IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Metopirone 250 mg Soft Capsules, from Laboratoire HRA Pharma.
The product is indicated for the management of Cushing's syndrome (CS) from all causes and as a diagnosis test for corticotrophin (ACTH) insufficiency and for the differential diagnosis of ACTH-dependent CS.
A comprehensive description of the indications and posology is given in the SmPC.
The legal basis for the application is under Article 10a of Directive 2001/83/EC (i.e. well established use). Metopirone has been authorised in Ireland since 1979 and is considered a well-established drug.

This is a repeat use MRP procedure with IE as RMS and Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Latvia, Lithuania, Romania, Slovakia and Slovenia as CMSs.

The first wave of the procedure was in 2013 IE/H/424/001/MR.

In the first wave procedure IE was the RMS, and AT, BE, DE, DK, ES, FI, FR, IT, LU, NL, NO, PL, PT, SE, were CMSs. The SmPC for Metopirone was also harmonised during this procedure.

Name of the product	Metopirone 250mg Capsules, soft
Name(s) of the active substance(s) (INN)	METYRAPONE
Pharmacotherapeutic classification (ATC code)	V04CD01 Tests for pituitary function
Pharmaceutical form and strength(s)	250mg Capsules, soft
Marketing Authorisation Number(s) in Ireland (PA)	PA23005/001/001
Marketing Authorisation Holder	Esteve Pharmaceuticals S.A.
MRP/DCP No.	IE/H/0424/001/E/01
Reference Member State	IE
Concerned Member State	BG CZ EE EL HR HU LT LV RO SI SK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Metopirone 250 mg Soft Capsules. Each capsule contains 250 mg of metyrapone. The product is packaged in a HDPE (high-density polyethylene) bottle with tamper evident screw cap containing 50 capsules.

II.2 Drug substance

The drug substance is metyrapone (INN) which is a pyridine derivative, chemically known as 2-methyl-1, 2-di-(3-pyridyl)-1-propanone, an established active substance described in the in the British Pharmacopoeia and the United States Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The drug substance specification is considered adequate to control the quality of metyrapone and it meets the current pharmacopoieal requirements. Batch analytical data demonstrating compliance with this specification have been provided. Stability studies under ICH conditions have been conducted on the drug substance stored in the registered container closure system and the results support the proposed retest period and storage conditions.

II.3 Medicinal product

P.1 Composition

The drug product is a white to yellowish-white, oblong, opaque soft gelatin capsule imprinted in red ink with "HRA" on one side and having faintly yellowish viscous to jelly-like contents.

Each capsule contains 250 mg of metyrapone.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form (soft gelatin capsule) and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients and their function in the formulation is scientifically justified. The product formulation has not changed since first authorisation in 1979.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably authorised manufacturing sites. The product is manufactured using conventional manufacturing techniques and the manufacturing process has been validated. The results show good production performance throughout production. All test results meet the requirements in the finished product specification and the data demonstrate reproducibility of the manufacturing process.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

The excipients are all well known pharmaceutical excipients and they comply with pharmacopoeial monographs or appropriate specifications. Gelatin is the only excipient of animal origin. All suppliers of gelatin hold valid TSE-Certificates of Suitability. There are no novel excipients used in the manufacture of the product.

P.5 Control of Finished Product

The finished product specifications cover appropriate parameters for this dosage form based on the relevant European guidelines and Pharmacopoieal requirements. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The analytical methods used are described in sufficient detail and are supported by validation data. Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with the relevant European guidelines.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Metopirone 250 mg Soft Capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This is a well-established use application, and the non-clinical dossier for this submission is solely based on data published in the scientific literature. Pharmacodynamic, pharmacokinetic and toxicological properties of metyrapone are well characterised. Metyrapone has been studied extensively in various preclinical models, and there is a long clinical experience with the substance. The company's report has been compiled by an expert professional whose respective qualifications and experience are considered appropriate to perform the review as set out in Article 12 and in accordance with Annex I, Part I 1.4 of the Directive 2001/83/EC. The non-clinical overview contains summaries of a sufficient number of references to provide an extensive overview of current knowledge of metyrapone.

III.5 Ecotoxicity/environmental risk assessment

The applicant has submitted an ERA consisting of a phase I estimation of exposure and logKow determination. Metyrapone PEC surface water value was above the action limit and hence phase II assessment was undertaken. Phase II assessment did not exceed the trigger values and LogKow assessed experimentally does not exceed the phase II action limit. Metyrapone is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The proposed marketing authorization application concerns the medicinal product **Metopirone® 250 mg Capsules soft**, used in the management of Cushing's syndrome (CS) from all causes and as a diagnosis test for corticotrophin(ACTH) insufficiency and for the differential diagnosis of ACTH-dependent CS. Cushings disease and Cushings syndrome are rare diseases.
The product is registered in 11 countries worldwide (Australia, France, Hong Kong, UK, Ireland, Israel, Japan, New Zealand, Switzerland, Netherlands, United States) and was first approved in the EU in 1973.
The drug substance is metyrapone (INN) which is a pyridine derivative, chemically known as 2-methyl-1, 2-di-(3-pyridyl)-1-propanone. Metyrapone inhibits the enzyme 11_-hydroxylase, which is responsible for the last step of the synthesis of the glucocorticoid cortisol, as well as the mineralocorticoid, aldosterone from their precursors. The consequent fall in the plasma concentrations of circulating glucocorticoids stimulates the production of corticotrophin (ACTH) by the anterior pituitary gland, which in turn, results in increased production of 11-deoxycortisol and other steroid precursors that are metabolised in the liver and excreted in the urine where they can be measured. Metyrapone is therefore used as a test of the feedback hypothalamic-pituitary mechanism in the differential diagnosis of Cushing's syndrome and to evaluate the ACTH reserve.

