9/8 is also observed at clinically relevant concentrations. Ketoconazole is also a P-gp inhibitor at clinically relevant concentrations. Inhibition of BCRP was demonstrated at higher concentrations, raising the possibility of an interaction at the intestinal, but not at the systemic level. Ketoconazole was shown to be an inhibitor of OATP1B1 (IC₅₀ of 43.4 μM) and OAT1 (IC₅₀ of 319 μM).

2.3.3. 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.

The toxicology profile of ketoconazole has been established from long term studies in rats (up to 18 months) and dogs (up to 12 months).

Toxicity arising from ketoconazole pharmacology (reduction of epididymis and accessory sex organ weights, increased in vaginal and ovary weights, reduction in uterus weight, spermatid retention in the seminiferous tubules, decrease of serum testosterone and of estradiol in males and females, respectively, increases in luteinizing hormone (LH) and follicular stimulating hormone (FSH), irregular estrous cycle and prolongation of the estrous cycle, decreases in thyroxin and triiodothyronine and increases in thyroid-stimulating hormone) were observed in male and female rats orally dosed at doses up to 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 also observed in rats and dogs (20-160 mg/kg/day).

In addition, female rats showed an increase in bone fragility and broken legs which were associated with reduced diameter of the tibial bone and irregularities in the mineralization of the compact bone, cancellous bone hyperplasia and spontaneous fractures which were the sites of callus formation with marked fibrosis eventually extended far into the neighbouring tissues.

Kidney changes (increments in weight and swelling of the distal tubules and/or loops of Henle) were observed in rats, but no in dogs. Additionally, in the 6-month toxicity study the urinalyses showed an increased excretion of urine, a decrease in creatinine and the presence of casts in the urine. These alterations are not considered clinically relevant because: a) they were only observed in rats, but no in the longer study performed in this species, b) clinical signs of renal insufficiency were not reported in rats with kidney alterations, c) available exposure data, despite of their limited relevance (as they do not correspond to the animals of the study where alterations were found), suggest that kidney findings are associated to exposures that were in excess compared to exposures reached in Cushing’s syndrome patients treated with the highest recommended dose (1200 mg/day) of ketoconazole and d) kidney damages have not been reported in patients during more than 30 years of clinical use.

The main toxicity observed was ketoconazole induced hepatotoxicity occurring in a dose and time-dependent manner. This toxicity results to increased liver weights, elevated liver enzymes, hepatocyte hypertrophy and
histological changes in cytoplasm (slight centrilobular swelling and/or finely granular or blurred aspect) and in hepatocytes (brown pigmentation). Although the exact mechanism 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. More specifically, this mechanism is mediated through direct covalent binding of the parent compound to hepatic proteins and binding of FMO generated metabolites (e.g. N-deacetyl ketoconazole) to both hepatic proteins and glutathione. Another mechanism considered was the effect of ketoconazole on bile acid synthesis. Both in vitro and in vivo studies showed that ketoconazole impaired/inhibited bile acid synthesis flow and biliary output. In conclusion, the hepatotoxicity need to be considered when assessing the benefit/risk of the product.

**Genotoxicity**

No evidence of genotoxic potential was found in vitro and in vivo. However, the doses tested in vitro are lower than those recommended by ICH and the assessment of the clinical relevance of the results from in vivo experiments is limited by the lack of exposure data. Therefore, the CHMP considered that the genotoxic potential of ketoconazole contains limitations when considering the proposed dosing regimen in the treatment of endogenous Cushing’s syndrome (higher doses/exposure).

**Carcinogenicity**

Carcinogenic potential was examined in an 18 month and 24 month carcinogenicity study in mice and rats. The overall incidence and type of tumour seen in these studies was not significantly different between treated or control animals. Moreover, ketoconazole was shown to reduce tumour incidence and progression in various carcinogenic models.

**Reproduction toxicity**

In fertility studies, ketoconazole impaired both male and female fertility in rats and dogs that were dose and duration dependent. Ketoconazole had no effect in female fertility at doses up to 40 mg/kg given in the food, but had clear maternal and foetal toxicity at a dose of 80 mg/kg in the rat. In males an oral dose of 200 mg/kg/day for 3 days decreased fertility, whereas a complete loss of fertility was observed at 400 mg/kg/day. In longer dosing periods (up to 3 months) decreased fertility in males was observed at a dose of 24 mg/kg/day. In dogs abnormalities in sperm were observed following oral dosing for 4 weeks with 25 mg/kg of ketoconazole. Some of these toxicities (e.g. early pregnancy failure) are presumably related to the antiandrogenic effects of ketoconazole.

Ketoconazole was both embryotoxic (increased resorbed foetuses & increased still births) and teratogenic (oligodactylia, syndactylia, a slight increased incidence of waved ribs, absence of metacarpal and/or metatarsal bones, cleft palate as well as numerous skeletal abnormalities in hand and forelimb bones) at maternally toxic doses (80 mg/kg/day and higher). Similarly in rabbits, an increase in the number of resorptions was seen at 10 and 40 mg/kg/day. An increased incidence of skeletal abnormalities were also seen at 40 mg/kg/day compared to control. The applicant presents various hypotheses for the mechanism for the teratogenic effects seen; inhibition of maternal steroid synthesis by ketoconazole based on the observed decreased incidence of external
and skeletal abnormalities in foetuses from dams supplemented with prednisone, as compared to dams given ketoconazole alone; inhibition of phospholipase A2, or disruption of the metabolism of endogenous retinoids. As a result of the teratogenicity seen, ketoconazole is contraindicated in pregnancy and this is adequately reflected in the proposed SmPC.

**Juvenile toxicity**

In juvenile animals, treatment related toxicities were indicative of the pharmacological action of ketoconazole. These included significantly reduced epididymal weights and increased serum testosterone and DHT levels (although the latter not considered statistically significant compared to control) in male rats. In female rats, body weight gains and onset of sexual maturity was delayed in the high-dose group only (100 mg/kg/day). However, adverse effects of ketoconazole on other organs as liver, adrenal and cardiovascular systems were not studied in juvenile animals. Thus, the safety of ketoconazole in paediatric population is not well evaluated and limited information is available from the non-clinical point of view. The concerns about safety of ketoconazole in paediatric population are resolved by an adequate labelling in the SmPC.

**Local tolerance**

Ketoconazole (100 mg/kg/day for 15 p.o.) had no effect on antibody response when rats were immunized with sheep red blood cells 6 days before the end of treatment. However, the antibody and delayed hypersensitivity responses (along with decreases in NK and phagocytic cell activities) to SRBC were reduced in mice treated for 14 days with a higher dose of 160 mg/kg/day and immunized with SRBC 4 days before the end of treatment. The Applicant was unclear if these reported differences were as a result of the different doses used or the protocol employed. Toxicity to the immune system observed in patients (autoimmune and allergic diseases) after ketoconazole administration is due to an enhancement instead of a suppression of the immune response. Therefore, suppression of the immune response observed in rats is considered no clinically relevant.

**2.3.4. Ecotoxicity/environmental risk assessment**

As Ketoconazole is a potential endocrine disruptor, a phase II ERA is requested as outlined in the guideline. The PEC surface water using the refined Fpen value of 0.023 microg/L as requested by the CHMP, triggered the threshold value of 0.01 microg/L.

Some data regarding aquatic effects are available in the literature and the applicant is requested to perform a full literature search in order to obtain all available information regarding ketoconazole effects on the environment, and to perform a gap analysis as a post-Marketing Authorisation commitment. A detailed program including missing studies necessary to complete the ERA for ketoconazole will be submitted for approval within 4 weeks after EC decision. Furthermore, a phase II ERA will be performed as a post Marketing commitment, as requested by the CHMP.
2.3.5. Discussion on non-clinical aspects

The pharmacology studies have shown ketoconazole to be a potent inhibitor of cortisol synthesis resulting from its ability to interfere with different cytochrome P450 enzymes in the adrenals: CYP17, acting primarily on the 17-20 lyase component of CYP17, but also on the 17α-hydroxylase, 11β-hydroxylase (CYP11B1), P450 side chain cleavage (CYP450ssc) and 21-hydroxylase. The individual contribution of each of these activities to the clinical treatment of patients with Cushing’s syndrome is unclear.

Ketoconazole has inhibitory activity against enzymes involved in the synthesis and metabolism of other steroids: a) CYP11B2, the enzyme involved in the synthesis of aldosterone; b) the activity 17, 20-lyase of the enzyme CYP17, which is involved in the synthesis of testosterone and c) the aromatase, the enzyme involved in the synthesis of estradiol from testosterone. Thus, ketoconazole, in addition to decreasing cortisol levels, decreased the levels of aldosterone, testosterone and estradiol in rats, dogs and humans. The potency of ketoconazole on each CYP enzyme seems different among the species and this difference could result in a different steroid pattern in each species (humans, rats and dogs) which hinders the assessment of the toxicological findings in animals.

Electrophysiological studies have shown that ketoconazole blocks the ion channels HERG, Kv1.5, IKir, IKdr and ICaL and prolongs the action potential duration at concentration higher than those expected in patients. Additionally, effects on the ECG were not reported in rats and dogs. In contrast, QT prolongation and Torsade de Pointes have been observed in patients after ketoconazole administration and the cardiovascular risk is managed at clinical level (refer to SmPC sections 4.3, 4.4, 4.5 and 5.3 and risk management plan).

Pharmacokinetic studies showed nonlinear pharmacokinetic with plasma levels increasing with the dose (in rats) and after repeating dosing (in dogs), presumably reflecting saturation of metabolizing enzymes and of tissue binding sites.

Ketoconazole is highly bound (99%) to human plasma proteins. It is widely distributed in tissues and crosses the placental barrier.

Ketoconazole is extensively metabolised to inactive metabolites in the liver through CYP3A4. Oxidation and subsequent scission and degradation of the imidazole ring, scission and degradation of the piperazine ring, scission of the dioxolene ring and oxidative O-dealkylation were reported as the major metabolic pathways. The predominant metabolite seen was N-deacetyl ketoconazole (DAK) which accumulated upon repeat ketoconazole dosing. DAK is metabolised to hydroxylamines and in turn to ring-opened dialdehyde which are thought to result in toxic consequences. The metabolic pathways of ketoconazole are very similar across species.

Ketoconazole is mainly excreted in the faeces (>80%) in rats and dogs as inactive metabolites being biliary excretion approximately 60% of the administered dose in rats, but no evidence of enterohepatic recirculation was found. Excretion of ketoconazole in milk was reported in Beagle dogs. The administration of ketoconazole in breast-feeding women is contraindicated.

Ketoconazole is an inhibitor of hepatic P450 enzymes (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9/8, CYP2C19, CYP2D6, CYP2E1 and CYP4A but especially of the CYP3A family), of UGT enzymes (UGT1A1, UGT1A9 and
UGT2B7) and an inducer of CYP1A1. Inhibition of CYP3A enzymes was observed at clinically relevant concentrations and interactions with CYP1A2, CYP2B6 and UGT1A1 seem likely in patients treated with the highest dose recommended. Ketoconazole is also an inhibitor of P-gp, BCRP, OATP1B1 and OAT1 and it inhibits P-gp at clinically relevant concentrations.

The toxicology profile of ketoconazole has been established from long term studies in rats and dog, but the assessment of the safety profile of ketoconazole is limited by the lack of toxicokinetic data and of a recovery period in the toxicity studies.

The main toxicity induced by ketoconazole is hepatotoxicity to be considered in the benefit/risk balance. Effects in adrenal and reproductive systems that probably are consequence of the ketoconazole pharmacological action have been also observed in rats and dogs. The same organs are also target of ketoconazole in humans and the risk is managed at clinical level. In addition, bone fragility and broken legs were observed in rats but no in other species. In conclusion, the risk in bone is described in the SmPC section 5.3.

Ketoconazole is not considered carcinogenic and no evidence of genotoxic potential was found in vitro and in vivo. However, the genotoxic potential of ketoconazole was not properly determined for the proposed dosing regimen in the treatment of endogenous Cushing’s as described in section 5.3 of the SmPC.

In reproduction studies, ketoconazole impaired fertility, and produced embryotoxic and teratogenic effects. The administration of ketoconazole during pregnancy and breast-feeding is contraindicated. (refer to section 4.3 and 5.3)

A post-Marketing Authorisation commitment to perform a Phase II ERA is recommended.

2.3.6. Conclusion on non-clinical aspects

The Applicant submitted an application for a well-established use product, and as such submitted no new non-clinical data. The extensive literature review of the pharmacology, pharmacokinetics and toxicology of ketoconazole is considered appropriate and acceptable to support the non-clinical profile of ketoconazole.

The concerns related to the hepatotoxicity of ketoconazole leading to the withdrawal of the product previously approved in treatment of fungal infections are discussed later in the context of the new applied indication. The hepatotoxicity of ketoconazole remains an issue to be considered and is further addressed in the benefit/risk of this report. Overall, the non-clinical profile of ketoconazole is considered to be well established as demonstrated by the literature review provided and is considered appropriate to support the proposed clinical use of ketoconazole for the treatment of Cushing’s syndrome.

2.4. Clinical aspects

2.4.1. Introduction

Ketoconazole has been used in clinical practice for the treatment of Cushing’s syndrome since the 1980’s thus for a period of more than 30 years. In the early 1980’s ketoconazole was reported to have steroidogenesis inhibitor effects linked to a broad inhibition of cytochrome P450 enzymes.
The applicant refers back to more than 350 publications showing that, the clinical use of ketoconazole has been documented since at least the mid-1980s.

**GCP**

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

### 2.4.2. Pharmacokinetics

The pharmacokinetics data in this application are supported by literature data and a bioequivalence study between the test drug and the product referred to in the literature Nizoral® 200 mg film-coated.

#### 2.4.2.1. Bioequivalence study

The applicant has conducted a randomized, blind, two-way crossover, bioequivalence study (04/AM/POL/2003) of test drug and the product referred to in the literature Nizoral® 200 mg film-coated tablets administered as 1 tablet containing 200 mg of ketoconazole in healthy subjects under fasting conditions with a washout of 14 days.

The study was conducted from August 09th, 2003 to August 24th, 2003 and according to current Good Clinical Practice guidelines and in line with the Declaration of Helsinki and its amendments.

All Ketoconazole plasma samples were analyzed within the established long-term stability.

ANOVA analysis has been performed correctly (sequence, period and treatment as fixed factor and subject [nested within sequence] as random factor).

Pharmacokinetic parameters of Ketoconazole and the evaluation of the bioequivalence AUC$_{0-tr}$, AUC$_{0-inf}$ and C$_{max}$ for Ketoconazole is presented below (N=23).

<table>
<thead>
<tr>
<th>PK</th>
<th>Test Mean (SD)</th>
<th>Reference Mean (SD)</th>
<th>Point estimator [%]</th>
<th>Lower limit [%]</th>
<th>Upper limit [%]</th>
<th>Intra-subject CV [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_{max}$</td>
<td>3109.26 (898.64)</td>
<td>3027.17 (832.62)</td>
<td>95.71</td>
<td>84.39</td>
<td>108.56</td>
<td>24.67</td>
</tr>
<tr>
<td>AUC$_{0-tr}$</td>
<td>9952.36 (3222.09)</td>
<td>10022.09 (3235.55)</td>
<td>94.28</td>
<td>82.09</td>
<td>108.28</td>
<td>27.18</td>
</tr>
<tr>
<td>AUC$_{0-inf}$</td>
<td>10651.87 (3693.78)</td>
<td>10729.47 (3232.41)</td>
<td>97.99</td>
<td>85.08</td>
<td>112.86</td>
<td>27.77</td>
</tr>
<tr>
<td>t$_{max}$</td>
<td>1.33 (0.37)</td>
<td>1.44 (0.43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kcl</td>
<td>0.372 (0.238)</td>
<td>0.372 (0.192)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t$_{1/2}$</td>
<td>4.11 (8.12)</td>
<td>2.65 (2.15)</td>
<td></td>
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</tr>
</tbody>
</table>

Based on the submitted bioequivalence study Ketoconazole 200 mg film-coated tablets manufactured by Polfarmex, S.A. when compared with Nizoral® 200 mg film-coated tablets, manufactured by Janssen-Cilag meet the bioequivalence criteria with respect to the AUC$_{0-tr}$ AUC$_{0-inf}$ and C$_{max}$.
2.4.2.2. Literature review

Absorption

KC is a weak dibasic agent and thus requires acidity for dissolution and absorption. Mean peak plasma concentrations of approximately 3.5 μg/ml are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal. Cmax and area under the curve (AUC) increase more than proportionally with dose. Four to six hours post dose, concentrations of 6 to 50 μg/mL were reported after doses of 400 to 1600 mg. However, Cmax of 6 μg/mL is referred to KC solution and 50 μg/mL is based on administration of 600 mg to 4 patients. Cmax reached with the maximum dose (i.e 1,600 mg) ranged from 2.85-12.14 μg/mL. These data needed further clarification. The applicant has provided more information regarding steady state pharmacokinetics of ketoconazole when used at higher doses (400 mg to 2.000 mg) that come from 5 publications involving healthy volunteers and patients with different pathologies (fungal infection and prostate cancer). This data has been included in section 5.2 of the SmPC. Also additional information was required on the linearity of pharmacokinetics. The Applicant was requested to clarify the increase in half-life of the terminal phase (stated to be 8 hours). From the data provided it seems that the terminal half-life is rather similar regardless of the dose. It is agreed that the lack of dose proportionally in exposure does not represent an issue.

According to information included in Nizoral 200 mg tablets SmPC (Nizoral UK SmPC 2010) absorption of ketoconazole under fasted conditions is increased. The references provided set different conclusions. The Applicant's proposal for the SmPC section 4.2 states that the "Ketoconazole HRA Pharma should be taken during meals for maximal absorption" considering the well-known effect of food. However, publications regarding the food effect are conflicting and taking into account that KC dose will be adjusted by cortisol levels, the statement regarding food restriction has been deleted.

The applicant was also requested to comment on the possibility to administer KC with other acidic beverages different to cola beverage. According to the data presented ketoconazole absorption could be improved with drinks with a pH below 4. Given that most of orange juices have pH < 4 this beverage has already been included as another example of acidic beverage and mentioned in the SmPC.

Distribution

The information provided from the literature shows that distribution of KC varies according to the tissue sampled, the underlying disease and the dose and duration of treatment. KC does not cross the intact blood-brain barrier, and crosses to only a limited extent in fungal meningitis. In the presence of renal failure, KC disposition was not altered, whereas in the presence of hepatic insufficiency, an alteration in disposition was suggested (Brass C. AAC 1982).

Additional information was requested to the applicant on the linearity of pharmacokinetics and to clarify the increase in half-life of the terminal phase (stated to be 8 hours). From the data provided, it seems that the terminal half-life is rather similar regardless of the dose. It is also agreed with the applicant that the lack of dose proportionally in exposure does not represent an issue.
According to different publications, ketoconazole half-life appears to be dose-dependent, increasing with increasing dose and after repeated dosing (Daneshmend 1981, 1983, 1984; Gascoigne 1981 and Huang 1986). Gascoigne described that the absorption of ketoconazole was rapid and the decline in plasma levels was biphasic, taking almost 10 h in the slower phase. The proposed wording for the SmPC states that mean peak plasma concentrations of approximately $3.5 \, \mu g/mL$ are reached within 1 or 2 hours, following oral administration of a single 200 mg dose taken with a meal is acceptable.

The Applicant was asked to discuss the linearity of binding to plasma proteins over the relevant concentration range. From the data provided, this has been characterised over a range of concentrations of 0.1 to 10 $\mu g/mL$.

**Metabolism**

Following absorption from the gastrointestinal tract, ketoconazole is converted into several inactive metabolites. The Applicant was requested to provide additional data to discuss the metabolism. According to both clinical and non-clinical responses, the complex metabolism of ketoconazole has been confirmed. Although there are scarce data regarding metabolism in humans, it appears quite similar to the metabolism in rats leading to a great number (i.e., 16-22) of inactive metabolites that do not play a role in the safety profile of ketoconazole.

The major identified metabolic pathways are oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. KC inhibits cytochrome P450 (CYP) enzymes and is a particularly potent inhibitor of human CYP3A4. In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of ketoconazole. Time dependency of CYP inhibition has been discussed by the Applicant. It was not clear if there is a time dependency of onset of the effect. In addition, the reversibility of the effect needed be further clarified as it appears to be reversible but slow. Reversibility of inhibition of transporters has been discussed by the Applicant as this was considered important in terms of recommendation to dose BCRP substrates at least 2 hours after administration. Data provided show that KC is a potent, mixed competitive and non-competitive reversible inhibitor of CYP3A4 with no time dependency of its effect. In addition, data suggest that the interaction would most likely be reversible. Given that the doses of ketoconazole included in the current submission are up to 1200 mg/day, it is mentioned in the ketoconazole SmPC that KC should be administered with caution to patients receiving drugs known to be BCRP substrates, and be carefully monitored for dose adjustment.

There is no specific pharmacokinetic study in the target population included in the references provided by the applicant. It is unexpected that pharmacokinetics would be different in the CS patients.

**Excretion**

The major route of excretion is through the bile into the intestinal tract. About 13% of the dose is excreted in the urine. Heykants et al. gave a single 200 mg oral dose of ketoconazole to 6 patients with severe renal failure and not found changes in the extent of absorption, although it appeared that peak concentrations were lower and attained later compared to patients with normal renal function. The applicant has provided PK information in patients with renal impairment that suggest that PK is not significantly different in patients with renal failure compared to healthy subjects and therefore, there is no need for dose adjustment. This has been reflected in the SmPC.
Special populations:

**Hepatic impairment**

Hepatotoxicity of ketoconazole is well-recognized adverse event. There is a wide range of presentation of this adverse event, from an increase in liver enzymes to fatal liver injury. However as there is a lack of data in the patients with hepatic impairment, a contraindication in the SmPC has been introduced for patients with acute or chronic liver disease and is mentioned in section 4.3. of the SmPC and further information in section 4.2 and 4.4 regarding the need of monitoring of liver enzymes prior and during treatment. (Refer to the safety part of the report)

The effect of gender, race or weight has been discussed by the applicant. No formal assessment of the influence of these variables on KC PK has been performed. This information has been included in the SmPC.

**Elderly population**

In relation to elderly patients, the applicant provide information of 22 patients >65y old with hypercortisolism of different origins treated with KC (i.e 17/24 Cushing’s disease, 6/24 EAS and 1/24 CS ACTH-independent malignant steroid cell ovarian tumour). They received a dose ranging from 400 to 1.200 mg. Although data are limited they suggest good response and no need of dose adjustment. This is appropriately mentioned in section 4.2. of the SmPC.

**Paediatric population**

As this is a well-established use application, no PIP is required. No PK data on children was provided. The applicant included data from 24 patients between 4 months and 17 years. 13/24 present CD, 3/24 an adrenal carcinoma, 5/24 EAS, 2/24 CS and 1/24 McCune-Albright syndrome. Ten out of 24 received KC pre-surgery. Further discussion is provided later in this report.

