IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Carbimazole 5 mg Tablets
Carbimazole
PA22865/006/001

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 data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Carbimazole 5mg & 20mg Tablets, for Renata Pharmaceuticals (Ireland) Limited on 18th November 2022 indicated for adults, adolescents and children (3 to 17 years of age) in all conditions where reduction of thyroid function is required. Such conditions are:

(1) Hyperthyroidism;
(2) Preparation for thyroidectomy in hyperthyroidism;
(3) Therapy prior to and post radio-iodine (RAI) treatment.

This decentralised marketing authorisation application was submitted in accordance with article 10(1) of Directive 2001/83/EC as amended (generic application). The reference member state is Ireland and the concerned member state is Malta.

The European reference medicinal product is NeoMercazole 5 mg (PA1142/002/001) by Amdipharm Limited, registered since 13/03/1995 in IE. The reference medicinal product for demonstration of bioequivalence is NeoMercazole 20 mg (PA1142/002/002) by Amdipharm Limited, registered since 13/03/1995 in IE.

The product will be subject to medical prescription that may be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Carbimazole 5 mg Tablets
Name(s) of the active substance(s) (INN)	Carbimazole
Pharmacotherapeutic classification (ATC code)	H03BB01
Pharmaceutical form and strength(s)	5 mg Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/006/001
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/1179/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Carbimazole 5 mg & 20 mg Tablets.

II.2 Drug substance

The active substance is carbimazole, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each tablet contains either 5mg or 20mg of carbimazole.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

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

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets and the tests and control limits are considered appropriate for this type of 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 Ph. Eur./EU legislation for use with foodstuffs requirements.

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.

Certificates of suitability issued by EDQM have been provided for carbimazole and compliance with the Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

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 Carbimazole 5mg & 20mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of NeoMercazole 5 mg and 20 mg tablets on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Carbimazole 5 mg & 20 mg Tablets is a generic product, it will not likely lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of carbimazole are well known. As carbimazole is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Carbimazole is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the EU reference product NeoMercazole 5 mg (PA1142/002/001) marketed by Amdipharm Limited.

For this generic application, the applicant has submitted one bioequivalence study (Study Code: ARL/19/307) in which the pharmacokinetic profile of the test product Carbimazole 20 mg tablets, Renata Pharmaceuticals (Ireland) Limited is compared with the pharmacokinetic profile of the reference product NeoMercazole 20 mg Tablets, Amdipharm Limited.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Carbimazole 20 mg tablets, Renata Pharmaceuticals (Ireland) Ltd, was compared to the reference product NeoMercazole 20 mg Tablets, Amdipharm Limited.

The 90% confidence intervals for C_{max} and AUC_{0-t} were 95.38-106.84% and 94.99-103.20% respectively, all of which are within the accepted ranges.

Table 08 (B): Geometric Means, Ratios and 90% Confidence Interval for Methimazole (N=28)

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for ln-transformed data		Bioequivalence
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit	
AUC_{0-t}	3131.4193	3162.7038	99.0108	94.9906	103.2012	YES
C_{max}	346.0174	342.7594	100.9505	95.3815	106.8447	YES

*Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.
N=Total No. of subjects considered for statistical analysis

Based on the pharmacokinetic parameters of active substance, the reference tablet NeoMercazole 20 mg Tablets marketed by Amdipharm Limited and test tablet Carbimazole 20 mg tablets, Renata Pharmaceuticals are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

For the 5 mg strength, the conditions of a biowaiver, as outlined in the relevant CHMP Note for Guidance are fulfilled.

The content of the SmPCs approved during the decentralised procedure is in accordance with that accepted for the EU reference product.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

No additional studies investigating the pharmacokinetic effects of Carbimazole 5 mg and 20 mg tablets were conducted which is acceptable for this generic application.

Absorption

Carbimazole is rapidly metabolised to thiamazole. After oral ingestion, peak plasma concentrations of thiamazole, the active moiety, occur at 1 to 2 hours.

Distribution
The total volume of distribution of thiamazole is 0.5 l/kg. Thiamazole is concentrated in the thyroid gland. This intrathyroidal concentration of thiamazole has the effect of prolonging its activity. However, thiamazole has a shorter half-life in hyperthyroid patients than in normal controls and so more frequent initial doses are required while the hyperthyroidism is active.

Biotransformation
Thiamazole is moderately bound to plasma proteins. Carbimazole has a half-life of 5.3 to 5.4 hours. It is possible that the plasma half-life may also be prolonged by renal or hepatic disease. Thiamazole crosses the placenta and appears in breast milk. The plasma:milk ratio approaches unity.

Elimination
Over 90% of orally administered carbimazole is excreted in the urine as thiamazole or its metabolites. The remainder appears in faeces. There is 10% enterohepatic circulation.

IV.3 Pharmacodynamics

No additional studies investigating the pharmacodynamic effects of Carbimazole 5 mg and 20 mg tablets were conducted which is acceptable for this generic application.

For further information see the SmPCs Section 5.1.

IV.4 Clinical Efficacy

No new Applicant-generated efficacy studies or bibliographical data were submitted in this application.

IV.5 Clinical Safety

No new Applicant-generated safety studies or bibliographical data were submitted in this application.

During the pivotal bioequivalence study, both the test and reference products were well tolerated by the subjects. There were no deaths, serious adverse events (SAEs) or adverse events (AEs) reported in this study.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Carbimazole. Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient.

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.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This decentralised marketing authorisation application was submitted in accordance with article 10(1) of Directive 2001/83/EC as amended (generic application).

One bioequivalence study was submitted (Study Code: ARL/19/307) in which the pharmacokinetic profile of the test product Carbimazole 20 mg tablets, Renata Pharmaceuticals (Ireland) Limited is compared with the pharmacokinetic profile of the reference product NeoMercazole 20 mg Tablets, Amdipharm Limited.

The 90% confidence intervals for C_{max} and AUC_{0-t} were 95.38-106.84% and 94.99-103.20% respectively, all of which are within the accepted ranges and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

With respect to the grant of a biowaiver for Carbimazole 5 mg tablets, the bioequivalence guideline requirements were found to have been met.

Carbimazole is a well-known active substance with established efficacy and tolerability. Carbimazole was first used clinically in the 1940s and has been marketed for several decades. The EU reference product for this application, NeoMercazole 5 mg Tablets, Amdipharm Limited has been on the market in IE since 1995. The safety results reported in the bioequivalence study were found to be consistent with the known safety profile of Carbimazole and no other safety studies were submitted in support of this study which is acceptable.

V. OVERALL CONCLUSIONS

Carbimazole 5 mg and 20 mg tablets are a generic form of NeoMercazole Tablets. Carbimazole is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the IE reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considers that Carbimazole 5 mg and 20 mg tablets marketed by Renata Pharmaceuticals (Ireland) Limited can be considered bioequivalent to the reference product and have been shown to have a satisfactory risk/benefit profile, and therefore have granted a marketing authorisation.

VI. REVISION DATE

The common renewal date shall be 5 years following authorisation.