LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Methenamine hippurate Zentiva (methenamine hippurate)

SE/H/2516/01/DC

This module reflects the scientific discussion for the approval of Methenamine hippurate Zentiva. The procedure was finalised at 2025-09-17. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Methenamine hippurate Zentiva, 1 g, tablet.

The active substance is methenamine hippurate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Methenamine hippurate Zentiva is the hippurate salt form of methenamine, a prodrug and inactive weak base that slowly hydrolyses in acidic urine to ammonia and the formaldehyde. Formaldehyde probably exerts its antibacterial effect by denaturation of protein. Depending on the urinary concentrations, formaldehyde is either bactericidal or bacteriostatic. Formaldehyde urinary concentrations are dependent on urine pH, volume, and flow rate. Formaldehyde acts as an antibacterial agent against gram-positive and gram-negative organisms. Methenamine is used as prophylactic against recurring uncomplicated urinary tract infections and catheter related asymptomatic bacteriuria.

The applicant proposes the indication:
Long-term prophylaxis after an initial treatment with a suitable chemotherapeutic agent in case of recurrent urinary tract infections.
Short-term prophylaxis for short-term catheterisation and instrumental interventions in the urinary tract.
Maintenance therapy in case of asymptomatic bacteriuria in long-term care patients caused by catheter, uridome, etc.

Proposed posology is 1g 2-3 times daily in adults, 0,5g 2 times daily in children and 1g 2 times daily in adolescents over 12 years. The product is contraindicated in patients with renal insufficiency and should be used with caution in patients with hepatic impairment and concurrent sulphonamide use.

The reference product, in Sweden called Hiprex 1g tablets (methenamine hippurate) by Viatris ApS, was first approved in Sweden on 25 May 1973.

II.2 General comments on the submitted dossier

The application for Methenamine hippurate Zentiva, 1 g, 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 DK, NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Haiprex, 1 g, tablet authorised in DK since 1972, with Viatris ApS as marketing authorisation holder.

The reference product used in the bioequivalence study is Haiprex, 1 g, tablet from DK with Viatris ApS 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 manufacturer(s) 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 clinical and bioanalytical site was inspected by MHRA (UK) in 2021 and by AEMPS (ES) in 2023 without critical findings. No inspection of the submitted study is 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 methenamine are well known. As methenamine is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Methenamine hippurate Zentiva is a generic product, based on consumption data of antibacterials within the ATC group J01X, introduction of Methenamine hippurate Zentiva will not lead to an increased exposure to the environment. A further environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Methenamine hippurate Zentiva from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Methenamine hippurate Zentiva, 1g, tablets with the reference product Haiprex, 1g, tablets.

Pharmacokinetic properties of the active substance
Methenamine hippurate is readily absorbed from the gastro-intestinal tract. Following an oral single dose of methenamine hippurate maximal plasma concentrations occur at approximately 1-2 hours. There are no restrictions with respect to food in the SmPC of the originator. The terminal half-life is 4 hours.

Study C1B01387
Methods
This was a single-dose, two-way crossover study conducted in 34 healthy volunteers (33 completed), comparing Methenamine hippurate Zentiva, 1g, tablets with Haiprex (methenamine hippurate), 1g, tablets, by Viatris ApS from the Danish market under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of methenamine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 31st May and 16th June 2022.

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 methenamine, n=33.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**86.88 ± 12.10**	**11.18 ± 2.36**	**1.25 (0.33-2.33)**
Reference	**84.37 ± 12.53**	**10.78 ± 1.75**	**0.83 (0.33-2.33)**
***Ratio (90% CI)**	**103.04 (101.64 - 104.45)**	**102.81 (99.66 - 106.06)**	**-**

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%.

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). It is acceptable to base BE on the parent drug (inactive prodrug) methenamine. The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Methenamine hippurate Zentiva, 1g, tablets are considered bioequivalent with Haiprex (methenamine hippurate), 1g, tablets.

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: Zentiva, k.s.

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 Methenamine hippurate Zentiva.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and 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 1.0 signed 12 Jun 2024 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, Methenamine hippurate Zentiva, is found adequate. There are no objections to approval of Methenamine hippurate Zentiva, 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.

In conclusion, the user test is considered acceptable.

V.5 Labelling

The approved Labelling is available in the MRI Product Index.

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
-	-	-	-	-	-