**Metabolism and Pharmacokinetic interaction studies**

As mentioned in the [Nizoral UK SmPC], ketoconazole in vitro is an inhibitor of CYP3A4 and of the efflux protein P-gp. Strong inhibition of CYP3A was demonstrated regardless of the substrate, with estimates of Ki in the nanomolar range for all four substrates, but variations were shown in ketoconazole potency among substrates. The mechanism of inhibition was reversible and appeared to be a mixed competitive-non-competitive process. The activity of ketoconazole against several CYP isoenzymes was investigated by Baldwin et al [Baldwin et al, 1995] on human liver microsomes from male and female donors. In this study, ketoconazole inhibited CYP3A4 with an IC50 value of 0.2±0.2 μM, and inhibited CYP1A2, 2B6, 2C9/8, 2C19 and 2D6 with lower potency, whilst inhibition of CYP2A6, and 2E1 was minimal. Data available do not show a potential to induce CYP3A4, 2B6, 1A1 or 1A2 enzymes and Pg-transporter. Propensity for time-dependent autoinduction is not suggested either.

The effect of ketoconazole on P-glycoprotein (P-gp) mediated transport has been investigated in vitro and in vivo. Ketoconazole was shown to be actively effluxed in Caco-2 cells; an increase in efflux was observed with increasing concentrations of ketoconazole. In an in vivo study ketoconazole was shown to increase the plasma
levels of digoxin after intravenous or oral administration. Ketoconazole administration prolonged digoxin elimination, reduced digoxin absorption time and increased its bioavailability. Although the effects of ketoconazole on the digoxin AUC could be explained by inhibition of both CYP3A and P-gp, the decreased mean absorption time can only be explained by inhibition of P-gp in the intestine. Inhibition of P-gp mediated transport has been demonstrated in vitro and in vivo. Since inhibition of CSA and digoxin transports were reported at low ketoconazole concentrations (0.03 μM for CSA in MDCKII-MDR1 and Caco-2 cell lines and 0.3 μM for digoxin in MDCKII-MDR1 cells), KC could block P-gp mediated transport at clinical concentration. A warning about potential interactions with digoxin is included in the SmPC (section 4.5). However, interactions with other P-gp substrates are probable and are described in the section 4.5 of the SmPC (see SmPC annotated).

BCRP (IC50 of 15.3 μM), OATP1B1 (IC50 of 43.4 μM) and OAT1 (IC50 of 319 μM) inhibition by KC has been already reported in the literature. Because KC is highly bound to plasmatic proteins, there is no risk of interaction with BCRP substrates at the systemic level, but ketoconazole may be an inhibitor of BCRP at the intestinal level at clinically relevant concentrations.

Data on interactions with transporter mechanisms are available for OAT1 and OATP1B1 [Choi et al, 2011] and for BCRP (the human breast cancer resistance protein) [Gupta et al, 2007]. Ketoconazole inhibited transport of reference substrates by OAT1 and OATP1B1, expressed in Xenopus laevis oocytes. Considering that ketoconazole is highly bound to plasma proteins the risk for ketoconazole to inhibit the transport of OATP1B1 substrates is considered as very unlikely. The same holds for systemic interactions with BCRP substrates. However, the list of substrates of OATP1B1 and BCRP transporters includes various HMG-CoA reductase inhibitors belonging to the family of statins. These medications are widely used in patients with Cushing’s syndrome to reduce their cardiovascular risk. Some of these drugs, but not all, are in addition metabolized by CYP3A4, and for this reason are already contraindicated in patients on ketoconazole treatment. Others such as rosuvastatin, pitavastatin or pravastatin are not metabolized by CYP3A4, but yet are actively transported by OATP1B1 or BCRP. Ketoconazole did not produce any change in rosuvastatin pharmacokinetics, thus confirming that coadministration of ketoconazole and rosuvastatin is unlikely to increase the risk of toxicity of rosuvastatin. However, with high doses of ketoconazole, a theoretical risk of inhibition of BCRP at the intestinal level cannot be totally excluded.

In summary ketoconazole is considered a universal inhibitor of CYP450 dependent monooxygenases. In vitro studies have shown that ketoconazole is a very potent inhibitor of CYP3A4, inhibition of CYP1A, CYP2B6, CYP2C9/8 is observed at higher but still at clinically relevant concentrations, whilst inhibition of CYP2A6, and 2E1 is minimal. Ketoconazole also inhibits the activity of CYP3A5 with Ki 4-fold higher as compared to Ki for CYP3A4. The presence of variable CYP3A5/CYP3A4 enzyme expression in the gut and the liver may contribute significantly to the inter-individual variability associated with ketoconazole-midazolam interactions. Ketoconazole is also a P-gp inhibitor at clinically relevant concentrations.

KC has been used in combination with other steroidogenesis inhibitors (metyrapone, mitotane and AGT), the somatostatin analogue pasireotide and the dopamine receptor agonist cabergoline. There are no data indicating that the KC dose had to be increased above the range used in monotherapy.
Drug interactions of KC with other medicinal products are well known and have been documented in the SmPC for Nizoral 200 mg Tablets (Nizoral UK SmPC). In vitro data show that ketoconazole inhibits BCRP (Breast Cancer Resistance Protein) with an IC50 of 15 μM, indicating that there is no risk of interaction with BCRP substrates at the systemic level. However ketoconazole may be an inhibitor of BCRP at the intestinal level at clinically relevant concentrations. Considering the rapid absorption of ketoconazole intake of BCRP substrates such as statins should be postponed 2 hours after ketoconazole intake.

In conclusion, KC is mainly metabolized though cytochrome CYP3A4 in the liver. The bioavailability of KC is significantly reduced by enzyme-inducing drugs. In addition, the metabolism of drugs via hepatic P450 enzymes, especially of the CYP3A family, can be inhibited by KC resulting in an increase and/or prolongation of their effects including adverse effects. Regarding the potential CYP1A2, 2B6, 2C9/8, 2C19 and 2D6 inhibition by ketoconazole, Ki values are reported in the range of 1.3-28 µM. According to the EMA Guideline on Investigation of Drug Interaction the cut-off value for enzyme inhibition in the liver is 50xCmax,u i.e. 15 µM following a 1200 mg dose. The risk for a clinical inhibition cannot be excluded for enzymes which are inhibited in vitro with a Ki <15 µM. For these enzymes, a literature review should be performed to address if DDI studies are available with selective substrates. Information on the risk for inhibition of enzymes other than CYP3A4 has been included in the SmPC section 4.5.

KC has been shown to inhibit cholesterol synthesis by blocking demethylation of lanosterol. These effects are mediated at least partly by inhibition of mitochondrial cytochrome P 450-linked enzymes activities resulting in a block of cholesterol synthesis.

The DDI profile of KC has been well addressed by the applicant describing the most important DDI of KC. Most of interactions are in line with the ones included in Nizoral UK SmPC and Nizoral US SmPC. The interactions described in the non-clinical summary are aligned with the interactions in humans. In vitro, KC behaves as a strong CYP3A4 inhibitor, inhibition of other CYP isoforms (i.e CYP1A, CYP2B6, CYP2C9/8) is observed at higher but still at clinically relevant concentrations. KC is also a P-gp and BCRP inhibitor at clinically relevant concentrations. All but CYP1A, CYP2B6, CYP2C9/8 isoforms have been also described in humans.

The applicant has included a specific discussion for some of the interactions (i.e concomitant administration with other steroidogenesis inhibitors, effects on lipoproteins and cholesterol levels). Most of the remaining interactions have been included in the product information based on Nizoral UK SmPC and Nizoral US SmPC. In a study evaluating the combination of ketoconazole 400 mg (2 intakes of 200 mg tablets, 12 h apart) and rosvastatin 80 mg (the highest dose) in healthy subjects, the plasma concentrations of rosvastatin over time were similar when rosvastatin was co-administered with ketoconazole and placebo [Cooper et al, 2003]. Results of this study could support the addition of rosvastatin in section 4.5 in order to inform that no interaction is expected when rosvastatin and KC are co-administered (see SmPC).

All relevant information regarding interactions has been included in the SmPC as requested by the CHMP during the procedure. However it is highlighted that, Ketoconazole plasma level could be significantly higher at the SmPC recommended doses than at the doses used to treat fungal infections. This could lead to previously unrecognised interactions. The Applicant was requested to comment on whether the proposed posology in
Cushing’s syndrome will have an effect on known interactions (i.e. more concomitant drugs which are contraindicated, more drugs which should not be used together with ketoconazole, etc.). After review, it was considered that given that clinical interaction studies were performed with KC 400 mg daily dose, it is expected that they detected the majority of interactions. No new interactions would be expected in case of higher doses to be administered. However, different degrees of interaction may be dependent on the ketoconazole dose given i.e. many results are reported following a 200 mg ketoconazole dose and a stronger interaction may be expected at a higher dose and/or shorter dosing interval.

The company is requested to provide more information post-authorization regarding some specific interactions (i.e potential CYP1A2, 2B6, 2C9/8, 2C19 and 2D6 inhibition by ketoconazole).

### 2.4.3. Pharmacodynamics


**Figure 1. Main pathways of adrenal steroid biosynthesis**

Ketoconazole is an inhibitor of cortisol synthesis resulting from its ability to inhibit several cytochrome P450 enzymes in the adrenal glands. Apart from adrenal blocking effect, KC may also have direct effects on corticotrophic tumour cells in patients with CD.

In contrast to subjects with an intact hypothalamic-pituitary-adrenal axis, patients with pituitary dependent CD may show no compensatory rise or stable plasma ACTH levels upon prolonged administration of KC. The marked
reduction in plasma and urinary cortisol levels induced by KC is thus not always followed by an increase in plasma ACTH. KC effects on ACTH levels were variable from one study to another, from no change to slight increase. Thus, although some in vitro studies of pituitary corticotrophs suggested an additional site of inhibition at the pituitary level, the clinical findings argue against this hypothesis and favour more a regulation of the pituitary-adrenal axis.

Aldosterone levels were lowered by KC. Since KC has a strong inhibitory effect on the 17,20-lyase activity and is a more potent inhibitor of cholesterol side-chain cleavage activity than metyrapone, the side effects of mineralocorticoid excess or worsening of hirsutism would not be expected. Inhibition of adrenal and gonadal testosterone production is observed in clinical studies.

KC also decreases total and LDL-cholesterol levels by 10 to 25% by inhibiting cholesterol synthesis at 14-α-demethylation of lanosterol and thus up-regulating LDL receptors activity. It has been used to treat familial hypercholesterolemia before the widespread use of HMG-CoA reductase inhibitors. Hence, the use of KC for the CS control may have beneficial effects on the management of dyslipidaemia.

Mechanism of action and pharmacodynamics has been discussed adequately.

2.4.4. Discussion on clinical pharmacology

This is a “well established use” use application therefore evidence is expected to be provided through references to publications. Results from a PK study have also been provided to bridge the literature data with the intended drug formulation, which is appropriate and acceptable.

The publications address all aspects of the pharmacokinetics and the applicant also provided upon request references to publications reflecting pharmacokinetics data for the higher doses required in the proposed indications.

Based on the submitted bioequivalence study Ketoconazole 200 mg film-coated tablets manufactured by Polfarmex, S.A. when compared with the product referred to in the literature Nizoral® 200 mg film-coated tablets, manufactured by Janssen-Cilag meet the bioequivalence criteria with respect to the AUC₀₋₅, AUC₀₋₅ and C₅ₐₓ.

As KC can be used in children, the applicant has discussed the posology for paediatric population and proposed to include adolescents in the indication. This is supported by the submitted publications which refer mostly to this age range. Data are not available and very limited in younger patients. According to the publications, the proposed posology for adolescents is the same as for adults. This is considered acceptable. (please also refer to discussions later in the report)

In general, the PK profile has been adequately assessed and the PK profile is considered to be adequately supported by the publications. The applicant has addressed PK in special populations such as those with renal or hepatic impairment, and the elderly, providing appropriate supportive data and analyses, and making appropriate updates for the relevant parts of the SmPC.
All relevant information regarding interactions has been included in the SmPC. However it is highlighted that, Ketoconazole plasma level could be significantly higher at the SmPC recommended doses than at the doses used to treat fungal infections. This could lead to previously unrecognised interactions. The Applicant was requested to comment on whether the proposed posology in Cushing’s syndrome will have an effect on known interactions (i.e. more concomitant drugs which are contraindicated, more drugs which should not be used together with ketoconazole, etc.). After review, it was considered that given that clinical interaction studies were performed with KC 400 mg daily dose, it is expected that they detected the majority of interactions. However, different degrees of interaction may be dependent on the ketoconazole dose given i.e. many results are reported following a 200 mg ketoconazole dose and a stronger interaction may be expected at a higher dose and/or shorter dosing interval.

In conclusion, the CHMP considered that all issues have been discussed and solved and the clinical pharmacology has been adequately demonstrated.

2.4.5. Conclusions on clinical pharmacology

The Applicant submitted an application for a well-established use product, and as such submitted literature review and a bioequivalence study Ketoconazole 200 mg film-coated tablets manufactured by Polfarmex, S.A. with the Product Nizoral® 200 mg film-coated tablets, manufactured by Janssen-Cilag in order to bridge the literature data with the intended marketed product.

Bioequivalence has been demonstrated and it is considered that the applicant has provided appropriate supportive data from the literature and answers to the CHMP clarifications.

The Drug-Drug interactions have been discussed and are considered appropriately described in the SmPC. However, the company is requested to provide more information in the post-authorization period regarding some specific interactions (i.e potential CYP1A2, 2B6, 2C9/8, 2C19 and 2D6 inhibition by ketoconazole).

2.5. Clinical efficacy

The Applicant submitted more than 350 articles supporting clinical pharmacology and clinical efficacy/safety. Data are presented on more than 800 patients in total, including 748 from 28 studies and 52 from individual case reports.

Thus the dossier is based on published scientific literature for the use of KC in the treatment of CS for the pharmacodynamics and efficacy evaluations.

Ketoconazole (KC) is an imidazole-dioxalone that has been authorized in several countries (in more than 20 countries) in the European Union (EU) since December 1980 for the treatment of fungal infections and was withdrawn following an Article 31 referral in July 2013.

The patients included in the studies are considered representative of the patient population as a whole as they cover a wide age range, from infants to the elderly, although it is not possible to determine exact numbers for any age-group and they include many of the different manifestations of CS and the subtypes.
2.5.1. Dose-response studies and main clinical studies

There are no specific studies regarding dose-response provided by the applicant.

From the review of the publications presented when KC is used as monotherapy the dosing range was 200-1,200 mg/daily and the most common dose used was 600-800 mg/daily. If combination therapy is considered, the dosing range was also 200-1,200 mg/daily but the most common dose seems to be lower at 400 mg/daily. There is only one article which describes the use of a higher dose in some patients (i.e 1,600 mg/daily).

It appears that higher doses are needed in case of adrenal carcinoma or EAS, although some cases are controlled with the standard doses (Sharma ST., et al.).

The duration of treatment for CS varies considerably in the studies, but this represents a reflection of the different strategies needed to manage this disease in different patients and the need to adjust posology on an individual patient basis depending on the corticol levels. It is noted that several patients treated very long term with ketoconazole were symptom-free.

Taking into account the different forms of Cushing’s Syndrome, the posology is quite similar amongst all of them.

Some publications point out the possibility of less efficacy in cases with lower dose or in patients who does not reach the maximal dose (Castinetti et al. 2014, Loli P., et al. 1986).

In conclusion, there is no clear dose response observed reflecting the need to individualise the posology on a patient basis according to the normalisation of the cortisol levels. The recommended range varies from 200mg/d to 1200mg/d.

2.5.1.1. Summary of main efficacy results

The applicant provides information regarding 800 patients treated with KC as a monotherapy or as a combination therapy. The studies include a description of efficacy in a group of patients or as individual case reports. Most of the studies are retrospective, non-controlled, and describe patients since 1985 to 2012 (Table 1).

Table 1. Classification of study population
Taking into account that CS is considered a rare disease, the number of patients included in this application is considered acceptable by the CHMP. Considering only the studies where the number of patients in CS subgroups are clearly identified, the distribution of patients was as follows: 78.6% (535+13/697) Cushing’s disease, 15.6% (91+18/697) ectopic ACTH syndrome including three patients with cyclic CS, 5.2% (36/697) adrenal-dependent CS.

2.5.1.1. Monotherapy studies – Review of the literature provided

The applicant provides 22 studies regarding the use of KC as monotherapy.

- **Cushing’s disease**

  **Angeli A., et al, 1985:** This is a report of the inhibitory effect on adrenocortical secretion and clinical improvement observed after long-term administration of KC in 5 women with Cushing’s disease and bilateral adrenal hyperplasia. All 5 women (aged 20-44) received KC 800 mg daily in four divided doses for at least 4 months; in 3 women the dose was then reduced to 600 mg daily. Plasma corticotropin and cortisol levels, and daily urinary free cortisol output were clearly decreased in all patients after 1-2 months of therapy; the changes were highly significant at the third month. However, the circadian periodicity of plasma cortisol was not restored despite attainment of normal 24 h urinary free cortisol and 8 am circulating cortisol. Clinical improvement was observed in all 5 women with a return to normal menstruation.

  **Bereselli ME., et al, 1987:** In this study, ACTH response to the CRH test was provided for 8 patients with CD before and during KC therapy. Both basal and stimulated ACTH levels did not increase on KC despite the marked decrease of cortisol levels. Although these data may suggest an additional KC effect on the pituitary level, aside its effects on the inhibition of adrenal steroidogenesis, this finding was not confirmed by further studies.

  **Boscaro M., et al, 1987:** In this exploratory study where data were published in two separate papers, authors have shown that basal and stimulated ACTH response are enhanced after 4 to 6 weeks of KC 600 mg/d treatment in 4 out of 6 patients and that both basal and post-CRH plasma cortisol and aldosterone levels were lowered. These findings indicate that KC has no additional inhibitory effect on ACTH secretion and confirm the
inhibitory effects of KC on cortisol secretion and also on aldosterone secretion (for patients with pre-therapeutic elevated levels).

**Calvo Romero JM., et al, 1999:** The objective was to determine the usefulness of KC for the control of arterial hypertension in CS. Eleven cases of CD were included. Three out of eleven presented hypertension, two of them received KC 400 mg/day and one 600 mg/day. In all normalization of arterial tension and urinary cortisol excretion was reached.

**Castinetti F., et al, 2008:** This is a French single centre retrospective study of 38 patients with CD treated with KC between 1995 and 2005. Reasons for initiation of KC treatment were as follows: unsuccessful pituitary surgery (n=17 patients); lack of image of adenoma on pituitary MRI (n=15 patients): refusal (1 patient) or contraindication (1 patient) of surgery; and awaiting antisecretory efficacy of Gamma Knife radiosurgery (4 patients). The patient population was subdivided into a “No pituitary surgery group” of 21 patients who were treated with KC as a primary treatment and an “After pituitary surgery group” of 17 patients. KC was always initiated at a low dose (200-400 mg/day) with weekly monitoring of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (γ-GT) during the first month. If necessary, to obtain biochemical remission, the dosage was increased by 200 mg/day every 10-14 days, with a liver function measurement at each titration step, up to a maximum of 1200 mg/day. 33 patients were treated on a long-term basis with KC at doses of 200 to 1200 mg/d and of these 17 were controlled and 16 uncontrolled. In the controlled group (n=17; 51.5% of those treated long term) mean follow-up was 22.6 months and doses of KC varied from 200 to 1000 mg/day (mean 529 mg/day). Blood pressure was normal in all controlled patients 3-6 months after initiation of KC. All five diabetic patients in the study had normalized 24-h UFC and metabolic control on the basis of blood glucose and glycosylated hemoglobin (HbA 1c) monitoring. In the uncontrolled group (n=16; 48.5% of those treated long term) mean follow-up was 10 months and doses of KC varied from 600 to 1200 mg/day (mean 890 mg/day). Five of them had initially been controlled, for a period of 3 months (n=2), 2 years (n=2), and 3 years (n=1), at doses varying from 600 to 1000 mg/day. Of the 16 uncontrolled patients, 8 presented a significant decrease in UFC: 5 of them normalized high blood pressure without modification of their anti-hypertensive therapy. The 24-h UFC was unchanged in the other 8 patients and the blood pressure status was not modified (n=3 had normal blood pressure at initiation of KC treatment). Half of the biologically uncontrolled patients displayed clinical regression of signs of hypercortisolism with mean loss of weight similar to that of controlled patients. The authors concluded that KC was an effective therapy for CD patients, either as a primary treatment or as a post-operative treatment (the only difference between these groups was the duration of treatment which was longer in the 2nd group). Seventeen out of the 33 patients (51%) who were treated on a long-term basis with KC at doses of 200 to 1200 mg/d were controlled i.e. had a normal 24-h UFC at 2 consecutive evaluations. Of the uncontrolled patients, five had initially been controlled and 50% presented a significant decrease in UFC. The 17 patients with normalized 24-h UFC also presented clinical regression of signs of hypercortisolism including lowering of blood pressure and loss of weight during the first 3 months of treatment, whereas blood pressure was unchanged in uncontrolled patients. However some of the uncontrolled patients displayed some clinical regression of other CS signs.
Casting F., et al, 2014: This was a French retrospective, multicenter study reviewing data from patients treated by ketoconazole as a single agent for CD, with the aim of clarifying efficacy and tolerance in order to better determine the benefits/risk balance. Data from 200 patients followed in 14 French centers were included in this retrospective study. All patients were treated with ketoconazole as a single treatment for active CD between 1995 and 2012. The diagnosis of CD was based on criteria defined according to current guidelines. The first evaluation of UFC (mean of 2–3 samples) was carried out in all centers after 0.25–1 month of treatment. Urinary cortisol secretion was usually monitored at 1–4 month intervals and if necessary, ketoconazole dosage was increased by 200 mg/d every 7–28 days depending on the investigator’s judgment until normalization was achieved. Patients were considered controlled if they had normal 24-hour UFC at 2 consecutive evaluations. Partial control was defined as a decrease in UFC superior to 50% without normalization. A lack of control was defined by a decrease in UFC of less than 50% and/or immediate clinical or biological intolerance leading to ketoconazole discontinuation. When the dose of ketoconazole was finally established, biological evaluation of hypercortisolism was performed at 3–6 month intervals. Each investigator also evaluated the changes in clinical signs of hypercortisolism including BP, as well as plasma potassium and glucose tolerance. Improvement in hypertension was defined as a decrease of at least 10 mmHg of systolic and/or diastolic BP in patients with hypertension. Improved glycemic control was defined as one or more of the following: a decrease of insulin dose (-10% of the total dose), a decrease in the number of antidiabetic drugs, and an improvement of HbA1c (-0.5% when available) without addition of other antidiabetic drugs. Regular monitoring (every 7–15 days) of aspartate aminotransferase (AST) (ASAT), alanine aminotransferase (ALT) (ALAT), and gamma-glutamyl transpeptidase (GGT) was performed during the first month of prescription, and then at each dose change. The mean age at diagnosis of CD was 41.9 +/-15.8 years, ranging from 8 to 87 years. Pituitary MRI reported a microadenoma in 106 patients (53.4%), a macroadenoma in 36 patients (18.2%), and the lack of obvious adenoma in 58 patients (29.4%). The following figure resumes the main results. At the time of ketoconazole initiation, all patients had clinical CD, 116/174 patients (66.7%) had hypertension, 39/174 (22.4%) hypokalemia and 55/174 (31.8%) diabetes mellitus. Data were not detailed for 26 patients. Mean initial 24h-UFC was 4.1 ± 5.3-times the ULN (range, 1.1– 40).

