Public Assessment Report

Scientific discussion

Ulcamed 120 mg Filmtabletten

Bismuth subcitrate

AT/H/0598/001/DC

Date: 10.12.2015

This module reflects the scientific discussion for the approval of Ulcamed 120 mg Filmtabletten. The procedure was finalised at 02.10.2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ulcamed 120 mg Filmtabletten, from Krka, d. d., Novo mesto.

The product is indicated for:
- Treatment of gastric and duodenal ulcers.
- Aid in *Helicobacter pylori* eradication in combination with other medications.
- Gastritis associated with dyspeptic disorder, when eradication of *Helicobacter pylori* is desired.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

Under the effect of gastric acid, a precipitate is formed from tripotassium dicitrato bismuthate, which adheres primarily to the ulcerated area and inhibits the activity of pepsin. Tripotassium dicitrato bismuthate also protects the mucosa by stimulating the synthesis and secretion of endogenous prostaglandins, hence increasing bicarbonate and mucin production. In addition, tripotassium dicitrato bismuthate has antibacterial activity against *Helicobacter pylori*. Eradication of this bacterium is followed by an improvement in the histological picture and symptomatic improvement.

Conditions pursuant to Article 21a of Directive 2001/83/EC have been agreed. For details please refer to section VI of this assessment report.

II. QUALITY ASPECTS

II.1 Introduction

Ulcamed 120 mg Filmtabletten is a film-coated tablet which is presented in a blister.

II.2 Drug Substance

The active substance in Ulcamed 120 mg Filmtabletten is bismuth oxide (as tripotassium dicitratobismuthate (bismuth subcitrate)). The specification of the active substance meets the current scientific requirements. The adequate quality of the active substance has been shown by submitting the appropriate control data. The stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.3 Medicinal Product

Ulcamed 120 mg Filmtabletten contains the following excipients:
Tablet core
Maize starch
Povidone K30
Polacrillin potassium
Macrogol 6000

Magnesium stearate (E470b)

Film coating
Polyvinyl alcohol
Macrogol 4000
Talc
Titanium dioxide (E171)

The manufacturer responsible for batch release is Krka, d. d., Novo mesto, Smarjeska cesta 6, 8501 Novo mesto, Slovenia.

The development of the product has been sufficiently made and deemed appropriate. The usage of all the excipients has been described.
The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.
The packaging of the medicinal product complies with the current legal requirements.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 24 months when stored in the original package to protect from moisture. This medicinal product does not require any special temperature storage conditions.

The pharmaceutical quality of Ulcamed 120 mg Filmtabletten has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

Pharmacodynamic and pharmacokinetic properties of bismuth subcitrate are well known. As bismuth subcitrate is a widely used, well known active substance, no further studies are required and the applicant provides none.

III.1 Toxicology

Colloidal bismuth subcitrate appears to be of low toxicity. The genotoxicity of bismuth citrate cannot be assessed due to inconsistencies (positive, negative findings) of experimental data.

Bismuth is not indicated for the treatment of paediatric and adolescent population or women of childbearing potential, since the preclinical and clinical data of this field are insufficient. Adequate measurements are stated in SmPC.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since the active substance has been on the European market with similar indications for a long time, this product is not supposed to lead to an increased exposure of bismuth to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The non-clinical overview is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

The marketing authorisation application for Ulcamed 120 mg Filmtabletten was submitted according to Article 10a of Directive 2001/83/EC, relating to applications relying on well-established medicinal use supported by bibliographic literature.

IV.2 Pharmacokinetics

Tripotassium dicitrato bismuthate exerts a local action. However, small amounts of bismuth are absorbed (less than 0.2 % of the dose) during therapy. Bismuth is distributed mainly into the kidneys. Only trace amounts can be detected in other organs. Tripotassium dicitrato bismuthate precipitates locally in the stomach under the influence of gastric acid, forming insoluble compounds, possibly bismuth oxychloride and bismuth citrate. The vast majority of the ingested bismuth is excreted with faeces. Of the small amount that is absorbed, urinary clearance is approximately 50 mL/min. At least a 3-compartment model is needed to describe the excretion of bismuth over time. The half-life is 5-11 days.

IV.3 Pharmacodynamics

The pharmacodynamic profile of bismuth subcitrate is well established. No additional pharmacodynamic study has been submitted by the applicant and none is required.

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IV.4 Clinical efficacy

The efficacy of bismuth subcitrate has been demonstrated in several clinical studies. Also standard manuals demonstrate the efficacy of bismuth subcitrate in the treatment of gastric ulcers, Helicobacter pylori eradication and gastritis associated with Helicobacter pylori.

Tripotassium dicitrato bismuthate contributes to the healing of a high percentage of gastric and duodenal ulcers. Its antibacterial effect is associated with a lower frequency of ulcer recurrence in the first year after treatment discontinuation compared to some other agents.

IV.5 Clinical safety

The safety of tripotassium dicitratobismuthate is well established. The present safety assessment does not reveal any new or worrying safety issues. The frequency and type of adverse events does not cause any concerns regarding safety.

IV.6 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 Bismutoxid Krka 120 mg Filmtabletten.

Routine pharmacovigilance activities are deemed sufficient at the moment.

Summary table of safety concerns as approved in RMP

Important identified risks	No important identified risk
Important potential risks	encephalopathy
Missing information	No missing information

No additional risk minimisation measures are planned at the moment.

IV.7 Discussion on the clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

V. USER CONSULTATION

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 PIL 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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Conditions pursuant to Article 21a of Directive 2001/83/EC:

The marketing authorisation holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP 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.

Sufficient (pre-)clinical information has been submitted to support this application.
The use of tripotassium dicitratobismuthate is well established. It has recognised efficacy and acceptable safety. A positive benefit/risk ratio can be concluded.
The pharmaceutical quality of Ulcamed 120 mg Filmtabletten has been adequately shown.

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
AT/H/0598/001/IB/001	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	No	03.09.2016	Approvable	N/A
AT/H/0598/001/IB/002	Change in storage conditions of the finished product or the diluted/reconstituted product	Yes	03.09.2016	Approvable	N/A
AT/H/0598/001/E/001	Including CMS	No	16.10.2017	Approvable	N/A
AT/H/0598/001/II/004	Update after RUP	Yes	22.05.2018	Approvable	N/A
AT/H/0598/001/R/001	Renewal	Yes	23.10.2020	Approvable	N/A