LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rytoggi
(dapagliflozin, metformin hydrochloride)

SE/H/2621/01-02/DC

This module reflects the scientific discussion for the approval of Rytoggi. The procedure was finalised at 2026-03-03. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Rytoggi, 5 mg/850 mg, 5 mg/1000 mg, Film-coated tablet.

The active substance is dapagliflozin, metformin hydrochloride. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD15

Mechanism of action
Rytoggi combines two anti-hyperglycaemic medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin
Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure.

Metformin
Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:
- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
- by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation in muscle;
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

II.2 General comments on the submitted dossier

The application for Rytoggi, 5 mg/850 mg, 5 mg/1000 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and EL as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data

protection period is Xigduo, 5 mg/1000 mg, film-coated tablet, authorised in EU since 2014, with AstraZeneca AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Xigduo, 5 mg/1000 mg, film-coated tablet from Germany with AstraZeneca AB as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturers responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided. The Applicant provided inspection outcomes from inspections performed from the years around when the study was performed. No critical issues regarding GCP have been identified. An inspection of the performed bioequivalence study is not deemed necessary.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of dapagliflozin and metformin are well known. As dapagliflozin and metformin is widely used, well-known active substances, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The Applicant has provided an updated ERA report for dapagliflozin and metformin which refers to the conclusions of the ERA provided for the reference product Xigduo during the initial market authorization application. Specific ERA study results for Xigduo have been removed in the updated ERA report. Based on the data in the reference ERA for both active substances it is concluded that the reference ERA is considered complete and the scientific conclusions remain applicable to the generic product under the current guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*)**.**

Conclusions
Considering the ERA data for the reference product Xigduo, neither dapagliflozin nor metformin are PBT or vPvB substances and the substances are not expected to pose a risk to the environment. Therefore, no environmental risk was identified based on the intended use of dapagliflozin and metformin.

There are no objections to approval of Rytoggi from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the application, the applicant has submitted one single-dose bioequivalence study in the fed state comparing Dapagliflozin/Metformin Hydrochloride, 5 mg/1000 mg, film-coated tablet, with the reference product Xigduo, 5 mg/1000 mg, film-coated tablet.

Pharmacokinetic properties of the active substance
Absorption:
Dapagliflozin has an oral bioavailability of 78 %. Following an oral dose of dapagliflozin maximal plasma concentrations occur at approximately 2 hours.

Metformin has an oral bioavailability of 50-60 %. Following an oral dose of metformin maximal plasma concentrations occur at approximately 2.5 hours.

There was no food interaction for the originator product but for tolerability reasons the product is recommended to be administered with food. The administration of the originator product in healthy volunteers after a high fat meal compared to after the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin. The meal resulted in a delay of 1 to 2 hours in the peak

concentrations and a decrease in the maximum plasma concentration of 29% of dapagliflozin and 17% of metformin. These changes are not considered to be clinically meaningful. The product should be given with meals to reduce the gastrointestinal adverse reactions associated with metformin.

Linearity:
The pharmacokinetics of dapagliflozin is linear within the dose range 0.1-500 mg.

Metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. However, according to publicly available data the non-linearity of metformin pharmacokinetics in the dose range is not large enough to meet EMA requirements (i.e. difference in dose-adjusted AUC is not more than 25%) and pharmacokinetics can, therefore be regarded as linear.
Elimination:
The terminal half-life of dapagliflozin is 12.9 hours.

The terminal half-life of metformin is 6.5 hours.

Study 393-23 - FED
Methods
This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Dapagliflozin/Metformin Hydrochloride, 5 mg/1000 mg, film-coated tablet, with Xigduo, 5 mg/1000 mg, film-coated tablet, under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of dapagliflozin and metformin were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2024-04-11 and 2024-06-03.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dapagliflozin, n=59.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**425.01 ± 81.08**	**66.54 ± 21.95**	**3.00 (1.67 - 10.00)**
Reference	**425.36 ± 96.05**	**67.65 ± 19.17**	**3.33 (1.00 - 8.00)**
***Ratio (90% CI)**	**100.72 (98.68-102.79)**	**97.28 (90.56-104.50)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for metformin, n=59.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**13927.63 ± 3415.68**	**1507.19 ± 480.76**	**4.33 (1.67- 8.00)**
Reference	**14274.96 ± 3722.74**	**1602.22 ± 575.16**	**4.00 (1.00 - 8.00)**
***Ratio (90% CI)**	**97.87 (94.61-101.24)**	**95.02 (89.16-101.25)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 5 mg/850 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

From a pharmacokinetic point of view, absence of studies with the additional strengths of 5 mg/850 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of dapagliflozin is linear between 0.1 mg and 500 mg, and the pharmacokinetics of metformin is regarded as linear in the dose range. For quality aspects of biowaiver, see the quality assessment report.

Based on the submitted bioequivalence study, Dapagliflozin/Metformin Hydrochloride, 5 mg/1000 mg is considered bioequivalent with Xigduo, 5 mg/1000 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH (RMS and CMS EL): Genepharm S.A.
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Rytoggi.

Part II Safety specification
The MAH has submitted the version 0.2 RMP dated 12-06-2025 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Urinary tract infection (dapagliflozin) • Lactic acidosis (metformin) • Renal impairment (dapagliflozin) • Diabetic Ketoacidosis including events with atypical presentation (dapagliflozin)
Important potential risks	• Liver injury (dapagliflozin) • Bladder cancer (dapagliflozin) • Breast cancer (dapagliflozin) • Prostate cancer (dapagliflozin) • Lower limb amputation (dapagliflozin)
Missing information	• None

Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate. It is in line with the Summary of safety concerns for the reference product Xigduo (RMP version 12).

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed follow-up questionnaires concerning urinary tract infection, lactic-/ketoacidosis, renal impairment, liver injury, hypersensitivity reactions, bladder cancer, breast cancer, prostate cancer and lower limb amputations, which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 12-06-2025 is considered acceptable.

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 RMS;
- 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, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

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.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Rytoggi, is found adequate. There are no objections to approval of Rytoggi, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results 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.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-