Figure 1. Flow-chart including the main characteristics of the cohort, and the main results.
Forty-one patients (20.5%) stopped the treatment due to poor tolerance. Increase in liver enzyme levels up to 5-fold normal values was reported in 30/190 patients (15.8%). Four patients presented 5–10-fold increase, and 1 patient (treated at a dose of 600 mg/d) presented a 40-fold increase of ASAT, ALAT and GGT, which remained high for 3 weeks after ketoconazole withdrawal. This patient was also concomitantly taking alcohol and acetaminophen. Liver enzyme levels in this patient eventually returned to normal 90 days after ketoconazole withdrawal. In all other patients, liver enzyme levels returned to normal within 2–4 weeks after dose decrease (50% of cases) or withdrawal (50% of cases). No fatal hepatitis was observed. The authors concluded that data showed that ketoconazole is a highly effective drug to reduce hypercortisolemia: 75.2% of patients had at least 50% decrease of UFC, including 49% with normal UFC at the last follow-up. Of the 49 patients with lack of control, only 9 reached the final dose of 1200 mg/d.

**Chou SC., et al, 2000:** This is a report on the treatment of three females (aged 37-49 years) with residual or recurrent Cushing's disease after unilateral adrenalectomy (n=1, relapse at 12 years) or transsphenoidal adenomectomy (n=2, relapse at 10.6 and 5.3 years). The patients initially received 200 mg KC per day, up to a maximum of 1200 mg/day. The duration of treatment was 65 to 86 months. The 24-hour urinary free cortisol excretion levels markedly decreased in all patients immediately after treatment and remained in the upper levels of the reference range. All the patients showed clinical improvement soon after beginning KC treatment.

**Dash RJ., et al., 1990:** This is a small clinical study of five female patients (aged 16-48 years) diagnosed with Cushing's disease treated with KC 400 to 800 mg/d for 7-10 weeks, 4 subsequently underwent surgery and the fifth was offered long term KC therapy. There was a significant improvement in the clinical features of CD by the end of the 3rd week which corresponded to near normalization of plasma cortisol. But in one case with invasive pituitary macroadenoma, an escape phenomenon was observed at the 6th week with 800mg/d dose.
Engelhardt D., et al., 1989: The short term and long term effects of KC administration on the pituitary and adrenals was studied in 10 patients with CD. Three patients were treated for 24 hours with 1000 mg. After this short-term administration of KC, there was a slight decrease in serum cortisol levels in the three patients with CD. Seven patients were treated with 600 mg/day of KC from 1 week up to 12 months. Three out of the 7 patients with CD were treated for at least 2 months. In the three patients with CD treated over 3, 10, and 12 months, there was a partial decrease of UFC levels but no normalization was achieved and one of them developed labile hypertension and low potassium levels.

Falló F., et al., 1993: Forty consecutive hypertensive patients with CS (N=32 with Cushing’s disease; N= 5 with an adrenal adenoma and N=1 with an adrenal carcinoma) were admitted. Twenty eight patients (Group 1) were treated with antihypertensive drugs including 12 with a resistant hypertension who received an association therapy with KC 400-800 mg/day (mean age 38±3 years; 9 women/3 men) for 10±2 months. Twelve patients (Group 2) received KC alone at the same doses (mean age 39±2 years; 10 women/2 men) for 7±2 months. Blood pressure normalization was obtained in 4 out of 28 patients belonging to Group 1 and who were not treated by KC. In those were KC was added, a parallel normalization of blood pressure and urinary cortisol occurred in 11 out of 12. In Group 2, KC alone lowered blood pressure within normal limits in 11 out of 12 patients and normalized cortisol levels in all. One patient with a hypertension preceding CS remained hypertensive despite KC.

Gomez RM., et al., 2007: Authors retrospectively assessed 71 CS patients who were admitted between 1978 and 2003 (60 women, 11 men; mean age 37.4 years with a range of 13-75), including 50 with CD. After KC therapy, a significant decrease in 24 hr UFC was shown. This was accompanied by a significant reduction in systolic and diastolic blood pressure values.

Invitti C., et al., 1999: A retrospective multicenter Italian study described the clinical features and therapeutic procedures carried out in 288 patients with CD. Medical therapy was carried out in 178 patients with Cushing’s disease before a surgical procedure, after surgical failure or relapse, and in association with pituitary irradiation. KC, the drug mostly used (the exact number of patients treated by KC was not provided), brought about a normalization or a reduction in UFC concentrations in 43% and 42% of patients respectively.

Loli P., et al, 1986: Seven patients (six women and one man) with pituitary-dependent Cushing’s disease were studied. Two patients previously had unsuccessful pituitary microsurgery (performed at another hospital) and one patient had recurrence of Cushing's disease 2 years after successful pituitary adenomectomy. The initial dose was 200 mg twice daily (every 12 h). The dose was increased in 200 mg increments in 13-40 days according to the individual's drug tolerance and treatment efficacy (evaluated on the basis of the clinical behavior and the changes in urinary cortical levels). A maximum of 800 mg KC (200 mg three times a day (tid)) was used in two patients. A marked decrease in urinary cortisol excretion occurred in each patient within the first week of treatment; thereafter, urinary cortisol remained near normal or within the normal range throughout therapy in all but two patients. Plasma cortisol levels decreased in each patient within the first month of treatment; thereafter, they changed little. Within 2 months after the beginning of treatment, the clinical signs of CS regressed.
Luisetto G., et al., 2001: This was a retrospective study to assess the effect of treatment with KC on the recovery of bone mineral density in 10 patients with CD. KC 300 to 600 mg/d was administered following unsuccessful pituitary surgery and treatment ranged from 10 to 100 months (44± 34). UFC was normalized in five patients (50%) on KC who achieved a mean level of 223±80 nmol/24h and remained elevated in the remaining 5 patients (mean UFC level: 631±223 nmol/24h); but bone mineral density remained low in the group as a whole with similar levels for patients with normal or elevated UFC levels. The percentage change of BMD ranged from -6% to + 3.8%. In the surgery group, BMD increased significantly after surgery.

Moncet D., et al, 2007: This study included 54 patients with proven CS undergoing KC treatment (44 women and 10 men), with a mean age at diagnosis of 38 ±13.1 (range 14-63) years. Cushing's disease was the final diagnosis in 37 patients. The duration of treatment ranged from 15 days to 13 years with 24 patients receiving long term therapy (defined as ≥1year) mean 3.6 years range 1-13 years. Normal or subnormal UFC was reached in 44/52 (85%) of patients evaluated. In seven patients not normalized, UFC decreased from 12 to 48% of pre-treatment values. Escape phenomenon was observed in six patients with CD after 4- 11 months on KC 400-800 mg/d and UFC normalized by increasing the dose in three. Clinical signs improved on KC treatment (Figure 2.7.3-6). Hypertension improved in 33 out of 41 patients (80%), blood pressure normalized in 18 patients on KC alone and 15 with reduced daily dosage of anti-hypertensive. Sixteen out of 21 pre-menopausal patients with menstrual disturbances normalized their menstrual cycles (76%). Diabetes improved, 8 out of 11 (73%) normalized their glucose levels with dieting and KC alone while two needed anti-diabetic drugs and one insulin.

Mortimer RH., et al., 1991: Eight subjects (6 females, age range:33-51y ; 2 males, age range: 26-33) with Cushing’s disease were treated pre-operatively with KC 200 mg orally four times daily for 2 weeks before pituitary surgery or radiotherapy and up to 2 years (in N=3 who failed or where unfit to surgery). Results showed a tendency for plasma cortisol to fall but this was non-significant. Plasma ACTH did not change significantly. There were highly significant increases in plasma progesterone, 17α hydroxyprogesterone and 11 β-deoxycortisol whereas DHEAS levels fell significantly. Plasma testosterone did not change. There were highly significant fall in UFC (p< 0.0001).

Sonino N., et al., 1985: In this study five patients with Cushing’s disease, aged 18 to 48 years (4 females and one male), were treated with KC for 2 to 6 months because hypercortisolism persisted after transsphenoidal surgery and for 2 cases because no or little response was observed after bromocriptine, for 1 case after intolerance to aminoglutethimide and for one case after metyrapone withdrawal for hirsutism. The initial KC dose was 800 mg/day, reduced to 600 mg/day after one month according to individual responses. At 6 weeks all patients were on 600 mg/day. Pituitary radiotherapy was started in 4 patients 1 to 3 weeks after KC initiation. Plasma cortisol decreased and there was a rapid normalization of 24hr UFC (within 1 week) for all 5 patients. A rapid clinical improvement was observed in all patients. After 4-6 weeks they gained normal appearance with regression of symptoms such as diabetes, hypertension and muscle weakness. Regression of hirsutism was observed in the four females.

Sonino N., et al., 1991: This study evaluated 34 patients (28 females, 6 males; age range: 14-67 years) with CS; there were 28 with Cushing’s disease. The reasons for starting KC included: preparation for surgery in
patients with risk factors such as diabetes, hypertension, coagulation abnormalities; management of the disease during and following pituitary radiation or in patients not suitable for surgery; persistent or recurrence of hypercortisolism after pituitary surgery. KC daily dose ranged from 400 to 800 mg/day in two divided doses and was 600 mg/day (200 mg in the morning and 400 mg at night) in most cases. Marked suppression of cortisol production by KC as indicated by urinary cortisol levels occurred immediately after starting treatment. Mean UFC decreased from 1296 ± 176 to 270 ± 69 nmol/d (N=34, p< 0.001). Urinary cortisol was then maintained within normal limits throughout treatment in 30 patients. Complications such as diabetes mellitus, hypertension and hypokalaemia, were quick to resolve and medication against diabetes and hypertension could be either reduced or withdrawn within 2 weeks.

**Tabarin A., et al., 1991:** The four patients with Cushing’s disease were treated with KC 400-800 mg/day for the first month. UFC fell to within the normal range in one patient but remained elevated in two and fell to below normal in one. The KC dose was maintained at the same dose in one patient, was increased in two patients and decreased from 600 mg/day to 400 mg/day with the addition of hydrocortisone (20 mg/day) in one. With this regimen UFC remained within the normal range in all patients for more than 6 months. Plasma cortisol decreased from basal mean of 688 ± 339 nmol/l to 265 ± 152 nmol/l after 6 months. All patients improved clinically they regained normal or near normal physical appearance with a reduction in total body weight. Hypertension and hypercholesterolaemia seen in one patient disappeared after 2 months while impaired glucose tolerance seen in another patient also disappeared.

**Terzolo M., et al., 1988:** Three patients (2 females aged 50 and 59 y, 1 male aged 20 y) with CD were treated with KC at an initial dose of 200 mg/d increasing by 200 mg/week for 6 months. The final dose was 600 mg/d (200 mg tid). Mean plasma cortisol and UFC levels were normalized. Each patient showed a clear clinical improvement within 4-6 weeks.

**Weber MM., et al., 1989:** The effects of KC on adrenal androgen secretion was examined in 15 patients (12 females; 3 males; aged 16-61 years) with elevated androgens including 12 with CS. There was 9 patients with Cushing’s disease. Treatment with KC 600 mg/d caused a significant reduction in serum androgen levels in patients with signs of androgen hypersecretion.

- **Ectopic ACTH syndrome (EAS)**

**Calvo Romero JM., et al, 1999:** Two cases of EAS were included. Both presented hypertension, one of them received KC 600 mg/day and one 800 mg/day. In both normalization of arterial tension and urinary cortisol excretion was reached.

In another article was included only one patient with EAS in whom serum and urinary cortisol levels returned to normal within one week with KC treatment (**Engelhardt D., et al., 1989**).

**Invitti C., et al., 1999:** The tumour responsible for ectopic secretion was resected in 15 out of 25 patients. Four of these patients had previously been submitted to pituitary surgery and another three to bilateral adrenalectomy. Eight patients were treated with medical therapy alone, resulting in transient improvement of ACTH secretion in less than half. Two patients were never treated. All together, 9 patients with ectopic secretion died 2–48 months after diagnosis (mean, 13 ± 5.2 months; median, 8 months).
Sonino N., et al in 1991 described a patient with EAS who has been controlled with KC 600 mg/day for more than a year until surgery. The authors explain this good response, in contrast with other reports, to prolonged treatment due to unilateral adrenalectomy in previous years.

Tabarin A., et al., 1991: The four patients with ectopic ACTH syndrome were treated with KC at 600 mg/day for one month. UFC decreased after 1 month but was above normal. The dose was increased to 1,200 mg/day but UFC remained above normal at 2 months (N=1) and 3 months (N=3). Plasma cortisol also remained above normal. There was no clinical improvement, except a transient improvement in one patient in whom diabetes, hypertension and hypokalemia disappeared after 1 month but returned at month 2. All patients underwent bilateral adrenalectomy.

- Adrenal-dependent CS

Calvo Romero JM., et al, 1999 described one case of adrenal carcinoma who received KC 800 mg/day and did not normalize arterial tension nor urinary cortisol excretion.

Engelhardt D., et al., 1989 described a patient with adrenal carcinoma who received KC 600 mg/day for more than a week normalizing urinary cortisol levels.

Invitti C., et al., 1999 Seventeen patients with adrenal carcinoma underwent radical surgery, followed by medical therapy in 8, it was not specified which drug was used. Five patients were treated with medical therapy alone, whereas 2 patients were not treated. Surgical treatment of adrenal adenoma was straightforward. All patients with nodular adrenal hyperplasia were submitted to bilateral adrenalectomy.

Loli P., et al, 1986 described one patient with an adrenal adenoma treated with KC 800 mg/day treated for 3 months with normalization of UFC.

Moncet D., et al, 2007 described 5 patients with adrenal tumors who received KC treatment. The article does not provided an evaluation by type of CS, but taking into account the global results it seems that KC was effective in these patients. The dose of KC ranged from 200 to 1,200 mg/d with a mean maintenance dose of 600 mg/d. The excretion significantly decreased after 40 days (30-45 d) of KC treatment. Normal or subnormal UFC was reached in 44/52 (85%) of patients evaluated. Clinical signs improved on KC treatment.

Sonino N., et al in 1991 described two patients with nodular adrenal hyperplasia, one with adrenal adenoma and one with adrenal carcinoma. Although it is not possible to obtain specific data from these patients, considering the global results it could supposed the efficacy in these four patients. A marked decreased in UFC occurred and was maintained within normal limits throughout treatment in 30 patients, but in two, it remained above normal and in two, it increased above normal after 6 months while they were at a dose of 600 mg/d. Complications such as diabetes mellitus, hypertension and hypocalcaemia, were quick to resolve and medication against diabetes and hypertension could be either reduced or withdrawn within 2 weeks.

2.5.1.1.2. Combination therapy – Review of the literature provided

- Cushing’s disease
Feelders R., et al., 2010: The study initially enrolled 17 patients (13 women, 4 men; mean age 45.7 years) with the main objective to normalize urinary free cortisol levels. In this prospective study, eight patients with Cushing’s disease received KC after having been previously treated and uncontrolled despite the combination of pasireotide and cabergoline for 60 days. The addition of KC 600 mg/d for 20 additional days led to a normalization of UFC levels in six out of the eight patients.

Kamenicky P., et al., 2011: The objective of this study was to assess the efficacy and safety of combination therapy with mitotane, metyrapone and KC in severe ACTH-dependent CS. Eleven patients (aged 18-75 years; 7 females/4 males) were included in the study and were treated with mitotane 3.0-5.0 g/day plus metyrapone 3.0-4.5 g/day plus KC 400-1,200 mg/day. Urinary free cortisol (UFC) levels were monitored. The authors’ hypothesis was that metyrapone and KC provide rapid clinical and biological control of hypercortisolism, thus covering the lag period before mitotane starts to act. All patients experienced a marked clinical improvement. UFC excretion fell rapidly from a median of 2737 μg/24 h (853-22,605 μg/24 h) at baseline to a median of 50 μg/24 h (18-298 μg/24 h) (P = 0.001) within 24-48 hours of initiation of therapy and remained low to normal on the combination therapy. All patients with Cushing’s disease were able to undergo pituitary surgery 5-22 months after the initiation of combination therapy, after an improvement in their clinical status (Table 2). The authors concluded that when surgical treatment for severe ACTH-dependent CS is not feasible, combination therapy with mitotane, metyrapone and KC is an effective alternative to bilateral adrenalectomy, which is a permanent procedure.

Valassi E., et al., 2012: The study aimed to evaluate the outcome of pre-operative therapy with KC alone or in combination with metyrapone in previously untreated patients with CS. They were treated between 1983 and 2010 and studied retrospectively. Within the study population that included 62 patients, 39 patients were treated by KC (17 received KC alone and 22 the combination therapy). The mean age at diagnosis was 41 ± 13 years (7-70 years). The overall median duration of pre-surgical medical treatment was 4 months (range: 1-30.7). Initial daily dose of KC ranged from 200 to 600 mg and was increased by 200 mg at a time. The results were as follows: group CO (controlled) included 11 patients (24%) with eucortisolism and significant clinical improvement; group NC (not controlled) 22 patients (49%) with persistent hypercortisolism and no control of symptoms; and group PC (partially controlled) 12 patients (27%) who, despite eucortisolism, had no real clinical improvement. It is not known from what is stated in the article whether partially controlled or uncontrolled patients were titrated to the maximal tolerated dose of KC or not.

Vilar L., et al., 2010: The aim of this study was to evaluate the effectiveness of cabergoline (at doses of up 3 mg/week), alone or combined with relatively low doses of KC (up to 400 mg/day), in 12 patients (8 females; 4 males; mean age: 22.8 ± 6.2 years) with CD unsuccessfully treated by transsphenoidal surgery. After 6 months of cabergoline therapy, normalization of 24 h urinary free cortisol (UFC) levels occurred in three patients (25%),
whereas reductions ranging from 15.0 to 48.4% were found in the remaining. KC was then initiated at low doses 100 mg/day which were progressively increased by 100 mg every month until normalization of UFC levels or a maximal dose of 400 mg/day was reached. The addition of ketoconazole to the nine patients without an adequate response to cabergoline was able to normalize UFC excretion in six patients (66.7%) at doses of 200 mg/day (three patients), 300 mg/day (two patients) and 400 mg/day (one patient). UFC levels decreased from $520 \pm 156$ to $149 \pm 124 \mu g/24\, h$ ($p < 0.001$). Overall, normalization in UFC excretion could be obtained in 75%. No treatment escape was observed. Authors concluded that they could demonstrate that cabergoline monotherapy was able to reverse hypercortisolism in 25% of patients with CD unsuccessfully treated by surgery and that the addition of relatively low doses of KC led to normalization of UFC in about two-thirds of patients not achieving a full response to cabergoline.

- **Ectopic ACTH syndrome**

**Kamenicky P., et al., 2011:** for more details see above. The following table shows the results on EAS.

**Table 3. Etiology of hypercortisolism, duration of treatment and treatment outcomes**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Etiology</th>
<th>Tumor</th>
<th>Duration of combination therapy (months)</th>
<th>Duration of mitotane monotherapy (months)</th>
<th>Follow-up (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>EAS?</td>
<td>Occult</td>
<td>6</td>
<td>13</td>
<td>19</td>
<td>Mitotane</td>
</tr>
<tr>
<td>6</td>
<td>EAS?</td>
<td>Occult</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>Death (respiratory distress)</td>
</tr>
<tr>
<td>7</td>
<td>EAS</td>
<td>Occult</td>
<td>4</td>
<td>2</td>
<td>35</td>
<td>Death (tumor progression)</td>
</tr>
<tr>
<td>8</td>
<td>EAS</td>
<td>Metastatic</td>
<td>4</td>
<td>10</td>
<td>14</td>
<td>Death (myocardial infarction)</td>
</tr>
<tr>
<td>9</td>
<td>EAS</td>
<td>Metastatic</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Surgery, remission</td>
</tr>
<tr>
<td>10</td>
<td>EAS</td>
<td>Metastatic</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>Death (tumor progression)</td>
</tr>
<tr>
<td>11</td>
<td>EAS</td>
<td>Metastatic</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>Surgery, remission</td>
</tr>
</tbody>
</table>

**Neary NM., et al., 2012:** Twelve patients (4 females; 8 males) with the ectopic ACTH syndrome due to a neuroendocrine thymic tumor were studied in this retrospective review over 25 years (between 1986 and 2010). Preoperatively, nine patients received medical treatment, 6 with KC. All patients underwent thymectomy, and nine of 10 tumors exhibited positive ACTH immunochemistry. Six patients recurred 20-28 months after surgery with metastases. All recurrent patients received KC and four later underwent bilateral adrenalectomy. Clinical resolution of CS features post operatively.

**Winquist EW., et al., 1995:** This is a retrospective chart review of the records of all patients with ectopic ACTH syndrome (EAS) who presented to the medical oncology service at The Toronto Hospital, General Division from 1980 to 1992. Fifteen patients with EAS and treated with KC were assessable for hormonal and/or biochemical responses. There were four women and 11 men with a median age of 59 years (range, 44 to 84). All patients had histologically confirmed metastatic tumors. KC was administered in dosages ranging from 400 to 1,200 mg/day, and the median duration of therapy was 26 days (range, 3 to 1,059). Only three patients received KC for more than 3 months, which included one patient who was treated for nearly 3 years. Two patients received short courses of aminogluthethimide and metyrapone until death after disease progression on KC. Nine patients received combination chemotherapy concurrently with KC. Of the 12 patients assessable for hormonal response by 24hr UFC levels, five had complete resolution, three had a reduction in UFC up to <50% of baseline (partial resolution), and two improved but had less than partial resolution. Improvements were observed in the clinical
manifestations of CS. Of 14 assessable patients with hypokalemia, 13 improved during KC therapy, but only five could discontinue potassium supplementation and potassium-conserving medications. Eight of 11 assessable patients with metabolic alkalosis had complete response. Of 10 assessable patients with new or worsened diabetes, insulin and oral hypoglycemic drugs were stopped in only one patient, but six other patients had improved glycemic control after starting KC therapy. All eight assessable patients with new or worsened hypertension responded, but antihypertensives were discontinued in only one patient. Most patients died of progressive malignant disease accompanied by escape from hormonal control by KC. The median survival duration of the group was 19 weeks (range, 1 to 154).

2.5.1.2. Review of the main efficacy results

A paper published by the European Registry on CS (ERCUSYN) (Valassi, 2011) shows that the main causes for 481 patients with CS are 66% pituitary-dependent, 27% adrenal-dependent, 5% ectopic source and 2% other causes. The number of patients with adrenal-dependent CS described in this application is lower than in the European Registry on CS.

Most of the studies presented described the use of KC as sole treatment in case of pre-surgery treatment, post-surgery in patients who do not respond or have a recurrence after surgery or waiting for the radiotherapy efficacy. Eight studies describe the use of KC in combination with other steroidogenesis inhibitors. The most common combination was KC + metyrapone. It has been used also in combination with mitotane, cabergoline, pasireotide in biotherapy or triple therapy.

The use of KC as combination therapy is described in 126 patients. Most of these patients presented EAS (around 65%), being the second one entity more frequent CD. It reflects the complexity and heterogeneity of the management of this disease and the need to use combination therapy in cases of EAS because of the severe hypercortisolism associated to this entity. The information provided by the applicant not only as monotherapy but also as a combination treatment is considered acceptable.

Most of them are retrospective studies without a clear objective stated. However, it could be said that the main objective of the provided studies was to describe the efficacy and safety profile of KC used to treat Cushing Syndrome.

Most of the studies included two main measures in order to describe the efficacy. The first one is a biological one consisted on change on urinary cortisol excretion during 24 hours (urinary free cortisol, UFC 24h) during treatment compared to the pre-treatment level. This measure has the advantage that provides information of cortisol production over a period of 24 hours. On the other hand, the two most relevant disadvantages are the dependency on renal function and the inconvenience for the patient to collect urine for 24 hours. Other studies measure plasma cortisol levels to establish efficacy. Both of them are considered valid methods for monitoring efficacy results.