Metyrapone is also used
- for the management of endogenous Cushing's syndrome through a decrease in glucocorticoid secretion by the adrenals.
- As a diagnostic test for ACTH insufficiency and in the differential diagnosis of ACTH-dependent Cushing's syndrome.
- For the management of patients with endogenous Cushing's syndrome.

IV.2 Pharmacokinetics

Metopirone is rapidly absorbed and eliminated from the plasma after oral administration
Absorption: Peak plasma concentrations are usually reached one hour after oral administration;
Distribution: After administration of 750 mg mean peak plasma concentrations are 3.7 µg/ml falling to 0.5 µg/ml 4 hours after administration.
Biotransformation: Metyrapol, the reduced form of metyrapone, is the main active metabolite. Eight hours after a single oral dose, the ratio of metyrapone in the plasma is 1: 1.5. Metyrapol takes about twice as long as metyrapone to be eliminated in the plasma.
Elimination: The plasma elimination half-life of metyrapone is about 2 hours after oral administration. Seventy–two hours after a first daily dose of 4.5 g Metopirone (750 mg every 4 hours), 5.3% of the total dose was excreted in the urine as metyrapone (9.2% in free form and 90.8% conjugated with glucuronic acid), and 38.5% in the form of metyrapol, the principal active metabolite (8.1% in free form and 91.9% conjugated with glucuronic acid).

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Diagnostic agent, test for pituitary function, ATC code: V04CD01
Metopirone acts by inhibiting adrenocorticosteroid synthesis. It reduces cortisol and corticosterone production by inhibiting the 11_-hydroxylation reaction in the adrenal cortex. Removal of the strong inhibitory feedback mechanism exerted by cortisol results in an increase in adrenocorticotrophic hormone (ACTH) production by the pituitary.
Continued blockade of the enzymatic steps leading to production of cortisol and corticosterone produces a marked increase in adrenocortical secretion of their immediate precursors, 11-desoxycortisol and desoxycorticosterone, which are weak suppressors of ACTH release, and a corresponding increase in plasma levels of these steroids and of their metabolites in the urine. These metabolites can easily be determined by measuring urinary 17-hydroxycorticosteroids (17 OHCS) or 17-ketogenic steroids (17-KGS). Metopirone is used as a diagnostic test on the basis of these properties, with plasma 11-desoxycortisol and urinary 17–OHCS measured as an index of pituitary ACTH responsiveness.
Metopirone may also suppress biosynthesis of aldosterone, resulting in mild natriuresis.

IV.4 Clinical efficacy

The legal basis for the application is an article 10a i.e. well established use.
Metopirone has been on the Irish market since 1979.
Supporting literature was provided for the authorised diagnostic and therapeutic indications. Data from the most recent studies carried out using metopirone was presented, for the proposed dosage and indications. Data from over two thousand subjects was provided, the majority of cases involving it's diagnostic use.

The product should only be used under the supervision of specialists having available the appropriate facilities for monitoring of clinical and biochemical responses.

Diagnostic Applications for which metopirone is authorised;
(i) Short single-dose test – diagnosis of ACTH insufficiency
(ii) Multiple-dose test – diagnosis of ACTH insufficiency and differential diagnosis of adrenocortical hyperfunction in Cushing's syndrome.

Therapeutic Uses for which Metopirone is authorised;

Adults
For the management of Cushing's syndrome, the initial dose of metyrapone may vary from 250 to 1,000 mg/day depending on the severity of hypercortisolism and the cause of Cushing's syndrome. The dosage of metyrapone should be adjusted on an individual basis to meet patient's requirements and depending on tolerability. The usual maintenance dose varies between 500 and 6,000 mg/day. The dose should be given in three or four divided doses.
The daily dose should be adjusted after a few days with the aim of lowering the mean plasma/serum cortisol levels and/or the 24 hour urinary free-cortisol levels to a normal target value or until the maximal tolerated dose of metyrapone is reached.
Mean serum/plasma cortisol levels may be calculated from the average of 5 to 6 plasma/serum samples obtained throughout a day or from cortisol levels obtained just before the morning dose.
Once weekly monitoring of plasma/serum cortisol levels and/or a 24-hour free urinary cortisol levels is necessary to allow further dose adjustments if needed. The dose-adjustment period is usually 1 to 4 weeks. When cortisol levels are close to the optimal levels, longer periods (generally once a month or every 2 months) are sufficient for the monitoring.