The second one parameter, which is as relevant as the previous one, is the clinical response. There are not established criteria regarding the clinical signs to evaluate the efficacy. The most frequently clinical signs
described were the improvement of hypertension, diabetes mellitus and hypokalemia. Others included in some studies were improvement of weakness, dermatological problems and moon face.

Both criterion, the biological and the clinical, were described by the applicant along the review of the published literature.

The Cushing’s syndrome affected approximately 0.9 in 10,000 people in the European Union (EU). This is equivalent to a total of around 46,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000 (EMA/COMP/528385/2012).

The total sample size was around 800 patients and represented patients from all the spectrum of Cushing’s Syndrome. The applicant included retrospective studies reviewing data from patients treated with KC including from 1 (i.e individual case reports) to 200 patients (Castinetti et al., 2014).

The patient population described is considered appropriate for the claimed indication which was further amended during the procedure to reflect the available published data.(see later in the report).

- **Persistence of Efficacy and/or Tolerance Effects**

The duration of treatment with KC in the patients presented ranges from a few weeks to 13 years. The treatment goal is to control the cortisol levels in the short-term to alleviate symptoms while investigations are ongoing or in anticipation of surgery. Longer-term therapy is required to supplement pituitary irradiation and in those patients who cannot undergo surgery or in whom it fails. In the Castinetti 2014 study, 69 patients, (including 21 patients who were never operated and 48 patients who had a persistent CS after a primary pituitary surgery) were treated for at least 6 months by ketoconazole as a sole therapy, i.e. they did not receive any other therapies including pituitary radiotherapy or a second pituitary surgery. The follow-up ranged from 6.1 months to 127 months (mean: 26.6 ± 26 months).

Ketoconazole dose ranged from 400 to 1200 mg/d. Fifty-one out of the 160 patients were treated with ketoconazole for more than 24 months (mean 108.5 ± 244.4 months, range 24.1 to 135 months). Eight patients had contra-indications to surgery, and were treated by ketoconazole as a first-line treatment.

At the last follow-up, mean final UFC was 1.48±1.27-fold ULN. At the last visit, hypertension was improved in 15/27 patients (55.5%), diabetes in 7/14 patients (50%), and hypokalemia in 7/8 patients (87.5%). UFC was normalized in 33/51 patients (64.7%), and it had decreased by at least 50% in an additional 12/51 patients (23.5%). The six remaining patients (11.7%) had final increase in UFC despite initial control, after a mean time of 64.3±27.3 months (24.4- 105.6 months). A number of patients included in the studies presented have been treated for a prolonged period (at least 6 months) with KC and these are summarized in Table 4.
Table 4. Long term treatment with ketoconazole

<table>
<thead>
<tr>
<th>Literature Reference</th>
<th>Diagnosis</th>
<th>Number of Patients</th>
<th>Treatment Regimen</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angeli 1985</td>
<td>Cushing's disease</td>
<td>5</td>
<td>KC 600-800 mg/d</td>
<td>6-18 mth</td>
</tr>
<tr>
<td>Bertelli 2007</td>
<td>Cushing's disease</td>
<td>8</td>
<td>KC 600-800 mg/d</td>
<td>5-13 mth</td>
</tr>
<tr>
<td>Castinetti 2008</td>
<td>Cushing's disease</td>
<td>13</td>
<td>KC Max 400-1200 mg/d</td>
<td>6-12 mth</td>
</tr>
<tr>
<td>Castinetti 2008</td>
<td>Cushing's disease</td>
<td>5</td>
<td>KC Max 400-1000 mg/d</td>
<td>18-24 mth</td>
</tr>
<tr>
<td>Castinetti 2014 in press</td>
<td>Cushing's disease</td>
<td>8</td>
<td>KC Max 200-1000 mg/d</td>
<td>30-72 mth</td>
</tr>
<tr>
<td>Chou 2000</td>
<td>Cushing’s disease</td>
<td>69</td>
<td>KC 400-1200 mg/d</td>
<td>6-127 mth</td>
</tr>
<tr>
<td>Engelhardt 1989</td>
<td>Cushing’s disease</td>
<td>3</td>
<td>KC 200-1200 mg/d</td>
<td>65-83 mth</td>
</tr>
<tr>
<td>Loh 1986</td>
<td>Cushing’s disease</td>
<td>2</td>
<td>KC 600 mg/d</td>
<td>10 and 12 mth</td>
</tr>
<tr>
<td>Luisetto 2001</td>
<td>Cushing's disease</td>
<td>10</td>
<td>KC 300-600mg/d</td>
<td>10-100 mth</td>
</tr>
<tr>
<td>Monocrot 2007</td>
<td>CS (69% Cushing's disease)</td>
<td>24</td>
<td>KC 200-1200mg/d, mean maintenance dose 600 mg/d</td>
<td>1-13y</td>
</tr>
<tr>
<td>NIH review Sharma</td>
<td>Cushing’s disease</td>
<td>1</td>
<td>KC + MET</td>
<td>9.7 mth</td>
</tr>
<tr>
<td>Ectopic ACTH syndrome</td>
<td>4 Cushing’s disease</td>
<td>5</td>
<td>KC initial, max and final, median 1200 range, 200-1800 mg/d</td>
<td>3-4.7y</td>
</tr>
<tr>
<td>Sonino 1991</td>
<td>Cushing’s disease</td>
<td>2</td>
<td>KC 400-600 mg/d</td>
<td>6mth and 9 mth</td>
</tr>
<tr>
<td></td>
<td>Ectopic ACTH syndrome</td>
<td>10</td>
<td></td>
<td>1y-3y</td>
</tr>
</tbody>
</table>

|                         |                                     |                    |                                    |                       |
| Adrenal carcinoma      | 1                                   | KC 400-1000 mg/d   | 6 mth                             |
| Tabarrani 1991         | Cushing's disease                   | 4                  | KC 400-1200 mg/d                  | >6mth                 |
| Terzolo 1988           | Cushing’s disease                   | 3                  | KC 600 mg/d                       | 6 mth                 |
| Valassi 2012           | CS (84% Cushing's disease)           | At least 1         | KC 400-600 mg/d +/- MET           | Up to 31 mth          |
| Vihar 2010             | Cushing’s disease                   | 9                  | KC 200-400 mg/d - cabergoline 3mg/wk | 6 mth                 |
| Winquist 1995          | Ectopic ACTH syndrome               | 1                  | KC 400-1200 mg/d                  | 2.9y                  |

KC: ketoconazole, MET: metyrapone, mg: milligram; d: days; y: years; mth: months; NS: not specified; Max: maximum
Some of these patients underwent surgery or died or suffered from complications related to the underlying condition. However, the mortality rate in these studies reflects the seriousness of the disease and it appears that most of the deaths were a result of the underlying pathology of the condition. In terms of persistence of effect, the cortisol levels represent a measure of the efficacy and the dose of KC should be titrated accordingly.

It is also acknowledged that the progression of the underlying pathology of the disease and the spontaneous fluctuations in cortisol hypersecretion in some patients will affect the treatment decisions over time.

- **Clinical studies in special populations**

**Paediatric population**

The majority of patients described are adult, probably because of the known epidemiology of Cushing syndrome and it is not possible to discern exactly what proportion of patients would be < 18 years or > 65 years. Clear information on the age of all patients in the studies is not available from the published data. However, a wide age range of between 4 months and 17 years has been included. Available data are limited but show that KC at doses ranging from 200 to 1200 mg/d might be useful in some cases of CS occurring during childhood and results in biochemical and clinical benefit with the restoration of a normal height and gonadal function.

The applicant presents a table with paediatric data from 24 children for treatment of endogenous Cushing’s syndrome (13 patients with Cushing’s disease, 2 patients with adrenal carcinoma, 5 patients with the EAS, one from a McCune-Albright syndrome, one with an adrenal adenoma and 2 from an indeterminate cause).

Regarding age groups, 16 were aged above 12 years old and 8 were aged below 12.
Regarding posology, the dose ranged from 200-1,200 mg/d, some cases received KC pre-surgery. In 13 out of 24 KC was considered as partially effective or effective therapy.

**Table. KC use in paediatric population**

<table>
<thead>
<tr>
<th>Literature Reference</th>
<th>Age; Gender</th>
<th>Diagnosis</th>
<th>KC Dose &amp; Duration (when specified)</th>
<th>Other Treatments</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castinetti 2014</td>
<td>M; 9y</td>
<td>CD</td>
<td>200-400 mg/d 65 mth</td>
<td>NS</td>
<td>Not effective. UFC levels remained stable at 1.3 times the upper limit of normal</td>
</tr>
<tr>
<td>Castinetti 2014</td>
<td>F; 11y</td>
<td>CD</td>
<td>600 mg/d 1 mth</td>
<td>NS</td>
<td>Not effective. UFC levels remained stable at 4 times the upper limit of normal. Liver enzymes increased.</td>
</tr>
<tr>
<td>Castinetti 2014</td>
<td>F; 13y</td>
<td>CD</td>
<td>800 mg/d 4 4 mth</td>
<td>NS</td>
<td>Effective therapy. Signs of adrenal insufficiency</td>
</tr>
<tr>
<td>Castinetti 2014</td>
<td>F; 14y</td>
<td>CD</td>
<td>800 mg/d 11 mth</td>
<td>NS</td>
<td>Effective therapy</td>
</tr>
<tr>
<td>Castinetti 2014</td>
<td>F; 15y</td>
<td>CD</td>
<td>400-1200 mg/d 9 mth</td>
<td>NS</td>
<td>Partially effective. UFC levels decreased by at least 50% from pre-treatment levels. Nausea, vomiting</td>
</tr>
<tr>
<td>Castinetti 2014</td>
<td>F; 15y</td>
<td>CD</td>
<td>800 mg/d 1 y</td>
<td>NS</td>
<td>Partially effective. UFC levels decreased by at least 50% from pre-treatment levels</td>
</tr>
<tr>
<td>Castinetti 2014</td>
<td>F; 15y</td>
<td>CD</td>
<td>600-800 mg/d 36 mth</td>
<td>NS</td>
<td>Partially effective. UFC levels decreased by at least 50% from pre-treatment levels</td>
</tr>
<tr>
<td>Castinetti 2014</td>
<td>F; 16y</td>
<td>CD</td>
<td>600-800 mg/d 24 mth</td>
<td>NS</td>
<td>Effective therapy</td>
</tr>
<tr>
<td>Dash 1990b</td>
<td>F; 16y</td>
<td>CD</td>
<td>Pre-operative therapy 800 mg/d 7-10 wk</td>
<td>NS</td>
<td>Plasma cortisol returned to near normal values and significant improvement in clinical features by the end of the 3rd week.</td>
</tr>
<tr>
<td>Harinarayan 1991</td>
<td>M; 9y</td>
<td>Adrenal carcinoma</td>
<td>KC 600-1200 mg/d 6 wk</td>
<td>Dexamethasone 0.5 mg</td>
<td>Significant fall in plasma and urinary cortisol levels. Normalisation of blood pressure, decrease in facial plethora. Hypotension</td>
</tr>
<tr>
<td>Harinarayan 1991</td>
<td>F; 17y</td>
<td>Adrenal carcinoma</td>
<td>KC 600-1200 mg/d 4 wk</td>
<td>Dexamethasone 0.5 mg</td>
<td>Significant fall in plasma and urinary cortisol levels. Janudice. Altered liver function tests at 22 days after KC 1200 mg/d. After KC sip, gradual rise in cortisol levels and liver enzymes returned to normal within 3 wk. And KC started again at 600 mg/d</td>
</tr>
<tr>
<td>Loli 1986</td>
<td>F; 16y</td>
<td>CD</td>
<td>Maximum 600 mg/d; 5 mth</td>
<td>NS</td>
<td>Marked decrease in 24hr UFC within the first week and plasma cortisol in the first</td>
</tr>
</tbody>
</table>
The clinical experience in children is limited as endogenous Cushing’s syndrome is extremely rare in the paediatric population. It is estimated that approximately 10% of Cushing’s syndrome cases occur in children (Stratakis, 2012).

Ketoconazole has a therapeutic utility in paediatric patients due to the paucity of medical options that may be used in the paediatric population. In addition there is no safety signal in the literature justifying a contraindication. However most of the data are from the use in adolescents above the age of 12 years.

<table>
<thead>
<tr>
<th>Monct 2007</th>
<th>F; 14y</th>
<th>CS from indeterminate cause</th>
<th>9y</th>
<th>NS</th>
<th>She achieved eucortisolism, normal height and had menarche 2y after starting KC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesry 2012</td>
<td>F; 7y</td>
<td>Ectopic ACTH syndrome - Thymic tumor</td>
<td>Pre-surgery (thymectomy)</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>Nesry 2012</td>
<td>M; 13y</td>
<td>Ectopic ACTH syndrome</td>
<td>Pre-surgery (thymectomy) and/or post-operatively</td>
<td>Further bilateral adrenalectomy</td>
<td>Death 22mth post-surgery (disease progression)</td>
</tr>
<tr>
<td>Nesry 2012</td>
<td>F; 14y</td>
<td>Ectopic ACTH syndrome</td>
<td>Pre-surgery (thymectomy) and/or post-operatively</td>
<td>Chemotherapy and further bilateral adrenalectomy</td>
<td>Death 90mth post-surgery (disease progression)</td>
</tr>
<tr>
<td>Sonimo 1991</td>
<td>M; 14y</td>
<td>CD</td>
<td>600 mg/d; 9 months</td>
<td>NS</td>
<td>Marked suppression of cortisol production immediately after treatment (24hr UFC) and regression of clinical signs of CD</td>
</tr>
<tr>
<td>Costeastro 2011</td>
<td>F; 12y</td>
<td>CD</td>
<td>Initial 200 mg/d gradually increasing to 800 mg/d over 8 mth. Remained on 800 mg/d for &gt;3mth (until surgery)</td>
<td>NS</td>
<td>24hr UFC normalized within 2 mth and at the 800 mg/d dose recovered growth rate and lost 10% of body weight</td>
</tr>
<tr>
<td>Dutta 2012</td>
<td>F; 4mth</td>
<td>Adrenal adenoma</td>
<td>200 mg/d (two divided doses). Until surgery</td>
<td>NS</td>
<td>Symptoms resolved after surgery</td>
</tr>
<tr>
<td>Fernandez 2011</td>
<td>F; 11y</td>
<td>CD</td>
<td>KC to control hypercortisolism until surgery</td>
<td>NS</td>
<td>Symptoms resolved after surgery</td>
</tr>
<tr>
<td>Leal-Cerro 1989</td>
<td>M; 14y</td>
<td>CS (type not specified, patient normosensitive)</td>
<td>800 mg/d until surgery &gt; 35wk</td>
<td>NS</td>
<td>Rapid normalization of plasma and urinary cortisol levels. Blood pressure increased after 31wks on KC. Increased levels of DOC</td>
</tr>
<tr>
<td>Matatuzzo 2011</td>
<td>F; 3y</td>
<td>Ectopic ACTH syndrome</td>
<td>300 mg/d (100 mg every 8 hr) for 1 mth.</td>
<td>NS</td>
<td>Serum cortisol normalized. Reduced hypercortisolism before surgical removal of the pancreatic tumor</td>
</tr>
<tr>
<td>Vong 2009</td>
<td>F; 5y</td>
<td>McCune-Albright syndrome with ACTH-independent hypercortisolism</td>
<td>2.5mg/kg/d for 2y</td>
<td>NS</td>
<td>Low cortisol levels indicating strong adrenal suppression. No abnormal liver function tests</td>
</tr>
<tr>
<td>Zollner 2001</td>
<td>F; 14y</td>
<td>CD</td>
<td>200mg/d for 7d 400mg/d for 26d Re-treatment after surgery 200mg/d for 7d 400mg/d for 49d</td>
<td>Transphenoidal resection</td>
<td>No efficacy results presented. Patient died of liver failure</td>
</tr>
</tbody>
</table>
The applicant was asked to provide further clarification detailed below whether paediatric patients should be included in the indication and provide further evidence and justification for posology recommendation for section 4.2 and sections 4.4, 4.8 and 5.1 as appropriate.

Ketoconazole efficacy data in the paediatric population

When ketoconazole has been used for Cushing’s disease in patients from 9 to 16 years old, the dose varied from 200-400 mg/day to 600-800 mg/day. It has been used up to 1,200 mg/day in one 15 years old patient. When used for adrenal carcinoma in patients from 9 to 17 years old, the dose ranged from 200 to 1,200 mg/day. When used for adrenal adenoma in infants, lower ketoconazole doses were used (~ 200 mg/day in 2 divided doses). When used for the ectopic ACTH syndrome, no specific information on dosing was available except in one case (a 3 year old patient treated by 300 mg/day).

In conclusion, from the publications it appears that the doses used in adolescents above 12 years old were similar to the doses used in adult patients with endogenous Cushing’s syndrome. In children and infants, no reliable information on posology is available because of the limited data. Two infants were treated by 200 mg/day and 300 mg/day respectively (Duta, 2012; Matarazzo, 2011). In a case report of McCune Albright syndrome in a 5 years old girl, ketoconazole dose was 2.5 mg/kg/day which induced a strong adrenal suppression (Vong, 2009).

Treatment with ketoconazole in paediatric patients allowed normalisation of urinary free cortisol levels and clinical improvement, including recovering of growth rate and gonadal function, normalisation of blood pressure, Cushing’s syndrome features and weight loss. Harinarayan, 1991 described 2 cases with adrenal carcinoma who had a significant fall in plasma and urinary cortisol levels, a normalisation of blood pressure and a decrease in facial plethora. Moncet 2007, reports that eucortisolism was achieved in a 14 year old girl treated with ketoconazole. She achieved a normal height and had menarche 2 years after starting ketoconazole. Sonino 1991, reports a 14 year old boy who was diagnosed with Cushing’s disease. On ketoconazole, he had a marked suppression of cortisol production immediately after treatment and regression of clinical signs of Cushing’s.

Costenaro 2011 reports a case of a 12 years old girl who was diagnosed with Cushing’s disease who was treated with ketoconazole until surgery. Urinary free cortisol levels normalized within 2 months and at the 800 mg/d dose, she recovered growth rate and lost 10% of body weight. In the McCune Albright syndrome patient, ketoconazole induced very low cortisol levels after 4 months, was well tolerated and was continued for 2 years as an alternative to adrenalectomy.

Ketoconazole safety data in the paediatric population

In total two cases out of 24 developed severe hepatoxicity including one case of fatal liver failure due to ketoconazole was reported in a 14 year-old girl while treated for Cushing’s disease with ketoconazole 200 mg twice daily (Zollner, 2001) and this is included in section 4.8 of the SmPC.

Ketoconazole pharmacokinetics in the paediatric population

Data on ketoconazole pharmacokinetics in the paediatric population are available from two publications in studies in antifungal indications (Ginsburg, 1983; Bardare, 1984). Main data indicate that there is no evidence for differences in half-life or exposure of ketoconazole in paediatric patients compared to adults.

Data on efficacy of ketoconazole in paediatric population is scarce as only 10% of all CS cases occur in children (Sarafoglou 2009). Around 75-90% of CS cases in children over age 5–7 years are due to CD (Lafferty 1999; Savage 2008). Adrenal causes are more common in the youngest age groups (Savage 2008). Primary pigmented nodular adrenal cortical are more commonly presented in the second or third decade of life, but they
are also seen in younger children, as early as in the first 2-3 years of life (Stratakis 2001). Ectopic ACTH syndrome is a very rare cause in children (More 2011).

The efficacy in this subset has been demonstrated although with limited data. Posology used in paediatric population, pharmacokinetics and the safety profile seem similar to those of adults.

Although prevalence of CS in children is low, it is important to include this population in the indication as well a posology recommendation. Based on the literature provided, it is considered that the use in patients of 12-17 years old is adequately demonstrated and thus it is agreed to include adolescents older than 12 years of age in the indication as well as the recommended posology for this subset.

The agreed wording related to the paediatric population in sections 4.2, 4.8 and 5.1 is detailed below:

**Paediatric population**

"The safety and efficacy of Ketoconazole HRA in children aged less than 12 years have not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on posology can be made. The posology in adolescents is the same as in adults."

The following information about the paediatric use in section 4.8 of the SmPC about the safety in adolescents:

"Frequency of hepatoxicity could be higher in adolescents than in adults. In the literature, among 24 paediatric patients treated with ketoconazole, two developed a severe hepatoxicity. A 14 year-old girl who was treated for Cushing’s disease with ketoconazole 200 mg twice daily presented one month later with jaundice, fever anorexia, nausea and vomiting. Ketoconazole was stopped but she deteriorated rapidly and died. A 17-year old girl was treated on ketoconazole 1200 mg/day for an adrenal carcinoma with liver metastasis and had altered liver function tests at 22 days. After ketoconazole withdrawal, liver enzymes returned to normal levels within 3 weeks."

The following information about the paediatric use in section 5.1 of the SmPC is agreed upon:

"Data on 24 paediatric patients with endogenous Cushing’s syndrome treated with ketoconazole are available in the literature, among which 16 were aged over 12 years old and 8 were aged less than 12 years old. Treatment with ketoconazole in paediatric patients allowed normalisation of urinary free cortisol levels and clinical improvement, including recovering of growth rate and gonadal function, normalisation of blood pressure, Cushing’s syndrome features and weight loss. The doses used in adolescents above 12 years old were similar to the doses used in adults’ patients with endogenous Cushing’s syndrome”.

**Pregnancy**

KC therapy is not recommended during pregnancy due to concerns on teratogenicity from studies in animals (Gross 2007; Vilar, 2007). It has been demonstrated that KC crosses the placenta in animal studies.

No guidelines for CS in pregnancy are available. However, surgical management is recommended whenever possible, except late in the third trimester, with medical therapy being a second choice until after delivery (Vilar, 2007). However, as KC is teratogenic we do not recommend its use during pregnancy.
There are scarce data about the use of KC in pregnancy. Due to teratogenicity, it is not recommended use KC in this population. The applicant position is agreed by the CHMP and appropriate information is mentioned in the SmPC.

**Elderly population**

Several studies included elderly patients but did not provide the exact number in the elderly population thus, clarification was provided. Finally, the applicant provided information about 24 elderly patients, 17 out of 24 was 65-74y, 4/24 75-84y and 2/24 >85y. 6 had EAS and the rest CD.

Available clinical data suggest that ketoconazole was used in elderly patients at doses ranging from 400 to 1200 mg/d and length of treatment was 2-30 months.

Although data are limited on the KC use in the elderly population, KC was a useful therapy for several elderly patients at doses ranging from 400 to 1200 mg/d, therefore at doses not different from those of the other age-groups. (see below detailed information)

Donovan et al. (1993) describe a 66y woman with a lipoid cell tumour in the ovary and a CS associated with the progression of the malignancy. She received up to 1,200mg/daily of KC without control of UFC excretion level. Previously other authors have published the association between this type of tumours and CS (Taylor and Norris 1967, De Lima 1966, Young and Scully 1987, Cleveland et al. 1987).

Kamenicky et al. (2011) described 11 patients who received mitotane, metyrapone and ketoconazole combination therapy in severe ACTH-dependent CS. Four of them were >65y, received a median dose of 800mg/daily of KC (range 400-1.200 mg/daily) and the symptoms were controlled and the UFC excretion remained low to normal throughout the period of combination therapy.

Brito et al. (2012) described an 83y woman with an ACTH-dependent CS probably of ectopic origin. She received 1.200 mg/day. The evolution of the disease was not known.

Valassi et al. (2012) describe at least one 70y old patient with CD.

Castinetti et al. (2008) described three women >65y who received 400-600 mg/daily of KC. In the ITT population 44.7% normalized their UFC excretion and they also presented a clinical regression of signs of hypercortisolism (i.e loss of weight, lowering of blood pressure and improving HbA1c).

Castinetti et al. (2014) the manuscript included 200 patients with KC treatment for active CD between 1995 and 2012. The mean age was 41.9±15.8y (range 8-87y). Maximal dosage was 1.200 mg/day. 75.2% of patients had at least 50% decrease of UFC, including 49% with normal UFC at the last follow-up. The applicant described more detailed data about patients >65y included in this study but in the manuscript provided we do not have these data.

On the basis of the above data, the CHMP considered that the data in patients older than 65 years are limited, but there is no evidence to suggest that dose adjustment would be required in these patients. This is adequately addressed in the SmPC section 4.2.
2.5.2. Analysis performed across trials (pooled analyses AND meta-analysis)

As discussed above, the studies presented cover a range of conditions within CS and therefore also include a range of different treatments apart from KC, such as pituitary radiation, adrenalectomy, transsphenoidal surgery, as well as other medical therapies (metyrapone, mitotane, and aminoglutethimide), which are important therapeutic options for use in patients with CS. KC has been used since the early 1980s for the treatment of CS from any cause, particularly for CS management when causal treatment is not possible or has failed.

- KC has been used both as sole medical therapy and in combination with other drugs or with radiation therapy. In 43 to 80% of patients, KC therapy resulted in a normalization of cortisol levels and in further 24 to 42%, a decrease of more than 50% of urinary free cortisol levels was shown (Castinetti, 2014; Castinetti 2008; Gomez, 2007; Invitti, 1999; Moncet, 2007; Sonino, 1991). Combined therapy with multiple steroidogenesis inhibitors has been shown to be effective in both rapid and chronic control of hypercortisolism. KC brings a major contribution to patients’ care in this rare and severe disease by effectively treating symptoms related to cortisol excess (Kamenicky, 2011; Feelders, 2010a).

- KC is characterized by a rapid onset of action. The cortisol response to ACTH stimulation is significantly blunted 3-4 hours after administration of 400 and 600 mg doses of KC (Pont, 1982) and 24 hour urinary free cortisol levels are decreased within one day. This allows its use in cases of severe CS or in cases where acute complications are critical.

- KC is an effective drug for reducing cortisol levels in all causes of CS.

- KC efficacy is usually maintained in the long-term, which allows a long-term control of hypercortisolism. Escape is rare once control is achieved.

- Biochemical and hormonal improvements are associated with clinical improvements in CS symptoms (depressive psychiatric symptoms, diabetes or glucose intolerance, hypertension, muscle weakness, hirsutism etc.). Co-morbid conditions of hypertension and diabetes in CS tended to improve on KC therapy (Castinetti, 2014; Fallo, 1993; Gomez, 2007; Loli, 1986; Moncet, 2007, Sonino, 1985).

- KC is also effective in the treatment of increased androgens levels and hirsutism.

Ideally, treatment of CS is by surgery, removing its cause, thus normalizing cortisol secretion with the resulting disappearance of the associated symptoms. However, surgery is sometimes not possible or may fail, leading to persistent or recurrent disease, and medical therapy can be used in these cases to restore a normal 24-hour production rate of cortisol. Alternatively, medical therapy can help control cortisol levels in Cushing’s disease patients while waiting for pituitary radiotherapy to become fully effective, which can take several years. In light of the wide-ranging conditions included in CS and the range of treatment options for each case, the diversity of treatments in the studies presented is a result of normal clinical practice. There will therefore inevitably be disparities in the groups of patients summarized below, but some broad conclusions can be drawn from the data. Dexamethasone was added in some cases when a block-and-replace regimen was used; but a dose titration
(block-only regimen) was mostly used. Cortisol levels, either in serum/plasma or urine, were used to assess the efficacy of the treatment, along with clinical symptoms. Plasma/serum cortisol measurements were also used to detect if there was any over-treatment. In some studies (Engelhardt, 1989; Mortimer, 1991; Weber 1989), other steroids were also assessed in an exploratory fashion. Basal and, in some cases dynamic, ACTH measurements were done for patients with CD.

**Cushing’s Disease**

Data from 535 patients with Cushing’s disease are presented, along with 13 individual case reports. The dose of KC administered in these patients ranges from 200 mg and 1200 mg per day. In patients with Cushing’s disease, KC has been used either alone in the period prior to pituitary surgery or after surgery failure, either in combination with pituitary radiotherapy or as single therapy. The duration of treatment varied from a few days to 13 years. KC is given at an initial daily dose of 200 to 400 mg/day with weekly control of AST, ALT and gamma-GT during the first month (Castinetti 2008; Castinetti, 2014; Sonino, 1991). The dose used is adjusted by 200 mg/day increments on the basis of the cortisol levels achieved (in serum/plasma and/or urine) in each patient. Liver function tests are conducted at each titration step and the dose reduced as necessary. The average dose was 800 mg/day. In all the reports the cortisol levels fell to around normal levels soon after initiation of KC therapy. Some patients required increasing doses to maintain response.

In the Castinetti 2014, study, 69 patients, (including 21 patients who were never operated and 48 patients who had a persistent CS after a primary pituitary surgery) were treated for at least 6 months by ketoconazole as a sole therapy, i.e. they did not receive any other therapies including pituitary radiotherapy or a second pituitary surgery. The follow-up ranged from 6.1 months to 127 months (mean: 26.6±26 months). Ketoconazole dose ranged from 400 to 1200 mg/d. The wide range in the duration of treatment reflects the different treatment modalities, and the patients receiving KC for a short duration (a few weeks) were generally being treated in preparation for definitive surgery or radiotherapy. The patients treated longer-term are those in whom surgery was not possible or failed or in whom treatment was associated with a radiation therapy of the pituitary. UFC and morning plasma cortisol levels were significantly decreased, however the cortisol circadian rhythm was not restored. In the largest study (Castinetti, 2014) that included 200 patients with CD, 75% of patients had at least a 50% decrease in UFC levels, including 49% with normal UFC at the last follow-up. These results were concordant with smaller studies previously reported. The median final dose of KC was 600 mg/day and among the 49 patients with the lack of response, only 9 reached the maximal dose of 1200 mg/d. In some patients long-term control of cortisol levels was achieved with KC, as discussed above, but in others bilateral adrenalectomy was necessary. In a prospective study (Feelders, 2010b), eight patients with CD received KC after having been previously treated and uncontrolled despite the combination of pasireotide and cabergoline for 60 days. The addition of KC 600 mg/d for 20 additional days led to a normalization of UFC levels in six out of the eight patients. Plasma ACTH levels were highly variable from one study to another. No remarkable change (Sonino, 1985; Loli, 1986; Terzolo, 1988), tendency to increased levels (Engelhardt, 1989; Mortimer, 1991) or no compensatory ACTH rise despite normalization of cortisol levels or even decreased ACTH levels (Angelli, 1985; Sonino, 1991) were reported, although in these last papers at least some patients received pituitary radiation therapy which may explain these findings. A study (Boscaro, 1987) showed an increased response of plasma
ACTH to the CRH stimulation test, whereas others (Loli, 1986) found it to be unchanged compared with pre-treatment response. In addition to the effects of KC on steroidogenesis inhibition, a direct effect of KC on corticotropic tumor cells/ pituitary ACTH secretion was suggested by in-vitro studies and thought to be the consequence of the occupancy of glucocorticoid binding sites with putative effects or the consequence of the inhibition of corticotropic tumor cell growth (Stalla, 1988; Terzolo, 1988; Feelders, 2010a Neuroendocrinology). However most authors (Biller 2008) believe that this phenomenon does not seem to involve a direct KC effect on plasma ACTH secretion, but rather an adjustment in the sensitivity of the hypothalamic-pituitary-adrenal axis. Clinical features were noted to improve after initiation of KC therapy, including facial features, muscle weakness, hirsutism in females and psychiatric disturbances. In addition, hypertension and glucose control in diabetics also often improved.

**Adrenal Tumours and Nodular Adrenal Hyperplasia**

Data from 17 patients with adrenal tumors and from 2 patients with primary nodular adrenocortical hyperplasia (NAH) are presented, along with 17 individual case reports of patients with benign or malignant tumors or NAH and 2 paediatric cases of McCune Albright syndrome. The dose of KC administered in these patients was between 200 mg and 1200 mg per day. The highest dose of 1200 mg/d was only used for malignant adrenal carcinoma. The duration of treatment varied from a few days to 6 months where specified. Again, the short duration of treatment reflects the use of KC therapy prior to surgery, in preparation for adrenalectomy, whereas patients who cannot have surgery or those in whom it is unsuccessful are more likely to have longer-term treatment. As above, KC is given at an initial daily dose of 200 to 400 mg/day with weekly monitoring of liver transaminases. The dose is titrated on the basis of the cortisol levels/cortical excretion achieved in each patient and adjusted based on the liver function test results. Improvement of clinical symptoms was noted in most patients after initiation of treatment. However in patients with adrenal carcinoma, response to KC was usually poor (Calvo Romero, 1999; Engelhardt, 1989; Hofle, 1998), but mainly useful in preparation for adrenalectomy (Kruimel, 1991; Sinnaeve, 1989; Contreras, 1985).

**Ectopic ACTH Syndrome**

Data from 91 patients with EAS are presented, along with 18 individual case reports. EAS covers a large spectrum of tumors from undetectable isolated lesions to extensive metastatic and aggressive malignancies and is often associated with severe hypercortisolemia. Occult EAS is one of the most intriguing challenges for the clinical endocrinologist, as in some cases no tumor is found even after long-term follow-up. The prognosis and treatment of EAS patients depend on the tumor type, and surgery can be curative in patients with localised tumors. However, detection of the tumor is sometimes difficult. KC is also used when total removal of the secreting tumor is not possible, in preparation for surgery or in the case of metastases to provide relief of CS symptoms. A 10 year (1980-1990) chart review of patients in Toronto Canada (Shepherd, 1992) with small cell lung cancer identified 23 patients (4.5%), 17 male and 6 female aged 43 to 77 years, with CS and ectopic ACTH production. The response to combination chemotherapy was low and the rate of complications was high. KC was used in the treatment of eight patients. A reduction in serum and urinary cortisol levels (partial hormone response) was observed in four out of seven patients receiving concurrent chemotherapy along with an improvement in their ACTH levels. A partial hormone response was achieved in one patient on KC without
concurrent chemotherapy. Although corticosteroid levels may be controlled with KC in patients with ectopic ACTH syndrome due to small cell lung cancer, survival remains poor. In a Canadian retrospective record review from 1980 to 1992 (Winquist, 1995) 15 patients with EAS and histologically confirmed metastatic tumors were treated with KC dosages ranging from 400 to 1,200 mg/day. The median duration of therapy was 26 days (range, 3 to 1,059), three patients received KC for >3 months and one patient was treated for nearly 3 years. Nine patients received combination chemotherapy concurrently with KC. Of the 12 assessable patients 10 showed a reduction in UFC, five had complete resolution, three had a reduction in UFC up to <50% of baseline (partial resolution), and two improved but had less than partial resolution. Two patients received short courses of aminogluthethimide and metyrapone until death after disease progression on KC. Clinical improvement in hypokalemia, metabolic alkalosis, diabetes mellitus, and hypertension occurred in the absence of complete hormonal response.

One case report (Steen, 1991) evaluated in-vitro ACTH secretion from a thymic carcinoid tumor. The addition of KC to the tumor culture inhibited ACTH production (maximal inhibition at concentration of 100 μmol/l) suggesting a possible KC direct effect on the tumor-cells.

**Combination therapy**

Combination therapies may be useful as a second line therapy in patients not completely responding to a single agent or in those requiring a dose reduction of each drug to improve clinical tolerance. Combination of KC with metyrapone is a common practice and allows benefiting from potential synergistic effects while limiting side effects through dose reduction. One article reported the usefulness of KC in combination with metyrapone + mitotane, in 11 patients with severe ACTH-dependent CS as an alternative to bilateral adrenalectomy (Kamenicky, 2011). Another study looked at the use of KC alone or with metyrapone as preoperative treatments and found that urinary cortisol levels were normalised in 49% of cases, but that concomitant clinical improvement was not always observed (Valassi, 2012). KC was an effective addition to the treatment with cabergoline (Villar, 2010) and pasireotide/cabergoline in combination (N=17 patients; Feelders, 2010b). Pasireotide monotherapy induced sustained normalization of urinary free cortisol (UFC) in 5/17 (29%) of patients, at day 28, cabergoline was included in the therapy of the non-responders but at day 60 UFC was still elevated in 8 patients. The addition of KC (600 mg/day) induced biochemical remission in 6 out of these 8 patients at day 80 (Feelders, 2010b). As in all KC-treated patients, the dose was adjusted in these specific populations on the basis of the cortisol levels achieved (in serum/plasma and/or urine) in each patient and on the basis of the clinical tolerance and clinical response to the therapy. Concluding remarks: In all these studies variable KC and metyrapone starting doses were used depending on the patients’ needs and the center’ experience. High doses of both metyrapone and KC were used in patients with very severe hypercortisolism. As in all patients receiving steroidogenesis inhibitors, doses were usually adjusted in these specific populations on the basis of the cortisol levels achieved in each patient and on the basis of the clinical tolerance. The maximal KC in this situation was 1600 mg/d.
2.5.3. Supportive studies

The applicant provided a list of case reports to complete the previous information. There are 13 CD, 18 EAS and 17 of adrenal origin and 2 McCune Albright syndrome.

**Monotherapy**

**Cushing’s disease**

The use of KC as monotherapy has been used pre-surgery, post-surgery or associated to radiotherapy.

KC was used as a pre-surgery therapy with doses of 400-1,200 mg/day during 6 months ([Blanco et al. 2001](#)) or 600 mg/day during 35 days ([Li et al. 1996](#)) reaching a normalization of UFC previous to surgery. [Costenaro et al 2011](#) used KC 200-800 mg/day pre-surgery during more than 11 months until normalization of UFC. [Fernandez et al 2011](#) also used KC until surgery, but dose was not specified.

Two articles described use of KC pre- and post-surgery. One was a pregnant woman who was treated pre-surgery with KC 400 mg/day, pregnancy was discovered at week 9 of KC treatment and KC was suspended. After surgery KC was re-started at the same dose. No data regarding evolution was provided ([Boronat et al. 2011](#)). The second one was a 14y female treated with KC 200-400 mg/day pre- and post-surgery. No efficacy data are presented for KC re-treatment since the patient died of liver failure ([Zollner et al 2001](#)).

[Dash et al.](#), [Ferrau et al.](#) and [Shimon et al.](#) used KC after surgery. Dash described a 40y female treated with KC 800 mg/day during 4 weeks with normalization of plasma cortisol, decreased of UFC and significant improvement in the clinical status. Ferrau described a 22y female treated with KC 400 mg/day for 3 years. Serum cortisol and UFC normalized and she recovered regular menses and became pregnant 4 months after KC withdrawal. Shimon described a 33y male treated with KC 400-800 mg/day after surgery failure. The patient received radiotherapy and continued on KC treatment during and after radiotherapy. After 15 months of treatment, KC was suspended and UFC, glucose and potassium levels and blood pressure remained normal.

[Salgado et al. 2006](#) treated a 49y female with surgery on a non-specified dose of KC. No efficacy data was provided.

[Berwaerts et al. 1999](#) described a 30y pregnant woman case treated with KC alone 600-1,000 mg/day during 8 months without UFC normalization. KC was associated to cabergoline 0.125-0.25 mg/d for more than 3 years with a normalization of UFC levels and clinical improvement.

**Ectopic ACTH syndrome**

The use of KC as monotherapy has been described in different articles ([Arteaga et al. 1999](#), [Brito et al. 2012](#), [Joubert et al. 2007](#)). The range dose used was 300-1,200 mg/d. In all but one surgery to remove the tumour and in some of them bilateral adrenalectomy was performed. In most of them the hypercortisolism improved ([Matarazzo et al 2011](#), [Rickman et al. 2001](#)), in some others UFC or plasma cortisol levels was normalized during treatment ([La Rosa et al. 2011](#), [Said et al. 2010](#), [Steen et al. 1991](#)). Clinical improvement was also observed, but efficacy is linked to surgery in most of the cases, mainly in localized tumours.
KC was also used in combination therapy with other steroidogenesis inhibitors (i.e. cabergoline, etomidate, metyrapone and mitotane) plus surgery. The KC dose range used was 400-1,200 mg/d with clinical and biological improvement in most cases. Two of them stopped KC due to adrenal insufficiency (Ahmed et al. 2012, Gabalec et al. 2011, Gani et al. 2011, Kornely et al. 1991, Parthiban et al. 1995)

Other Cushing’s Syndrome types

Two articles (Sharma et al. 2012, Krysiak et al. 2012) reported cyclic Cushing’s Syndrome partially controlled with KC plus surgery.

In all but one cases of adrenal origin KC was used as monotherapy associated to adrenal surgery. The dose range used was 200-1,200 mg/d with decrease in plasma and urinary cortisol levels and clinical improvement in most cases (Amado et al. 1990, Contreras et al. 1985, Harinarayan et al. 1991, Hocher et al. 1993, Hofle et al. 1998, Holgado-Galicia et al. 2011, Kong et al. 1992, Kruimel et al. 1992 and Li et al. 1996).

There were two cases of McCune Albright syndrome (females 4 months and 5y), the younger one received 200 mg/d pre-surgery and symptoms was definitely resolved with surgery. The oldest one received 2.5 mg/kg/d and serum and urinary cortisol levels decreased avoiding bilateral adrenalectomy (Dutta et al. 2012 and Vong et al. 2009).

2.5.4. Discussion on clinical efficacy

Design and conduct of clinical studies

This is a well-established use application, therefore the efficacy is based on literature data. Most of the studies are retrospective, non-controlled or case reports, and describe patients since 1985 to 2012.

In total, data are presented on more than 800 patients including 748 from 28 published studies, some of which are retrospective case reviews, and 52 from individual case reports. As in the multi-centric Italian study (Invitti, 1999), the exact number of patients treated with ketoconazole was not clearly mentioned, the applicant arbitrarily considered that there were 110 patients with CD treated with KC, which was considered a conservative estimation as the authors stated that ketoconazole was the drug mostly used among the 178 patients treated medically.

The applicant states that the patients included in the studies are representative of the patient population as a whole as they cover a wide age range, from infants to the elderly, although it is not possible to determine exact numbers for any age-group and they include many of the different manifestations of CS and the subtypes.

Most of the studies presented described the use of KC as sole treatment in case of pre-surgery treatment, post-surgery in patients who do not respond or have a recurrence after surgery and waiting for the radiotherapy
efficacy. Eight studies described the use of KC in combination with other steroidogenesis inhibitors. The most common combination was KC + metyrapone.

Most of the studies included two main measures in order to describe the efficacy. The first one is a biological one consisted on change on urinary cortisol excretion during 24 hours (urinary free cortisol, UFC 24h) during treatment compared to the pre-treatment level. The second one parameter, which is as relevant as the previous one, is the clinical response (i.e normalization of hypertension, improvement on diabetes and normalization of hypokalemia). However, the clinical parameter is sometimes difficult to evaluate because of the retrospective design of the studies.

**Efficacy data and additional analyses**

Cushing’s syndrome (CS) is a rare condition with symptoms and signs resulting from chronic exposure to excess glucocorticoid. Establishing the diagnosis is often difficult because none of the symptoms or signs are pathognomonic of the syndrome. There is a large spectrum of manifestations from subclinical to overt syndrome, depending on duration and intensity of excess steroid production. In 80% of cases CS is ACTH-dependent and only in 20% of cases is ACTH-independent.

ACTH-dependent CS includes:

- Pituitary adenoma (Cushing's disease): 65 to 70% of patients
- Ectopic secretion of ACTH by non pituitary tumours: 10 to 15% of patients
- Ectopic secretion of corticotropin-releasing hormone (CRH) by non-hypothalamic tumours causing pituitary hypersecretion of ACTH: less than 1% of patients
- Iatrogenic or factitious Cushing’s syndrome due to administration of exogenous ACTH (not glucocorticoids): less than 1 percent

ACTH-independent CS consists of:

- Adrenocortical adenomas and carcinomas: 18 to 20% of patients
- Primary pigmented nodular adrenocortical disease: less than 1% of patients
- Bilateral ACTH-independent macronodular hyperplasia: less than 1% of patients

A consensus statement on ACTH-dependent CS published in 2008 (Biller, 2008) highlighted the need for a multi-disciplinary and individualised approach to patients’ management. Generally speaking, transsphenoidal surgery is the treatment of choice although this it is not always possible. Second-line treatments include more radical surgery, radiation therapy, pharmacological therapy and bilateral adrenalectomy. Because of the significant morbidity of Cushing’s syndrome, early diagnosis and prompt therapy are warranted.

Pharmacological treatment is considered under the following circumstances:

- contraindication or refusal of surgery or radiotherapy
- waiting for radiation to be effective or pre-surgery
- persistence or recurrence of hypercortisolism after surgery
- lack of detection of adenoma by imaging

Pharmacological therapy plays an important role in several situations. Treatment has to be defined on a case-by-case basis because of the heterogeneity in patients’ presentation and associated morbidities. Consequently there are no official national or international guidelines or treatment algorithm for management of Cushing’s Syndrome. The aim is usually to achieve normal plasma/serum cortisol or a normal 24 hour urinary free cortisol level.

Several drugs with different mechanism of action are being used for treatment of CS, like ketoconazole, pasireotide, metyrapone, mitotane or mifepristone. Nevertheless, the availability of drugs in Europe is limited.

**Ketoconazole is often given to control the condition prior to definitive therapy**, such as pituitary or adrenal surgery, or to control severe hypercortisolism in patients who are acutely ill, or in case of Cushing’s disease, while awaiting benefit from pituitary irradiation or in case of surgery failure.

**Ketoconazole has been used both as monotherapy and in combination** with other drugs (mainly with metyrapone, but also with mitotane, cabergoline and pasireotide) in more severe patients. Evidence suggests that it leads to a normalisation of cortisol levels in about 43 to 80% of patients. An additional 24 to 42% have a decrease in urinary free cortisol (UFC) levels of more than 50% as compared to pre-treatment values and may have some clinical benefit.

The Applicant has presented data from the literature, including more than 800 patients in total, to support the indication in the treatment of Cushing’s Syndrome.

Efficacy of KC in the treatment of **Cushing’s disease** was based on 535 patients and 13 case reports. Taking into account the epidemiology of the disease, it seems to be an acceptable number of patients. Regarding Cushing’s disease the overall response on decreasing urinary cortisol was between 40-85% depending on the articles.

The efficacy of KC on treatment of **ectopic ACTH syndrome** was based on 91 cases. The dose ranged was similar to the one used in CD. In most of the series KC was used in combination with other drugs and surgery. The efficacy results showed 40-50% with a reduction of urinary cortisol levels. In most of the cases the complete recovery was achieved with surgery.

The efficacy of KC on treatment of **CS of adrenal origin** is based on 36 patients, including 2 patients with a primary adrenocortical hyperplasia and 2 paediatric cases of McCune Albright syndrome. The dose ranged from 200 mg/d to 1,200 mg/d and the duration of treatment varied from days to 6 months. The efficacy is difficult to assess because not all of the studies specified the results by type of CS. Most of the case reports (12 out of 17) reported a decreased of plasma and urinary cortisol levels and an improvement of clinical symptoms. 5 out of 17 received surgery apart from KC and three received concomitant medications (i.e mitotane and aminoglutethimide). The number of patients is very limited. It seems that KC is efficacious for controlling urinary
cortisol levels, but clinical improvement (i.e. normalization of hypertension, improvement on diabetes and normalization of hypokalemia) was not always described.