Assay methods
A reliable assay without cross-reactivity with steroids precursors, such as a specific immuno-assay or a liquid chromatography-mass spectrometry (LC-MS/MS) method, to measure plasma/serum and urine cortisol levels is recommended to allow accurate metyrapone dose adjustment.

Special populations

Paediatric population i.e. in Children
The paediatric dosage recommendation is based on limited data. Case reports showed that there is no specific dosage recommendation for paediatric use in the treatment of Cushing's syndrome. The dose should be adjusted on an individual basis as a function of cortisol levels and tolerability.

Elderly population:
Recommended dosage is as for adults. There is limited data available on the use of metyrapone in elderly (_ 65 years old). Clinical evidence indicates that no special dosage recommendations are required in all indications.

IV.5 Clinical safety
The authorised SmPC reflects the adverse event and reactions reported. There is limited data available for use in the paediatric population. There is a limited amount of data from the use of metopirone in pregnant women. Metopirone is not recommended during pregnancy when used as a diagnostic test or for the management of endogenous Cushing's syndrome unless clearly necessary (in this case, blood pressure should be monitored and hypertension managed appropriately). Metopirone is also not recommended in women of childbearing potential not using contraception. There is insufficient information on the excretion of metopirone in human milk. A risk to newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with Metopirone.
The effect of metyrapone on human fertility has not been investigated in clinical studies. In animals, metyrapone has been shown to cause adverse effects on spermatogenesis and ovarian follicular development. These effects were abolished in

animals co-administered with metyrapone and corticosterone, and were therefore attributed to metyrapone inhibition of corticosterone synthesis; however no formal fertility studies have been conducted.

Metopirone should be used with caution in the following situations i.e.
Diagnostic Applications
- In patients with reduced adrenal secretory capacity and serious hypopituitarism. The test should be performed in hospital with close monitoring in case of suspected adrenocortical insufficiency.
- In patients with reduced liver function as patients with liver cirrhosis often show a delayed response to Metopirone due to liver damage delaying the plasma elimination half-life of cortisol.
- In patients with hypothyroidism or taking drugs affecting the hypothalamo-pituitary adrenal axis

In cases of thyroid hypofunction, urinary steroid levels may rise very slowly, or not at all, in response to Metopirone. Before the Metopirone test is carried out, drugs affecting pituitary or adrenocortical function should be discontinued. If adrenocortical or anterior pituitary function is more severely compromised than indicated by the results of the test, Metopirone may trigger transient adrenocortical insufficiency. This can be rapidly corrected by giving appropriate doses of corticosteroids.

Therapeutic Use
- In patients with ectopic Cushing's syndrome who are at risk for opportunistic infections such as *Pneumocystis jirovecii* pneumonia during Metopirone treatment. Appropriate prophylactic treatment may be considered in this population.
- Long-term treatment with Metopirone can cause hypertension as the result of excessive secretion of desoxycorticosterone.

IV.5 Clinical Safety

Risk Management Plan

The current RMP in place for Metopirone is RMP version 2.2, with November 2017 as the date of final sign-off. The summary of safety concerns outlined below adequately reflects the risks associated with the use of Metopirone in the indicated population.

Summary of safety concerns	
Important identified risks	· Adrenal insufficiency – diagnostic or therapeutic use · Hypertension · Interference with interpretation of diagnostic test due to drug interactions · Haematological disorders Interference with interpretation of diagnostic test in patients with hepatic impairment
Important potential risks	· Opportunistic infections
Missing information	· Use in pregnancy · Use during breastfeeding · Use in patients with renal impairment · Use in paediatric population · Use in elderly population (≥ 65 years) · Long term use

Routine pharmacovigilance activities and routine risk minimisation measures are proposed for Metopirone and this is considered sufficient based on the current data available.

One post-authorisation efficacy study (PROMPT study) is ongoing. The primary objective of this study is to assess the efficacy of Metopirone to normalize cortisol levels (Urinary Free Cortisol – UFC) after 3 months of treatment. The final study report is expected in December 2020.

Periodic Safety Update Report (PSUR):

With regard to PSUR submission, the MAH should take the following into account:

• PSURs shall be submitted 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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
• For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

V. OVERALL CONCLUSIONS

The legal basis for this application is Article 10(a) of i.e. well established use.
The medicinal product **Metopirone® 250 mg Capsules, soft**, used in the management of endogenous Cushing's syndrome (CS) and as a diagnosis test for corticotrophin (ACTH) insufficiency and for the differential diagnosis of ACTH-dependent CS.
The Applicant has submitted extensive literature and post marketing data in support of the Application for the proposed indications.
The Applicant has demonstrated the usefulness of Metyrapone for the proposed indications and the benefit-risk is considered positive.

VI. REVISION DATE

July 2025

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MA transfer	N/A	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Esteve Pharmaceuticals S.A., New PA number: PA23005/001/001		11/07/2025