The efficacy of KC in Cushing’s syndrome is considered supported by the data provided. It was based on a considerable number of publications and most of them included biological (i.e. UFC or serum cortisol levels) and clinical response (i.e. normalization of hypertension, improvement on diabetes and normalization of hypokalemia). However, medical treatment in CS is used when surgery fails or is not an option, waiting for the effect of radiotherapy. The indication proposed by the applicant has been justified taking into account the place of ketoconazole in the treatment of Cushing’s syndrome described above. The limited data in certain subtypes and other medical therapies, this suggest that the indication could be restricted to treatment of endogenous Cushing’s syndrome. This is acceptable by CHMP.

Taking into account the proposed indication the applicant has discussed the posology in adults and paediatric population. Section 4.2 of the SmPC has been amended in order to reorganize the recommendations on initial dose, maintenance dose and taper phase as required.

There are scarce data about the use of KC in pregnancy. Due to teratogenicity KC is contra indicated in pregnant women. The applicant position is agreed.

The applicant provided information about 24 elderly patients treated at dose ranged from 400-1,200 mg/d and length of treatment was 2-30 months. There is no need for dose adjustment in this population.

Long term treatment could be a possibility in some patients, especially those waiting for radiotherapy effect or when surgery fails or it cannot be performed. There were 194 patients who received KC for more than 5 months (range 5 months to 13 years). Most of them presented CD and received a dose range from 200 to 1,800 mg/d. There were few patients with EAS or ACTH-independent Cushing’s syndrome who were treated for more than 6 months.

Approximately 28% (194 out of 700 patients) of patients received ketoconazole for more than 6 months and they do not seem to have lost efficacy (only in 10-15% an escape phenomenon is observed) or have more adverse events.

The discussion provided and the amendments proposed in the SmPC are considered acceptable.

In approximately 10 to 15 % of ketoconazole treated patients, an "escape phenomenon" is observed and reinforces the need for a long-term clinical and biochemical follow-up of these patients. If such a phenomenon occurs, a further dose increase may be required to maintain cortisol levels within the normal range. This information is appropriately addressed in the SmPC.

**Assessment of paediatric data on clinical efficacy**

The efficacy in this subset has been demonstrated although with limited data. Posology used in paediatric population, pharmacokinetics and the safety profile seem similar to those of adults.

Data on efficacy of ketoconazole in paediatric population is scarce. Although prevalence of CS in children is low, it is important to include this population in the indication as well a posology recommendation at least for the most commonly subset described in the literature (patients of 12-17 years old). It has also been included in the SmPC that safety and efficacy of ketoconazole in children younger than 12 years have not been established.
2.5.5. Conclusions on the clinical efficacy

Overall, review of the literature suggests that ketoconazole is an effective drug for normalising cortisol levels in Cushing’s syndrome from all causes and, if well tolerated, ketoconazole treatment can be maintained for a long period which allows a long-term control of hypercortisolism. Biochemical and hormonal improvements was associated with clinical improvements in Cushing’s Syndrome symptoms. The clinical experience suggests that ketoconazole is a valuable drug for the short-term or the long term medical management of the patients with Cushing’s Syndrome, whenever a medical therapy is indicated. The hormonal changes caused by ketoconazole are dose-dependent and fully reversible. The posology needs to be adjusted on an individual basis and varies between 200 and 1200 mg/d depending on patients’ requirements to restore normal cortisol levels, and clinical tolerance. The maintenance dose is usually of 600-800 mg/d.

The indication has been justified taking into account the place of ketoconazole in the treatment of Cushing’s syndrome and the CHMP agreed that the applicant provided sufficient literature data demonstrating the efficacy for the treatment of endogenous Cushing’s syndrome in adults and in adolescents above the age of 12 years.

In summary, the applicant provided adequate data showing that this application fulfils the criteria for a well-established use application.

2.6. Clinical safety

2.6.1. Background information – EU Referral procedure

In July 2013, further to the referral procedure under article 31 of Directive 2001/83/EC, the European commission suspended the marketing authorization of oral ketoconazole containing products authorised in the treatment of fungal infections. This decision was based on the CHMP opinion concluding that the benefit/risk ratio of oral KC containing products for antifungal treatment had become unfavourable due to its hepatotoxicity and the availability of newer molecules for such antifungal treatment. However, KC remained accessible in some member states through compassionate use in the CS treatment until recent discontinuation of supply.

The hepatotoxicity of KC in the setting of fungal infections treatment was summarized by the EMA in the following way (Nizoral - EC Decision): A summary from EC decision is provided below:

"Results from non-clinical toxicity studies indicated the liver and endocrine system as primary target organs. Several potential mechanisms for this toxicity have been identified but uncertainties still remain.

The clinical safety of oral ketoconazole was evaluated in 4735 subjects in 92 company-sponsored clinical trials of ketoconazole tablets (or suspension), administered either to treat a variety of fungal infections in patients or to healthy-volunteer subjects. Based on this analysis, the point-estimate risk, in terms of the commonly-used Frequency Categories in the SmPCs, was "Common" (≥ 1/100 to < 1/10) for any Hepatic Function Test result being abnormal, and "Rare" (≥ 1/10,000 to < 1/1,000) for Hepatitis and/or Jaundice.

Of the 1,505 cases of interest; 880 (58%) were medically validated serious of which 18 life-threatening cases did not present any confounding factors and therefore are supportive of a causal role of ketoconazole. Seven
fatal/life-threatening cases were reported with event dates after 2006 i.e., after the CCDS update that contained substantial hepatotoxicity-related revisions.

The incidence of symptomatic hepatic reactions in the setting of treatment with oral ketoconazole was estimated in several epidemiology studies to be between 1/10,000 and 1/15,000 patients.

The review of the literature and post-marketing data provided by the MAHs showed that:

- hepatotoxicity with ketoconazole has been reported at a daily dose of 200 mg (median) which is the recommended daily dose;
- the incidence and seriousness of hepatotoxicity associated with the use of oral ketoconazole is higher than with the use of other antifungals, with the highest crude incidence rate per 10,000 patients for acute liver injury among other oral antifungals and with its use associated with the development of chronic hepatitis and cirrhosis;
- the onset of hepatotoxicity with ketoconazole usually occurs between 1 and 6 months after initiation of treatment (55% of the cases when the time to onset was documented) but has also been reported earlier than 1 month (including few days) after initiation of treatment (35% of the cases when the time to onset was documented);

It was concluded that the results of the current analysis of all cases of potential hepatotoxicity with oral ketoconazole-containing medicinal product confirm the risk of serious hepatotoxicity associated with the use of oral ketoconazole, best demonstrated by the causality assessments of fatal/life-threatening hepatotoxicity cases.”

KC has been used off-label in several EU countries as a standard of care to treat Cushing’s syndrome for more than 2 decades. The most important safety issue is hepatotoxicity, the applicant provided data on this issue based on the published literature in order to establish the benefit/risk for the proposed indication.

Data are available from small studies and retrospective chart reviews of up to 200 patients (Castinetti, 2014). The dose used for ketoconazole in the majority of studies presented varied between a minimum of 200 mg/d to a maximum of 1,200 mg/d with an average maintenance dose of 600 mg/d. The doses used in the studies are in line with the dosage regimen recommended for the treatment of CS in the proposed SmPC for this application.

2.6.2. Patient exposure

KC has been used for the treatment of fungal infections for more than 30 years as well as, off label or in clinical trials, for the treatment of prostate cancer, increased androgen levels/hirsutism, hypercholesterolemia and CS. There is therefore considerable clinical experience and safety data in a wide range of patient populations. The following sections address exposure in CS only.

In total, safety data are presented, including 646 patients from 27 studies and 52 from individual case reports giving an overall total of 698 patients.

The patients treated with KC alone or in combination could be classified as follows: Cushing’s disease (n=443), ectopic ACTH syndrome (n=109), adrenal tumors (n=25), nodular adrenal hyperplasia (NAH) (n=3) and
McCune-Albright syndrome (n=1). For the remaining patients the cause of CS was not established, not specified or impossible to determine.

Ketoconazole was administered as monotherapy in 21 studies, including a French retrospective study on ketoconazole outcome (FReSKO) reviewing data from patients treated with ketoconazole as a single treatment for CD (Castinetti, 2014). In total 200 patients (44 males and 156 females) were followed in 14 French centres with the aim of clarifying the efficacy and tolerance, particularly hepatic tolerance of ketoconazole in order to better determine the benefits/risk balance. In another study, 54 patients with CS were treated with ketoconazole at doses up to 1,200 mg/d and 24 patients received treatment for greater than 1 year (1 to 13 years) (Moncet, 2007). The dose used for KC in the majority of studies presented varied between a minimum of 200 mg/d to a maximum of 1,200 mg/d with an average maintenance dose of 600 mg/d to 800 mg/d.

The duration of treatment with KC in the patients presented ranges from a few days to 13 years. The treatment strategy is to control the cortisol levels in the short-term to alleviate symptoms while investigations are ongoing or in anticipation of surgery. Longer-term therapy is required to supplement pituitary irradiation and in those patients who cannot undergo surgery or in whom it fails.

Around 200 patients with CS received KC for ~ 6 months up to 13 years. In addition, there are 13 case reports in which treatment ranged from 6 months to 13 years.

The extent of population exposure to KC was about 700 patients, 193 received KC for more than 6 months. Taking into account the rarity of the disease, it is considered acceptable. The most relevant issue is that the dose proposed for the new indication is higher and the length of treatment is longer than the one used to treat fungal infections. Although long term treatment is not frequent some patients waiting radiotherapy effect could be treated with KC for a long period of time (at least 6 months) and some others in which surgery is contraindicated of failed.

The applicant was requested to discuss the evidence for long term treatment with ketoconazole in the proposed indication from the safety point of view. It was concluded that most of hepatotoxicity cases occur at the beginning of treatment and within the first month. Long-term treatment with ketoconazole does not seem to increase the risk of hepatotoxicity (see discussion later in the report under safety and benefit risk parts). However, given that the majority of cases are idiosyncratic reactions and therefore no dose-dependent, some precautions to the SmPC in reference to treatment lasting longer than six months are included.

2.6.3. Adverse events

In addition to the literature review, the applicant provided a review adverse drug reactions observed in clinical trial or in post-marketing surveillance for Nizoral tablets.

Adverse drug reactions observed in Study Narratives

The applicant provided publications from two studies including depressed patients treated with KC. The first one included depressed hypercortisolemic patients, while in the second one the baseline cortisol levels were normal. The first one showed an improvement in clinical symptoms without any effect on cortisol levels. In the second
one ketoconazole lead to partial improvements in depressive symptomatology, no changes in plasma cortisol concentrations, no relevant increase in CRH or ACTH. The role of KC in depressed patients without hypercortisolism is not clear. KC was well tolerated without any significant increases of hepatic enzymes.

The applicant presents one study regarding autoimmune or allergic diseases after CS remission. Overt autoimmune and allergic diseases were diagnosed in 11 (16.7%); eight (72.7%) were noted for the first time, and three (27.3%) were exacerbated after remission of CS. Regarding the new onset autoimmune diseases there were 2 patients with psoriasis, 3 patients with rash (generalized, rosacea-like or eczematous), 1 patient with sarcoidosis, 1 patient with primary biliary cirrhosis and 1 with Graves disease. 6 out of 11 were on hydrocortisone treatment at the time of immune dysfunction onset. The KC dose received and the length of treatment were variable. There were previous publications regarding the development of immune dysfunctions following CS remission including thyroiditis, sarcoidosis, SLE, arthritis, psoriasis... The applicant has discussed the implications of these dysfunctions, the possible relation with allergic adverse events and the need to include this information in the SmPC. Hypercortisolism, both exogenous and endogenous produce a depletion of immune system which could lead to infections and also to exacerbation of autoimmune disorders. Of note, reactivation of autoimmune diseases after normalization of cortisol levels regardless of the treatment used has been previously described. The explanation for these events could be the existence of a latent autoimmune process inhibited or reduced in intensity by hypercortisolism. Therefore, when cortisol levels normalise autoimmune disorders become evident.

Although this phenomenon occurs with any kind of treatment normalising cortisol levels, the applicant has included this information in section 4.4 of the SmPC. This is agreed by CHMP.

**Adverse events of special interest**

The most significant adverse effect during treatment with KC is *hepatotoxicity*.

Lewis and Zimmerman published an analysis of 33 cases of hepatic injuries associated with ketoconazole (Lewis, 1984) as an antifungal therapy. This was a retrospective review of 54 cases implicating ketoconazole as a cause of acute hepatic injury in the US that were reported to the FDA and to the manufacturer between July 1980 and January 1983. Of these 54 cases, 33 reports (including one fatal) were considered likely (i.e. probable or possible) cases of KC-related injury.

Lake-Bakaar, 1987 published a review of adverse event reports of hepatotoxicity possibly associated with ketoconazole used in the treatment of systemic fungal infections. Eighty two (82) reports of possible hepatotoxicity associated with the drug, including five deaths, were received. An analysis of the 75 cases that had been adequately followed up among these 82 reports of possible hepatotoxicity, suggested that 16, including 3 deaths, were probably related to treatment with the drug. Of the 16 cases of hepatotoxicity with a probable association to drug treatment, 11 patients (69%) were women. The mean (SD) age of the group was 57.9 (±13.1) years (range 36 to 79). The mean duration of treatment before the onset of symptoms of hepatitis was 61.2 (±5) days (range 5-195). The results of serum liver function tests suggested hepatocellular injury in 10 (63%); the rest showed a mixed pattern. In contrast, the results of histological examination of the liver often
showed evidence of cholestasis. There were three deaths. In two patients treatment had been continued after symptoms of hepatitis and jaundice had developed. The third patient seemed to be asymptomatic for two months after the drug had been stopped, severe hepatitis and liver failure developed later. The cause of clinically apparent ketoconazole-induced hepatotoxicity is unknown. However, it may correlate with the ability of ketoconazole to inhibit mammalian sterol synthesis. Acute liver injury is clearly idiosyncratic.

The retrospective, multicenter review of 200 patients treated by KC as a single agent for CD is the most recent, representative and comprehensive source of information to assess hepatic tolerance (Castinetti, 2014). Forty patients were treated with KC as a pre-surgical treatment. Mean initial KC dose in these patients was 585±242.4 mg/day; mean final dose was 755±284 mg/day. KC was given to 160 patients as a primary treatment because of contra-indication or refusal of surgery (n=32, 20%), and as a secondary treatment because of unsuccessful surgery (n=93, 58.1%), or in order to control hypersecretion while waiting for radiotherapy to be effective (n=35, 21.8%). In these patients, KC was initiated at a mean dose of 542.7±198.7 mg/day for a mean period of 40.1±147.7 months. At the last follow-up, mean final dose of KC was 714.1±273.7 mg/day (final vs. initial dose, p<0.0001).

Regular monitoring, every 7-15 days, of ASAT, ALAT and GGT was performed during the first treatment month, and then at each dose change. Patients had the usual co-morbidities, hypertension, hypokalemia and diabetes. Liver enzymes increases, ≤ 5N or > 5N, were observed in ~16% and ~2.5% of patients respectively occurring mostly within the first month of treatment.

Mild transient increases of less than 5-fold normal of liver enzyme levels were observed in 30 patients. Among the patients with increases of less than 5-fold normal for whom more details were available, authors reported one case with levels at 1.5 times the upper limit of normal (ULN), one case with 2 times the ULN, 6 cases with 3 times the ULN, 4 cases with 4 times the ULN and 3 cases with 5 times the ULN.

In this review, five patients (2.5%) had increases in excess of 5-fold normal. Among these, four patients presented a 5-10 fold increase and one patient, treated at a dose of 600 mg/day, had a 40 fold increase. This patient was also concomitantly taking alcohol and acetaminophen.

In all instance, liver enzyme levels returned to normal within 2-12 weeks after dose decrease (50% of cases) or withdrawal of KC (50% of cases). No fatal hepatitis was observed. Hepatotoxicity did not appear to be dose dependent.

The authors concluded that "a close follow-up of liver enzymes (once weekly) for 1 month after dose change could potentially avoid any risks of severe hepatotoxicity. All potential associated factors of hepatotoxicity, and abnormal liver enzyme levels detected before KC initiation should be taken into account before considering KC as a treatment. These results suggest that, first, in case of an increase in liver enzyme levels inferior to 5-fold to the ULN values, the dose should be decreased to at least 200 mg, while weekly surveillance is continued; and second, that treatment should be stopped if liver enzyme levels increase up to 5-fold normal values, with a close monitoring until normalization. Of note, as this was a retrospective study, monitoring of liver enzymes was not homogeneous across all the centers; each investigator thus decided to decrease the dose and follow closely (and stop in case of further increase) when there was a what was considered as moderate liver enzyme increase (i.e.
less than 5 times the ULN) as they considered that the benefits/risk balance was in favor of maintaining KC. As our study was not a prospective study primarily aiming at better defining this side effect, there is obviously no evidence that such an approach should be the preferred one in comparison with a systematic withdrawal when liver enzymes increase moderately”.

Study narratives regarding hepatotoxicity in CS

One case (Zöllner, 2001) of fatal liver failure in a 14 year-old girl with Cushing’s disease treated with 400mg/d KC for 56 days, post-surgery, has been reported. In contrast to this, there are six reports of paediatric patients with CS, aged from 4 months to 14 years, receiving KC therapy for up to 2 years with no hepatic side effects.

In a retrospective review of 38 patients with CD treated with KC 200-1200 mg/d at one centre in France for 1 week to 72 months (Castinetti, 2008), one patient experienced a five fold increase of GGT (normal AST and ALT) in the first week of treatment and KC 200 mg/day was stopped. Of the 33 patients continuing treatment transient hepatic adverse events were observed in four patients. Three patients experienced a moderate increase of GGT at the initiation of therapy (not exceeding 2-3 fold upper limit of normal) which spontaneously regressed at 3 months. One patient had AST and ALT levels of 8-fold ULN when the KC dose was increased to 1200 mg/day, this subsided after decreasing the dose to 1000 mg/day.

In a 54 patient study (Moncet, 2007) with KC 200 to 1200 mg/day, mean maintenance dose of 600 mg/d, transient subclinical hepatic injury developed in six patients (11%) after 15. days to 17 months of starting therapy. In four of these patients alterations in hepatic biochemical tests disappeared after switching to aminogluthetimide, while the other two were kept without enzyme blocking therapy.

In a study of 8 patients with Cushing’s disease (Mortimer, 1991) treated with KC 800 mg/d, two patients had transitory, mild, asymptomatic elevations of hepatic transaminases without significant increase in plasma bilirubin or alkaline phosphatase.

In a study of 34 patients (Sonino, 1991) treated with KC 600 mg/day (range 400 to 800 mg/day), a female patient aged 67 years with nodular adrenal hyperplasia experienced hepatotoxicity. After 4 days on KC she experienced abdominal pain (right upper quadrant) with markedly high ALT, AST, GGT and ALP, bilirubin was slightly elevated. Upon KC withdrawal, abdominal pain improved in 3 days and her liver functions became completely normal within 2 weeks. Asymptomatic liver function abnormalities also occurred in three patients (all females aged 47, 36 and 50 years), with transient elevation of ALT, AST and GGT values. In the patient aged 47 years, in whom KC treatment was subsequently resumed, liver functions remained within normal limits throughout treatment (overall period 3 years).

In one case report (Harinarayan, 1991) a 17 y female developed altered liver function tests on 22nd day when she was on a dose of 1200 mg/day. Liver function tests returned to normal 3 weeks after stopping KC and she was started again on KC.

In a study of 5 patients with Cushing’s disease (Angeli, 1985) treated with 600-800 mg/d, KC gastrointestinal disturbances and a rise in serum transaminase levels were reported in 1 patient. In a 14-patient study (Engelhardt, 1989), one patient showed signs of liver toxicity with GGT 580U/l, AST (GOT) 129U/l and ALT
(GPT) 254U/l (no normal ranges provided), this patient completed 3 months treatment with KC at 600mg/day. Increased transaminases were observed in 3/25 patients (Weber, 1989) treated with 600mg/day KC from 2 to ~36 weeks. Minor and transient changes in liver enzymes were observed in two patients and KC was discontinued in one case where increasing transaminases were found in association with considerable alcohol consumption. In another study (Valassi, 2012), an increase in transaminases was observed in 3 out of 17 patients on KC monotherapy but none of the 22 patients on combination therapy with metyrapone. In one patient there was a four-fold elevation after 1 week which led to the discontinuation of KC. In the other two patients the elevation was mild, KC dose was reduced in one case and temporarily suspended in the other. In a study of 24 patients treated with KC, 12 patients in monotherapy and 12 patients with associated antihypertensive drugs, one patient had transient liver function abnormalities (Fallo, 1993). Increases in transaminases but no symptomatic worsening of liver function were observed in patients treated with a combination of KC, metyrapone and mitotane (Kamenicky, 2011). Increases in AST levels were observed in 2 patients, ALT in 3 patients and there was a significant elevation in GGT in 9 patients (p=0.002). Liver toxicity led to a reduction in the KC dose in two patients and to withdrawal of this drug in one patient.

In study of 9 patients with Cushing’s disease (Vilar, 2010) treated with cabergoline 3mg/week and KC 200-400 mg/d, mild transient elevation of transaminases was found in one patient (11.1%) after the addition of KC.

Increases in hepatocellular enzymes have been recorded in five case reports. In one case increases were transient and did not result in the discontinuation of KC while in the other four KC was discontinued and the follow-up in two reports showed levels had returned to normal.

The mechanism of hepatotoxicity has been discussed along the available literature. Some articles supported the theory of cytotoxicity mediated by KC primary metabolite (N-deacetyl ketoconazole), using post-natal rat hepatocytes, Rodriguez and Acosta (Rodriguez and Acosta, 1997b) showed that DAK was more cytotoxic than ketoconazole, suggesting that DAK may, at least in part, be responsible for the hepatotoxicity associated with ketoconazole. Other articles concluded that ketoconazole-hepatotoxicity might be due to direct covalent binding of the parent compound to hepatic proteins and the binding of FMO-generated metabolites to both hepatic proteins and GSH (Rodriguez and Buckholz, 2003). Another mechanism investigated for the hepatotoxicity of ketoconazole involved reduction of bile acid synthesis that was observed in vivo and in vitro (Princen et al, 1986; Kuipers et al, 1989; Azer et al, 1995).

Some other authors suggested dose-independent hepatotoxicity and an immune-mediated mechanism (Chin-Lin Lin et al., 2008).

The mechanism of KC hepatotoxicity still remains uncertain. The majority of cases of drug-induced liver injury (DILI) are related to idiosyncratic reactions. The principal characteristic of this type of reaction is the apparent unpredictability of the liver injury in humans. The latent period between exposure to the drug and the sensitivity reaction is variable, although it is generally about one to three months. A threshold dose may be required. Although the parent compound may directly lead to idiosyncratic DILI, it is most often a toxic metabolite that is at fault. Idiosyncratic drug toxicity may be either nonallergic (metabolic) or immunologic/allergic; however, overlap likely exists. Some other authors include KC in the group of metabolic DILI, probably due to genetically
determined aberrant metabolism of the drug in susceptible patients. The duration of exposure before the development of toxicity varies from weeks to months, and reactions can develop several weeks after drug discontinuation. The disease occurs within many days to weeks after rechallenge. Features of hypersensitivity are absent. It has been hypothesized that local accumulation of toxic metabolites results in covalent binding of the metabolite to cellular proteins, lipids, and DNA.

The applicant reviewed hepatotoxicity along the literature. Castinetti et al., reported patients with liver enzyme increases ≤5ULN in 16% patients and >5ULN in 2.5%. Liver enzymes returned to normal levels after KC withdrawal or after dose decrease.

In conclusion, the CHMP agreed that the hepatotoxicity has been adequately documented in Cushing syndrome at the posology used (200-1200mg/d). From the publications previously discussed, the higher dose used in Cushing’s syndrome, does not seem to expose to an additional hepatotoxicity risk. The higher dose used has been adequately documented and the risk is considered manageable with an adequate monitoring of liver function prior, during treatment and regularly in case of increase of dose.

Besides, contra-indication in patients with acute or chronic liver disease and/or if liver enzymes are above 2ULN has been implemented. The CHMP also requested to increase the liver monitoring initially proposed by the applicant, in particular by weekly measurement of liver function during one month and whenever the dose was increased as well as recommendation of monitoring in patients with long-term treatment. Strict criteria for stopping the treatment in case of increase in liver enzymes are also clearly indicated for the prescriber and the patient.

The agreed monitoring is summarized below:

**Monitoring of liver function**
Liver enzymes should be monitored in all patients receiving Ketoconazole HRA. Due to the risk of serious hepatic toxicity, close follow-up of patients is required.

**Before starting the treatment, it is mandatory:**
- to measure liver enzymes (ASAT, ALAT, gammaGT and alkaline phosphatase) and bilirubin
- to inform the patients about the risk of hepatotoxicity, including to stop the treatment and to contact their doctor immediately if they feel unwell or in the event of symptoms such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. If these occur, treatment should be stopped immediately and liver function tests should be performed.

Due to the known hepatotoxicity of Ketoconazol, the treatment should not be initiated in patients with liver enzymes levels above 2 times the upper limit of normal (see section 4.3).

**During the treatment:**
- close clinical follow-up should be undertaken
- measurement of liver enzymes (ASAT, ALAT, gamma GT and alkaline phosphatase) and bilirubin, should be performed at frequent intervals:
  - weekly for one month after initiation of the treatment
  - then monthly for 6 months
  - weekly during one month whenever the dose was increased.
In the case of an increase in liver enzymes of less than 3 times the upper limit of normal, more frequent monitoring of liver function tests are requested and the daily dose should be decreased by at least 200 mg.

In the case of an increase in liver enzymes equal to or greater than 3 times the upper limit of normal, the treatment should be stopped immediately and should not be reintroduced due to the risk of serious hepatic toxicity. In addition, the treatment should be discontinued without any delay if clinical symptoms of hepatitis develop.

**In case of long term treatment (more than 6 months)**

Although hepatotoxicity is usually observed at treatment initiation and within the first six months of treatment, monitoring of liver enzymes should be done under medical criteria. As a precautionary measure, in the case of a dose increase after the first six months of treatment, monitoring of liver enzymes should be repeated on a weekly basis for one month.

**Adrenal insufficiency (AI)**

AI is commonly observed on KC when used to treat CS, as this is the case for other CS therapies, either if there is an overtreatment or in the situations of stress (especially infection). In the FReSKO study (Castinetti, 2014), 10/190 patients (5.4%) presented with clinical and biochemical AI, the KC dose ranged from 400 to 1200 mg/day. Three of these patients were being treated with a block and replace strategy: they had moderately increased initial UFC (1.1 to 3-fold upper limit of normal) and normal UFC on KC. However, the dose was increased by 200 mg/day (up to 1200 mg/day) and hydrocortisone was added (20 mg/day).

Ten out of 54 patients (18.5%) experienced AI (Moncet, 2007) five to 90 days after starting treatment with KC at doses of 400-800 mg/d, four patients before day 10. The patients recovered either on reducing the KC dose (n=4) or by reducing the dose and the addition of glucocorticoid treatment (n=6).

In a study of 8 patients with Cushing’s disease (Mortimer, 1991) treated with KC 800 mg/d, one patient developed mild symptoms of glucocorticoid insufficiency which did not require treatment.

AI with clinical signs (nausea, vomiting and persistent abdominal discomfort) was observed in one patient (Dash, 1990a) after 7 days on KC 800 mg/day, treatment was stopped. One out of 8 patients (Tabarin, 1991) developed mild systemic adrenal insufficiency after 1 month on KC 600 mg/day, hypoadrenalism disappeared spontaneously within 24h after KC withdrawal. KC was restarted at 400mg/day with 20 mg/day hydrocortisone due hypercortisolism and treatment continued for at least 6 months. AI was observed in one patient treated with 1200 mg/day KC (Chou, 2000) and the symptoms subsided on reducing the dose to 400 mg/day.

AI was observed in 4/11 patients treated with a combination of KC, metyrapone and mitotane and attributed to inappropriate glucocorticoid substitution (Kamenicky, 2011). Dose dependent hypocortisolism was observed in two out of 17 patients treated with KC alone (Valassi, 2012). Hypoadrenalism episodes documented by low plasma cortisol levels were reported in three out of 15 patients with ectopic ACTH syndrome (Winquist, 1995). One of these patients was treated with KC for 3 years had 2 episodes of hypoadrenalism associated with symptoms of respiratory infection. At the earliest sign of infection KC therapy was interrupted, maintenance corticosteroid dose increased and antibiotic therapy begun.

Therefore AI is related to the pharmacodynamic effects of KC and may be due to over treatment or to the combination of several steroidogenesis inhibitors or to a relative cortisol deficiency in situations of stress. The
occurrence of hypoadrenalism seems related in part to the level of hormonal control. Main presenting symptoms such as fatigue, anorexia, and weight loss are non-specific, thus AI diagnosis is sometimes delayed unless a periodic monitoring of cortisol levels is set up and the patient is educated. AI due to overtreatment may be prevented by careful monitoring of cortisol levels, adequate KC dose-adjustment and transitory KC withdrawal in case of suggestive AI symptoms.

In patients with good hormonal control, the cortisol response to stress/infection may be impaired due to an increased glucocorticoid demand (for patients on a block-only regimen) and/or due to an insufficient glucocorticoid replacement (for the patients treated with a block-and-replace regimen).

The applicant provided data based on at least 40 patients with adrenal insufficiency or hypocortisolism during KC treatment. This adverse event could be considered as the second most relevant. It appears not to be associated with a specific dose and develops between 5-90 days after initiation of treatment, although cases after 3 years of treatment have been reported.

Therefore, recommendations for the prescribers about monitoring of adrenal function are included in the proposed SmPC, despite the fact that CS patients are usually managed in experts centers who are used to deal in routine with the endocrine workup of the pituitary-adrenal function. This is acceptable by the CHMP.

Due to the seriousness of this adverse event, it is considered that the patient should be warned regarding the symptoms in order to inform his doctor, as described in the package leaflet. The warnings included in the SmPC are also acceptable.

**Gastrointestinal events**

In the FReSKO study (Castinetti, 2014), 25/190 patients (13.1%) presented with gastrointestinal complaints, the KC dose ranged from 400 to 1,200 mg/day. In a retrospective review of 38 patients with Cushing’s disease (Castinetti, 2008), KC 200 mg/day was stopped in the first week of treatment in 5 patients due to nausea and diarrhea. Two patients experienced nausea and diarrhea when increasing the KC dose to 1,200 mg/day.

Two out of 54 patients (3.7%) experienced moderate digestive intolerance and improved after 2 months treatment with KC (Moncet, 2007). In a 34 patient study (Sonino, 1991), gastrointestinal side-effects occurred in three patients treated with KC 400 to 800 mg/day. One dyspepsia, one abdominal discomfort and episodic diarrhea associated with pruritus and one abdominal discomfort and episodic diarrhea. A fourth patient with adrenal carcinoma was treated with 1000 to 1200 mg/day KC for 3 out 6 months therapy and experienced diffuse abdominal pain and diarrhoea on the 1200 mg/day dose.

In a study of 24 patients treated with KC, 12 patients in monotherapy and 12 patients with associated antihypertensive drugs, one patient had dyspepsia (Fallo, 1993).

Transient nausea and vomiting were observed in 7/11 patients treated with a combination of KC, metyrapone and mitotane (Kamenicky, 2011).
When KC was used as an antifungal the most frequently reported adverse events were of gastrointestinal origin, i.e. nausea and vomiting. The applicant provided information of this AE based on around 50 patients. Most of gastrointestinal symptoms were mild and transient. These adverse events have been previously described as the main reason for discontinuation. In the literature referring to CS treatment, it is difficult to assess the reason for discontinuation. Gastrointestinal disorders are included in section 4.8 and are acceptable.

**Pruritus and rash, gynecomastia and hypogonadism** were also assessed in different publications, although the number of adverse events was low.

**Other relevant adverse events described were hyperkalemia and QTc prolongation.**

Taking into account the mechanism of action of KC hyperkalemia would be an expected adverse event. In the literature, some patients presented hypokalemia and required oral potassium supplementation or even spironolactone.

The applicant has further discussed the mechanism of QT prolongation and increase risk of TdP. There are different mechanisms which may lead to this severe adverse event. Therefore, is essential to state in the SmPC all the information necessary to detect it as early as developed and consider ECG monitoring. The detailed information is provided below;

Ketoconazole and other azole antifungals (for example, fluconazole and miconazole) have been associated with acquired Long QT Syndrome (LQTS) and ventricular arrhythmias (Khazan, 2002; Roden, 2001; Han 2011 and Kikuchi, 2005)

Ketoconazole can prolong the QT interval and increase risk of TdP by several mechanisms:

- **Drug-drug interaction** by inhibiting multiple cytochrome P450 enzymes in the liver and gastrointestinal tract (Dresser, 2000 and Zhang, 2002) which is the main potential cause for QT prolongation. Ketoconazole’s arrhythmogenic mechanism is likely to involve a rise in the plasma concentrations of QT interval-prolonging drugs that use the same metabolic pathway (Tonini, 1999). Tsai has described a TdP episode with concomitant use of astemizole and ketoconazole (Tsai, 1997) and Zimmermann et al. a TdP episode with concomitant use of ketoconazole and terfenadine (Zimmermann, 1992). A pharmacokinetic interaction between KC and domperidone that lead to QT prolongation was also described in healthy volunteers by Boyce (Boyce, 2011). Chaikin described a pharmacokinetic interaction between ketoconazole and ebastine/loratidine with modest increases of QT (Chaikin 2005).

- **Direct effect** of ketoconazole and miconazole on ventricular conduction have been reported to directly block human Ether-à-go-go-Related Gene (hERG) currents (Kikuchi, 2005 and Takemasa, 2008). Moreover, one report has shown that ketoconazole directly inhibits the hERG current and reduces the surface membrane expression of hERG channels by disrupting channel protein trafficking (Takemasa, 2008). Please refer to module 2.4 and module 2.6.2 for further preclinical and clinical data presentation and discussion.

- **Ketoconazole** is to be used in Cushing’s syndrome patients, a population who has a number of characteristics associated with an increased risk of LQTS: female predominance, hypokalemia, polymedication, cardiovascular comorbidity.

Due to the coexistence of these three mechanisms and considering the ketoconazole doses that are used in Cushing’s syndrome, despite the rarity and the non-fatal nature of clinical events that have been published, the CHMP agreed to recommend screening for QT prolongation before initiating treatment and on treatment is acceptable. (see below)
Moreover, if an agent known to increase QTc interval is introduced in a ketoconazole-treated patient, it is advisable to monitor ECG.

"Monitoring of the QTc interval"

"Monitoring for an effect on the QTc interval is advisable and ECG should be performed prior to the start of Ketoconazole HRA, within one week after the beginning of the treatment and as clinically indicated thereafter. In case of co-administration of an agent known to increase QTc interval (see section 4.5), ECG monitoring is recommended."

Doses of ketoconazole are adjusted to each patient with specific comorbidities and concomitant medications with the goal to normalize cortisol levels. The applicant therefore recommends performing a second ECG at steady state i.e. within one week of treatment initiation in order to detect a QTc prolongation promptly if any.

These recommendations are acceptable and in line with the recent recommendation of Jardin: "Of the population receiving QTc Meds, only a small portion had a baseline ECG, identifying a large population at risk of QTcP without appropriate monitoring " (Jardin 2014).

It is not clear if ketoconazole per se or interactions with other drugs when it is co-administered are responsible of QTc prolongation.

In the clinic, ketoconazole has mainly been shown to be pro-arrhythmic with concomitant use of QT interval-prolonging drugs. Prolongation of QTc has been reported in subjects following concomitant intake of ketoconazole (200 mg 12-hourly) and domperidone (10 mg, at 4h intervals for 7 days (Boyce, 2010), astemizole (Tsai, 1997) and terfenadine (Zimmermann, 1992).

Ketoconazole monotherapy for treatment of fungal infection (200 mg, b.i.d for five days) in a woman with coronary artery disease was reported to induce a markedly prolonged QT interval and torsades de pointes (TdP). Her QT interval returned to normal upon withdrawal of ketoconazole. Genetic study did not find any mutation in her genes that encode cardiac IKr channel proteins. The authors postulated that by virtue of its direct blocking action on IKr, ketoconazole alone may prolong QT interval and induce TdP and recommended attention when ketoconazole is administered to patients with risk factors for acquired long QT syndrome (Mok, 2005).

In conclusion, the CHMP aged that in case of co-administration with a pro-arrythmic agent ECG monitoring is advisable as recommended in the SmPC.

Other Adverse Events

Other adverse reactions have been reported in studies where ketoconazole was administered in combination with metyrapone and/or other steroidogenesis inhibitors. Some of these were also observed in studies and case reports where ketoconazole was administered as monotherapy.

Two case reports (Leal-Cerro, 1989) and two studies reported worsening hypertension in some patients (Engelhardt, 1991; Valassi, 2012;). One of these studies reported 30 cases of uncontrolled/worsening hypertension which was managed with antihypertensive medications (Valassi, 2012). But it is not possible to determine whether the patients were on metyrapone alone, or on ketoconazole alone, or on combination therapy with ketoconazole in this study. There were two case reports of hypertension in patients treated with ketoconazole alone at 800 mg/d (Leal-Cerro, 1989).
Headache was reported in 1/17 on ketoconazole alone, associated with hypertensive crisis, and 3/22 on ketoconazole or metyrapone (Valassi, 2012).

Dizziness was reported by one patient out of 190 (0.6%) in the FReSKO study (Castinetti, 2014) at a ketoconazole dose of 1,200 mg/day. Dizziness and confusion were observed in 1/11 patients treated with a combination of ketoconazole metyrapone and mitotane (the concomitant plasma mitotane concentration was 15.3 mg/L) (Kamenicky, 2011).

Leg oedema was observed in two patients out of 190 (1%) in the FReSKO study (Castinetti, 2014). In a study of patients treated with ketoconazole or metyrapone alone or in combination, 9 cases of onset of peripheral oedema were reported (Valassi, 2012), none of these were on ketoconazole monotherapy.

Hypokalaemia can occur spontaneously in CS. In a study of 11 patients treated with a combination of, ketoconazole, metyrapone and mitotane (Kamenicky, 2011), all patients initially experienced hypokalaemia. The lowest potassium concentration during treatment was 2.9 mmol/l (range 2.6-3.5 mmol/l). Nine patients required oral potassium supplementation, 8 also received spironolactone. A long term improvement in plasma potassium concentrations occurred during treatment.

2.6.4. Serious adverse events and deaths

The majority of deaths occurring during treatment with KC are attributable to the underlying condition. An exception is the case of a 14 year-old girl with Cushing’s disease treated with 400mg/d KC for 56 days, post-surgery who died of liver failure (Zöllner, 2001). This has been adequately clarified by the Applicant. The other deaths occurred in patients with aggressive tumours (i.e EAS or adrenal tumour) who despite the treatment with chemotherapy plus ketoconazole did not control the extension of the tumour. Although it is difficult to prove or discard the relation with ketoconazole treatment it is more probable that the tumor per se could be the responsible of the deaths.

There was one serious case report (Brito, 2012) of iatrogenic heart block following treatment with KC. An 83 year-old female with a history of hypertension, treated chronically with verapamil 360 mg/day, was diagnosed with CS. She was administered KC 900 mg/day (300 mg tid) and 2 days later the dosage was increased to 1,200 mg (300 mg qid). On the third day, the patient developed severe hypotension, bradycardia and altered mental status. Electrocardiogram (ECG) showed complete heart block with a slow junctional escape rhythm. Verapamil and KC were discontinued immediately. The next day the patient recovered completely. The authors conclude that the case strongly suggests a possible drug-drug interaction.

2.6.5. Laboratory findings

No extrinsic factors have been identified in these studies that would preclude the use of KC. The most frequent laboratory finding in patients treated with KC was increase in liver enzymes. However, hypokalemia has been found in some patients and should be included in section 4.8 of the SmPC.
2.6.6. Safety in special populations

KC has been administered to patients in all age groups. For the treatment of CS, a wide dosage range is proposed and the dosage used, as indicated in the literature review, is individually adjusted on the basis of the cortisol levels achieved (in serum/plasma and/or urine) in each patient, which needs to be reviewed periodically, and on the basis of the clinical tolerance.

KC is contraindicated in pregnant women due to its teratogenicity. It is to be noted that four healthy babies have been delivered after KC treatment for CS during pregnancy.

Furthermore, since KC is excreted in the milk; mothers who are under treatment should not breast-feed whilst being treated. This is appropriately reflected in the SmPC. (section 4.3)

A discussion on whether the safety profile is similar in special populations (i.e children, elderly, hepatic and renal impairment) to the general population or not has been provided by the Applicant and no new safety concerns have been identified for these populations apart from the possibility of a higher rate of hepatotoxicity in adolescents. Two out of twenty-four paediatric patients developed hepatic injury (i.e 8.3%). Although the available data are scarce, the wording proposed by the applicant for section 4.8 in order to describe the safety profile in this group of age is agreed upon.

2.6.7. Safety related to drug-drug interactions and other interactions

KC 200 mg tablets have the potential for clinically important drug interactions and co-administration is contraindicated with a range of CYP3A4 substrates. The information provided is essentially the same as in the UK Nizoral SmPC and was used as the basis for the Product Information for the current indication. There is no evidence of any specificity regarding drug interactions in CS but the following paragraph describes situations of particular interest in CS.

In the context of CS treatment, the following drug interactions are of particular interest:

- Lipid lowering drugs and mainly HMG-CoA inhibitors may be used in the treatment of patients with CS to reduce their cardiovascular risk. Simvastatin, lovastatin and atorvastatin are metabolized through CYP 3A4 and thus their plasma concentrations are increased in KC-treated patients, with the risk of myopathy including rhabdomyolysis and thus are contra-indicated. In case a statin is needed, pravastatin and rosuvastatin are preferable as they are excreted unchanged and their plasma concentrations are not significantly increased by CYP3A4 inhibitors (Greenman, 2010).

One study specifically evaluated the combination of KC 200 mg every 12 h and rosuvastatin 80 mg (the highest studied dose) in healthy subjects. The geometric mean plasma concentrations of rosuvastatin over time were similar when rosuvastatin was coadministered with KC and placebo. KC did not produce any change in rosuvastatin pharmacokinetics, therefore, coadministration of KC and rosuvastatin is unlikely to increase the risk of toxicity of rosuvastatin. (Cooper, 2003).

However as statins are BCRP substrate, we recommend to separate the administration of the statin and KC by 2 hours.
As pasireotide (Signifor, PI) has been shown to prolong the QT interval on the ECG, we have advised in the proposed SmPC against concomitant use since the combination can potentially lead to QT prolongation in patients with known cardiac rhythm disorders.

Metyrapone is the most frequent associated therapy to KC in the management of CS. When the 3 steroidogenesis inhibitors (mitotane 3.0-5.0 g/day plus metyrapone 3.0-4.5 g/day plus KC 400-1200 mg/day) were concomitantly used at an initial high dose in patients with a very severe CS (Kamenicky, 2011), acute AI was observed in 4/11 patients and was due to inappropriate glucocorticoid replacement therapy during episodes of vomiting. No particular safety issue was mentioned. No symptomatic worsening of liver function was observed during combination therapy, although increase in liver enzymes led to the reduction of KC dose in 2 patients and to withdraw it in one. The doses were maintained in the other patients.

There is no evidence to suggest that the KC dose has to be increased above the range used in monotherapy in combination with other steroidogenesis inhibitors (metyrapone, mitotane), the somatostatin analogue pasireotide and the dopamine receptor agonist cabergoline. However as mitotane is a CYP 3A4 inducer and thus could affect the metabolism of KC, this information was included in section 4.5 of the proposed SmPC interaction with other medicinal products and other forms of interaction.

**Discontinuation due to AES**

The information on treatment discontinuations due to adverse events is usually reported as part of prospective controlled clinical trials. In the case of this application, this information is either none existent or incomplete as data are based on retrospective studies.

It is agreed with the Applicant that information on discontinuation due to AEs that come from literature is difficult to assess. Castinetti et al. reported a high percentage of discontinuation although the description of adverse events which lead to such discontinuations is not provided by the author and it is not known the percentage of patients who decided to re-start treatment. The conditions in which ketoconazole treatment should be stopped have been described in section 4.4 of the SmPC and are acceptable.

**2.6.8. Discussion on clinical safety**

The European Medicines Agency’s Committee on Medicinal Products for Human Use (CHMP) recommended following a referral under Article 31 of Directive 2001/83/EC that the marketing authorisations of oral ketoconazole-containing medicines should be suspended throughout the European Union (EU) (26 July 2013, EMA/458028/2013) as the benefit of oral ketoconazole in the treatment of all antifungal indications do not outweigh the risks.

In its conclusion the following conclusions were made:

- The mechanism of hepatotoxicity has not been elucidated and some uncertainties still remain. Some authors support the theory of a metabolic mechanism. On the other hand, some others advocate for an autoimmune mechanism.
- Although hepatotoxicity is considered a class effect of azole antifungals, there has been more frequently reported associated to KC treatment. Hepatotoxicity was reported with the KC dose use as an antifungal (daily dose 200 mg), the risk of hepatotoxicity with KC is higher than with other antifungals and the onset of hepatotoxicity with ketoconazole usually occurs between 1 and 6 months after initiation of treatment.

- The most significant safety issue during treatment with ketoconazole is hepatotoxicity, primarily of the hepatocellular type. Fatal cases have been reported particularly when treatment is continued despite liver enzyme elevation.

The doses proposed for treatment of Cushing syndrome will be higher than the ones used to treat fungal infections, hepatotoxicity seems to be not fully predictable and its mechanism remains not well-known.

As discussed before, in the treatment of CS, mild (≤ 5N) and major (> 5N) increases in liver enzymes were observed in ~16% and ~2.5% of patients respectively occurring mostly within the first month of treatment and up to 6 months. However, liver enzyme levels returned to normal within 2-12 weeks of dose decrease or withdrawal of KC. Thus the higher dose used in Cushing syndrome (200-1200mg/d) would not be considered as an additional concern.

Nevertheless, it appears that most of the cases occur at the beginning of treatment and within the first month. In case of liver enzymes elevation, ketoconazole is stopped or the dose is reduced depending on the severity of the liver enzymes rise.

Long-term treatment with ketoconazole does not seem to increase the risk of hepatotoxicity. However, due to the majority of cases of drug-induced liver injury are related to idiosyncratic reactions, the CHMP suggest to add a warning to the SmPC for treatments lasting longer than six months.

Recent reviews of CS treatment suggest that the hepatotoxicity of ketoconazole can be managed by appropriate medical/endocrinology specialist when the SmPC is followed and contraindications are respected; concurrent use of other potential hepatotoxic drugs is avoided and liver enzyme monitoring is performed at treatment initiation and throughout treatment for at least the first 6 months.

In conclusion, considering the posology used (200-1200mg/d), the CHMP agreed that the hepatotoxicity has been adequately documented in Cushing syndrome. The risk is considered manageable with an adequate monitoring of liver function prior, during treatment and regularly in case of increase of dose.

Contraindication in patients with acute or chronic liver disease and/or if liver enzymes are above 2ULN has been implemented. The CHMP also requested to increase the frequency of the liver monitoring initially proposed by the applicant, in particular by weekly measurement of liver function during one month and whenever the dose was increased as well as recommendation of monitoring in patients with long-term treatment. Strict criteria for stopping the treatment in case of increase in liver enzymes are also clearly indicated to the prescriber and the patient.

The possibility of a higher rate of hepatotoxicity in adolescents is an additional safety issue that deserves to be mentioned. Although only two out of twenty-four paediatric patients developed hepatic injury (i.e 8.3%) the CHMP agree with the applicant's proposal for section 4.8 of the SmPC.
In conclusion, hepatotoxicity remains a concern that needs to be followed up post approval and the CHMP requested the applicant to collect post approval data through a registry and submit annually results for review.

Ketoconazole is a substrate and potent inhibitor of CYP3A4. Ketoconazole may decrease the elimination of drugs metabolised by CYP3A4 thereby increasing their concentrations. Inducers of CYP3A4 may decrease the plasma concentration of ketoconazole. Other inhibitors of CYP3A4 may increase plasma concentration of ketoconazole. The proposed Product Information is based on the Nizoral tablets SmPC and provides detailed information for prescribers and contraindications of a number of concomitant treatments. Guidance is also provided in the proposed Product Information to advise for use of statins with no major CYP3A4 interaction potential.

The risk of QTc prolongation with ketoconazole is low and has mainly been shown with concomitant use of QT interval prolonging drugs which should therefore be avoided as indicated in the proposed Product Information. The applicant has further discussed that different mechanisms could cause QT prolongation and increase risk of TdP. The product information includes this information.

Adrenal insufficiency (AI) due to overtreatment may be prevented by careful monitoring of cortisol levels, adequate dose-adjustment or transitory ketoconazole withdrawal and patients’ education. KC can in some cases induce hypogonadism resulting in erectile dysfunction and gynecomastia.

Appropriate information is provided with monitoring of adenal insufficiency in section 4.4.

Other AE associated with ketoconazole use include nausea, vomiting, abdominal pain, pruritis/rash, dizziness and headache (Nizoral SmPC UK, 2010).

Increased blood pressure and oedema were also reported occasionally with ketoconazole.

Ketoconazole should not be used during pregnancy as there have been reports of exposure to ketoconazole during pregnancy and in all four cases healthy infants were delivered.

In general, when contraindications are respected, a close monitoring is undertaken under the supervision of endocrinology/internal medicine specialists, ketoconazole appeared to be well tolerated, for short and long-term treatment of CS.

Reactivation of autoimmune diseases after normalization of cortisol levels regardless the treatment used has been previously described. The explanation for these events could be the existence of a latent autoimmune process inhibited or reduced in intensity by hypercortisolism thereafter. When cortisol levels are normalised autoimmune disorders become evident.

Although this phenomenon can occur with any kind of treatments which normalise cortisol levels, the applicant has proposed to include this information in section 4.4 of the SmPC. This is agreed by the CHMP.

2.6.9. Conclusions on clinical safety

The applicant has reviewed the literature and has provided a thorough review of the safety of ketoconazole in the treatment of Cushing’s syndrome. Hepatic adverse reactions are of concern, especially considering the referral under Article 31 od Directive 2001/83/EC and the opinion of the CHMP, followed by the EC Decision, that
the benefit risk ratio was negative for the use of ketoconazole in the treatment of fungal infections. However, the claimed indication in Cushing’s syndrome is associated with an unmet medical need and serious comorbidities compared to the antifungal infection. Based on the data submitted, hepatotoxicity seems to be not fully predictable and its mechanism remains not well-known. Overall the publications submitted for the CS indication describe that despite the higher dose used in Cushing syndrome, the hepatotoxicity appears manageable and reversible if the treatment is interrupted. Therefore, hepatotoxicity did not appear to be dose dependent, thus the higher dose used in Cushing syndrome (200-1200mg/d) would not be considered as an additional concern.

It appears that most of the cases occur at the beginning of treatment and within the first month. In case of liver enzymes elevation, ketoconazole is stopped or the dose is reduced depending on the severity of the liver enzymes rise.

Recent reviews of CS treatment suggest that the hepatotoxicity of ketoconazole can be managed by appropriate medical/endocrinology specialist when the SmPC is followed and contraindications are respected; concurrent use of other potential hepatotoxic drugs is avoided and liver enzyme monitoring is performed at treatment initiation and throughout treatment for at least the first 6 months.

Long-term treatment with ketoconazole does not seem to increase the risk of hepatotoxicity. However, as the majority of cases of drug-induced liver injury are related to idiosyncratic reactions, the CHMP suggest to add a warning to the SmPC for treatments lasting longer than six months.

In conclusion, considering the posology used (200-1200mg/d), the CHMP agreed that the hepatotoxicity has been adequately documented in Cushing syndrome. The risk of hepatic adverse reactions can be managed or minimised by ensuring prescription is under the supervision of relevant specialists, and with an adequate monitoring of liver function prior, during treatment and in case of dose increase. Adequate contra indication and stopping rules have been mentioned in the SmPC.

There is also a need for adrenal insufficiency monitoring and ECG monitoring during treatment. Regarding Drug Drug interactions, there are described and detailed in section 4.5 and where necessary warning and contraindications have been introduced.

In conclusion the safety profile and concerns related to the use of ketoconazole is adequately documented and are acceptable in the context of the treatment of Cushing Syndrome.

Nevertheless, given the above concerns related to safety, the CHMP considers necessary to continue to investigate the safety profile of ketoconazole in routine daily practice and a Post Authorisation safety study is recommended by the PRAC and agreed with the CHMP.

The CHMP considers the following measures necessary to address issues related to safety:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
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<tbody>
<tr>
<td>A Post Authorisation safety study : Multi-country, observational registry to</td>
<td>Yearly</td>
</tr>
<tr>
<td>collect clinical information on patients with Cushing Syndrome patients</td>
<td>submission</td>
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<tr>
<td>exposed with Ketoconazole (preferably using the existing European Registry</td>
<td></td>
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<tr>
<td>on Cushing’s syndrome (ERCUSYN) registry where feasible ), to assess drug</td>
<td></td>
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<tr>
<td>utilization patterns and to document the safety (eg</td>
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In addition, the PRAC and CHMP agreed on the need to inform selected prescribers prior to launch via a Dear Health Care professional Letter highlighting specific recommendations related to the safety profile of ketoconazole (eg hepatotoxicity).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP v1.3 as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Hepatotoxicity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td></td>
<td>QT/QTc interval prolongation/Torsade de Pointes due to interaction of ketoconazole with CYP3A4 substrates</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Use in pregnancy and lactation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>QT/QTc interval prolongation/Torsade de Pointes</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td></td>
<td>Immune dysfunctions following Cushing’s Syndrome remission</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing information</th>
<th>Use in paediatric population under the age of 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety in the elderly</td>
</tr>
<tr>
<td></td>
<td>Long-term use</td>
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</tbody>
</table>
**Pharmacovigilance plan**

<table>
<thead>
<tr>
<th>Study/activity Type, title and category (1-3)</th>
<th>Objectives</th>
<th>Safety concerns addressed</th>
<th>Status (planned, started)</th>
<th>Date for submission of interim or final reports (planned or actual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCUSYN, European web-based registry</td>
<td>To provide descriptive data (if any) on the use of ketoconazole in Cushing syndrome population, through the European Registry on Cushing’s syndrome (ERCUSYN). The aims of ERCUSYN are to gather data at a European level on clinical features in patients with Cushing’s syndrome of all causes (except in adrenal cortical carcinoma).</td>
<td>Hepatotoxicity QT/QTc interval prolongation/Torsade de Pointes QT/QTc interval prolongation/Torsade de Pointes due to interaction of ketoconazole with CYP3A4 substrates</td>
<td>Planned</td>
<td>The date for the submission of the results of the feasibility study of adding safety items into the ERCUSYN database for ketoconazole-treated patients will be within 3 months after the EC Decision. In case of positive results the due date for the submission of the study protocol will be within 3 months after the submission date</td>
</tr>
<tr>
<td>Study/activity Type, title and category (1-3)</td>
<td>Objectives</td>
<td>Safety concerns addressed</td>
<td>Status (planned, started)</td>
<td>Date for submission of interim or final reports (planned or actual)</td>
</tr>
<tr>
<td>--------------------------------------------</td>
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<tr>
<td>Named patient basis program in France (ATU de cohorte)</td>
<td>To further characterize the risk in terms of frequency, symptoms in a real life use, potential risk factors, and consequences.</td>
<td>Hepatotoxicity QT/QTc interval prolongation/Torsade de Pointes</td>
<td>Started on 23 June 2014</td>
<td>The study protocol is actually already available since the study has started in June 2014, the study protocol can therefore be submitted upon request. The Applicant proposes to submit to the Agency a study report on 27 February 2015 covering the study period from June 2014 to December 2014 and a second study report on 25 September 2015 covering the period from January 2015 to June 2015 as well as cumulative data.</td>
</tr>
</tbody>
</table>
## Risk minimisation measures

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>Section 4.2 on posology and method of administration recommends dose adjustments and monitoring of liver enzymes in order to prevent the effects associated with this risk. Related contraindications are presented in section 4.3. Special warnings and precautions for use are stated in section 4.4. Interactions with other medicinal products and other forms of interaction relevant to this risk are mentioned in section 4.5. Undesirable effects observed in published literature are included and listed in section 4.8. Section 5.1 on pharmacodynamic properties informs that no hepatotoxicity case was observed in association with ketoconazole use in ectopic ACTH syndrome. Section 5.3 summarises the preclinical safety data relative to the risk of hepatotoxicity. Prescription only medicine and prescription by specialists.</td>
<td>A targeted DHPC with the aim of raising the awareness among prescribers about the exact time intervals that liver function tests are to be performed according to the SNrPC.</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Section 4.2 on posology and method of administration recommends dose adjustments in case of adrenal insufficiency. Monitoring of adrenal function is advised in section 4.4. Section 4.5 on the interaction with other medicinal products and other forms of interaction informs that bioavailability of ketoconazole may increase upon its administration with potent inhibitors of CYP3A4 and therefore patients should be monitored closely for signs and symptoms of adrenal insufficiency if ketoconazole is co-administered with these drugs. Undesirable effects observed in published literature are listed in section 4.8. Section 4.9 instructs that in case of signs suggestive of an adrenal insufficiency following ketoconazole overdose, in addition to the general measures to eliminate the drug and reduce its absorption, a 100 mg dose of hydrocortisone should be administered at once, together with saline and glucose infusions. Section 5.1 associates this risk with ketoconazole’s mechanism of action. Section 5.3 includes preclinical safety data relevant to this risk. Prescription only medicine and prescription by specialists.</td>
<td>None proposed</td>
</tr>
<tr>
<td>QT/QTc interval prolongation/Torsade de Pointes due to interaction of ketoconazole with CYP3A4 substrates</td>
<td>Related contraindications are presented in section 4.3. Section 4.4 includes special warnings and precautions associated with the risk of interactions. Section 4.5 provides crucial information on the interaction of ketoconazole with other medicinal products and also on other forms of interaction. Section 5.3 summarises the preclinical safety data relative to this risk. Prescription only medicine and prescription by specialists.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Use in pregnancy and</td>
<td>Section 4.3 contraindicates the use of oral</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
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<tr>
<td>Lactation</td>
<td>Ketoconazole during pregnancy and lactation. Section 4.6 informs about the impact of ketoconazole on fertility, pregnancy and lactation. Section 4.8 lists undesirable effects on the reproductive system and breast disorders. Preclinical safety data are summarised in section 5.3. Prescription only medicine and prescription by specialists.</td>
<td>None proposed</td>
</tr>
<tr>
<td>QT/QTc interval prolongation/Torsade de Pointes</td>
<td>Section 4.3 contraindicates the use of ketoconazole in co-administration with CYP3A4 substrates due to the association with this risk. Also, ketoconazole is contra indicated in patients with congenital or documented acquired QTc prolongation. Section 4.4 includes special warnings and precautions for use relevant to this risk and recommendations for performing an ECG before starting treatment, one week after start and when clinically relevant. Section 4.5 completes the previous information. Section 5.2 describes pharmacokinetic properties of ketoconazole which provides broader background information relative to this risk. Preclinical safety data related to this risk are summarised in section 5.3. Prescription only medicine and prescription by specialists.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Related contraindications are presented in section 4.3. Section 6.1 lists the excipients for the complex information on the composition of “Ketoconazole HRA 200 mg tablets”. Undesirable effects are listed in section 4.8. Prescription only medicine and prescription by specialists.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Immune dysfunctions following Cushing Syndrome remission</td>
<td>Special warnings and precautions for use in patients with coexisting inflammatory/autoimmune disorders are stated in Section 4.4. Prescription only medicine and prescription by specialists.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Use in paediatric population</td>
<td>Pharmacology in section 4.2 indicates this safety concern. Section 4.8 on undesirable effects informs that frequency of hepatotoxicity could be higher in adolescents than in adults. Section 5.1 on pharmacodynamic properties and</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
### 2.9. Product information

#### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*
3. Benefit-Risk Balance

Benefits

Beneficial effects

Cushing's syndrome is a rare and heterogeneous disease for which transsphenoidal surgery as first option treatment is not always possible. In these cases pharmacological therapies and radiation treatment are well-established options.

Cushing Syndrome is divided into ACTH-dependent forms, either due to a corticotropic pituitary adenoma i.e. a Cushing’s disease (CD) or due to an ectopic ACTH production by a neuroendocrine tumor or an unknown source (occult ectopic ACTH syndrome), and ACTH-independent forms, due to adrenal adenoma/carcinoma or nodular adrenal hyperplasia. The clinical consequences of excess endogenous cortisol exposure are generally severe.

Ketoconazole is an inhibitor of cortisol synthesis resulting from its ability to inhibit several cytochrome P450 enzymes in the adrenal glands. Apart from adrenal blocking effect, KC may also have direct effects on corticotrophic tumour cells in patients with CD.

The well established use is adequately supported by a comprehensive list of publications showing the use of Ketoconazole in clinical practice for the treatment of Cushing’s syndrome since the 1980’s thus for a period of more than 30 years.

Review of the literature suggests that ketoconazole is an effective drug for normalising cortisol levels in Cushing’s syndrome from all causes and, if well tolerated, ketoconazole treatment can be maintained for a long period which allows a long-term control of hypercortisolism. Biochemical and hormonal improvements (measure of decreases or normalization of urinary free cortisol levels) are usually associated with clinical improvements in Cushing’s Syndrome symptoms. The clinical experience suggests that ketoconazole may be a valuable drug for the short-term or the long term medical management of the patients with Cushing’s Syndrome, whenever a medical therapy is indicated. The hormonal changes caused by ketoconazole are dose-dependent and fully reversible. The ketoconazole dose varied between 200 and 1200 mg/d depending on patients’ requirements and need to be individualised to restore normal cortisol levels, clinical tolerance and centres’ experience with a usual dose of 600-800 mg/d.

The indication has been justified taking into account the place of ketoconazole in the management of Cushing’s syndrome and the CHMP agreed to restrict the indication to the treatment of endogenous Cushing’s syndrome.

Regarding the paediatric population, although prevalence of CS in children is low, it is important to consider the use in this population. Based on the literature provided, it is considered that the use in patients of 12-17 years old is adequately demonstrated and thus it is agreed to include adolescents older than 12 years of age in the indication. Due to limited data in younger patients, the CHMP considered that the use has not been adequately demonstrated in this subset.
**Uncertainty in the knowledge about the beneficial effects**

As this is a well-established use application only data coming from literature are available. All the studies provided are retrospective and non-controlled. Due to these characteristics, it is difficult to assess a clinical response in all of the studies. 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 Cushing's. There is relatively little information on associated clinical effects such as improvement in glucose tolerance (reduction in glycosylated haemoglobin); hypertension; or hypokalaemia. Long term treatment could be needed in some patients, especially those waiting for radiotherapy effect or when surgery fails or it cannot be performed. Data available do not suggest a loss of efficacy in the long-term use, but data remain limited.

**Risks**

**Unfavourable effects**

A thorough review of the safety of ketoconazole in the treatment of Cushing’s syndrome has been documented. Hepatic adverse reactions are of concern, especially considering the referral under Article 31 of Directive 2001/83/EC and the CHMP’s opinion that the benefit risk ratio was negative for the use of ketoconazole in the treatment of fungal infections and considering the higher dose used in Cushing syndrome.

Based on the data submitted, hepatotoxicity seems to be not fully predictable and its mechanism remains not well-known. However, a number of publications describe that despite the higher dose used in Cushing syndrome, the hepatotoxicity appears manageable and reversible if the treatment is interrupted. Therefore, hepatotoxicity did not appear to be dose dependent, thus the higher dose used in Cushing syndrome (200-1200mg/d) would not be considered as an additional concern.

It appears that most of the cases occur at the beginning of treatment and within the first month. In case of liver enzymes elevation, ketoconazole is stopped or the dose is reduced depending on the severity of the liver enzymes rise.

Recent reviews of CS treatment suggest that the hepatotoxicity of ketoconazole can be managed by appropriate medical/endocrinology specialist when the SmPC is followed and contraindications are respected; concurrent use of other potential hepatotoxic drugs is avoided and liver enzyme monitoring is performed at treatment initiation and throughout treatment for at least the first 6 months.

Long-term treatment with ketoconazole does not seem to increase the risk of hepatotoxicity.

Adrenal insufficiency is a problem which can occur during treatment. Some others have been described as hypocortisolism, autoimmune reactions, hypokalemia, QTc prolongation.
Consequently, there is also a need for adrenal insufficiency monitoring and ECG monitoring during treatment. Regarding Drug Drug interactions, there are described and detailed in section 4.5 and where necessary warning and contraindications have been introduced.

**Uncertainty in the knowledge about unfavourable effects**

Uncertainties relate to the limited experience in treating patients at higher doses or for long periods at these high doses. Additionally there are limited information in younger children <12 years.

**Importance of favourable and unfavourable effects**

Currently pasireotide and metyrapone are the only authorised pharmacological treatment for Cushing’s disease. Therefore, there is a need for additional treatment options for situations when surgery is not indicated or fails. Ketoconazole is a drug used off-label for treatment of Cushing’s syndrome and its efficacy and safety has been adequately demonstrated through its use in clinical practice since the mid 1980s. Based on the data provided, KC has shown efficacy both from the biological and clinical point of view. The initial therapeutic indication has been restricted to the treatment of endogenous Cushing’s syndrome considering the current role of ketoconazole in the management of this syndrome. Posology has been further justified by the applicant both for adults and adolescents above 12 years based on the data available.

Hepatotoxicity is the main safety concerns that could have an impact on the benefit risk in the treatment of endogenous Cushing syndrome and considering the posology used (200-1200mg/d).

The CHMP agreed that the risk of hepatic adverse reactions can be managed or minimised by ensuring prescription is under the supervision of relevant specialists, and with an adequate monitoring of liver function prior, during treatment and in case of dose increase. Adequate contra-indication and interruption of treatment rules have been mentioned in the SmPC.

Nevertheless, given the above concerns related to safety, the CHMP considers necessary to continue to investigate the safety profile of ketoconazole in routine daily practice and a Post Authorisation safety study is recommended by the PRAC and agreed with the CHMP.

The CHMP considers the following measures necessary to address issues related to safety:

<table>
<thead>
<tr>
<th>Description</th>
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</tr>
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<tbody>
<tr>
<td>A Post Authorisation safety study : Multi-country, observational registry to collect clinical information on patients with Cushing Syndrome patients exposed with Ketoconazole (preferably using the existing European Registry on Cushing’s syndrome (ERCUSYN) registry where feasible ), to assess drug utilization patterns and to document the safety (eg hepatotoxicity, QT prolongation) and effectiveness of ketoconazole</td>
<td>Yearly submission</td>
</tr>
</tbody>
</table>

In addition, it is considered important to inform prescribers prior to launch via a Dear Health Care professional Letter highlighting specific recommendations related to the safety profile of ketoconazole (eg hepatotoxicity).
Benefit-risk balance

Discussion on the benefit-risk assessment

As support of this well-established use application, the applicant has presented comprehensive publications data endorsing the efficacy and safety of this product that can be considered acceptable. All issues raised have been adequately addressed by the applicant mainly the wording of the therapeutic indication, the recommendations for posology in adults and adolescents and more importantly the safety profile (eg hepatotoxicity).

Currently only pasireotide and metyrapone are on the market and are the only. There is a need for pharmacological treatment options for Cushing's disease in particular for situations when surgery is not indicated or fails.

Ketoconazole has been used off label during more than 30 years demonstrating its recognised therapeutic value in the treatment of endogenous Cushing syndrome in adults and adolescents above 12 years, as documented in this application.

The CHMP considered that the risk of hepatic adverse reactions can be managed or minimised by ensuring prescription is under the supervision of relevant specialists, and with an adequate monitoring of liver function prior, during treatment and in case of dose increase. Adequate contra indication and interruption of treatment rules have been mentioned in the SmPC.

Nevertheless, given the above concerns related to safety, the CHMP considers necessary to continue to investigate the safety profile of ketoconazole in routine daily practice and assess the effectiveness of the risk minimisation measures. Therefore, a Post Authorisation safety study is recommended by the PRAC and agreed with the CHMP.

The CHMP considers the following measures necessary to address issues related to safety:

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<td>Yearly submission</td>
</tr>
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</table>

In addition, it is considered important to inform selected prescribers prior to launch via a Dear Health Care professional Letter highlighting specific recommendation related to the hepatic safety profile of ketoconazole

Conclusions
The overall Benefit Risk of Ketoconazole HRA Pharma is positive in the treatment of endogenous Cushing’s Syndrome in adults and adolescents above the age of 12 years.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that ketoconazole HRA is not similar to Signifor (paresotide) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

See appendix 1

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of ketoconazole HRA in the treatment of endogenous Cushing’s syndrome in adults and adolescents above the age of 12 years is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Conditions and requirements of the Marketing Authorisation

- Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- Obligation to complete post-authorisation measures
The MAH shall complete, within the stated timeframe, the below measures:

<table>
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<tr>
<td>A Post Authorisation safety study: Multi-country, observational registry to collect clinical information on patients with Cushing Syndrome patients exposed with Ketoconazole (preferably using the existing European Registry on Cushing’s syndrome (ERCUSYN) registry where feasible), to assess drug utilization patterns and to document the safety (eg hepatotoxicity, QT prolongation) and effectiveness of ketoconazole</td>
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</tr>
</tbody>
</table>

*Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.*

Not applicable.

These conditions reflect the advice received from the PRAC.
7. List of references

Articles published: 459


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**Articles not published: 1**

410. NIH study - manuscript