

Public Assessment Report

Scientific discussion

**Zavedos, 1 mg/ml solution for injection
(idarubicin hydrochloride)**

NL License RVG: 119049

Date: 17 January 2019

This module reflects the scientific discussion for the approval of Zavedos, 1 mg/ml solution for injection. The marketing authorisation was granted on 15 May 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
Ida i.v.	Idarubicin freeze dried
Ida RTU	Idarubicin Ready-To-Use
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RTU	Ready-To-Use
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Zavedos, 1 mg/ml solution for injection, from Pfizer B.V.

The product is indicated in:

Adults:

- For the treatment of acute myeloid leukaemia (AML), for remission induction in untreated patients or for remission induction in relapsed or refractory patients.
- For second-line treatment of relapsed acute lymphoblastic leukaemia (ALL).

Paediatric population:

- For first-line treatment of acute myeloid leukaemia (AML), in combination with cytarabine, for remission induction.
- For second line treatment of relapsed acute lymphoblastic leukaemia (ALL).

This product may be used in combination chemotherapy regimens involving other cytotoxic agents.

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

This national procedure concerns a line extension to existing marketing authorisation for Zavedos, powder for solution for injection 5 mg and 10 mg (NL License RVG 14201) registered by Pfizer B.V. since 3 September 1990 via a national procedure.

The current application adds a new pharmaceutical form, an solution for injection, to the marketing authorisation of Zavedos. Zavedos was originally formulated as a freeze-dried powder, containing 5 mg, 10 mg or 20 mg of idarubicin hydrochloride for reconstitution prior to injection. Before administration, the vial contents are to be reconstituted with 5 ml, 10 ml or 20 ml. respectively, with water for injection to give a final concentration of 1 mg/ml of the active compound. Handling of the powder and preparation of the idarubicin solution can be potentially hazardous for health care personnel as direct skin contact with the drug and/or inhalation of drug particles may occur. The risk of occupational exposure is known for the freeze dried preparation of other injectable anthracyclines such as doxorubicin and epirubicin. In order to reduce this hazard and provide a prompt reconstitution-free preparation, idarubicin has been successfully formulated as a ready-use aqueous solution.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC. Except for a safety study, no new clinical or non-clinical studies were conducted as the data are the same as those submitted for Zavedos, powder for solution for injection 5 mg and 10 mg. The safety study compared the local safety and effect on serum osmolality of Zavedos, 1 mg/ml solution for injection versus the same product in the form of freeze-dried idarubicin hydrochloride powder for solution.

Scientific advice

For this application, regulatory advice has been sought in October 2012 from the Dutch Medicine Evaluation Board (MEB).

II. QUALITY ASPECTS

II.1 Introduction

Zavedos is an orange-red, clear solution with a pH between 3.0 and 4.0. Each ml of solution contains 1 mg of idarubicin hydrochloride.

The solution for injection is packed in polypropylene vials which are closed with a siliconised, halobutyl rubber stopper and sealed with an aluminium cap with a plastic flip off top.

The excipients are: glycerol, water for injection and hydrochloric acid for pH adjustment.

II.2 Drug Substance

The active substance is idarubicin hydrochloride, an established active substance described in the United States Pharmacopeia (USP). Idarubicin hydrochloride is an orange-red crystalline powder and slightly soluble in water. The active substance has six stereocentres and all of these stereocentres are known to be stable. Polymorphism is not relevant as the product concerned is a solution.

Manufacturing process

The manufacturing process consists of nine chemical steps and is described sufficiently. The starting materials, reagents and solvents are adequately described and acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph USP with additional requirements for specified impurities, residual solvents and silver. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance

Stability data on the active substance have been provided for a sufficient number of batches stored at long term and accelerated conditions, in tightly closed type III amber glass bottles closed with polypropylene screw caps. As no significant changes were observed, and all parameters stayed within specification, the re-test period of 24 months without a maximum temperature is justified. Each vial is for single use only and should be used immediately after opening. If not used immediately, in use storage times and conditions are the responsibility of the user.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. In order to reduce the hazard of occupational exposure and provide a prompt reconstitution-free preparation, idarubicin has been successfully formulated as RTU (ready to use) aqueous solutions. The RTU, preservative free solution was already registered earlier between 1997-1998 in several EU countries and in the USA. The NL registration was withdrawn for business reasons.

The objective of the development program was to formulate a solution for injections, containing 1 mg/ml idarubicin hydrochloride. Suitable product development data have been submitted with this application. The low pH of 3.5 (lower limit 3.0) is acceptable in view of the stability of the active substance and still acceptable for intravenous injections.

No new clinical efficacy studies have been performed. As the proposed product Zavedos 1 mg/ml aqueous solution for injection is equivalent to the currently registered Zavedos powder for solution for injection (5 mg and 10 mg: RVG 14201), and, also contains 1 mg of idarubicin hydrochloride in every ml of solution when administered, this is no objection. The composition proposed is identical to the composition of the previously authorised product (RVG 22475). A local toxicity report on the proposed product has been included.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The product is manufactured by an aseptic filtration process which consists of four manufacturing steps:

compounding, sterilisation, aseptic filling and labelling and packaging. Process validation data on the product have been presented for batches in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with their respective European Pharmacopoeia monographs. The specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, pH, assay, related substances, extractable volume, visual inspection, clarity, particulate matter, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for sufficient pilot and production scale batches stored at long term (2 – 8 °C) (in accordance with applicable European guidelines demonstrating. On basis of the data submitted, a shelf life was granted of 36 months. The storage instruction to store the product in the original package, to protect from light is justified in view of the USP monograph for the injection Each vial is for single use only and should be used immediately after opening. If not used immediately, in use storage times and conditions are the responsibility of the user.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Zavedos has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

As this product is intended for substitution with other products on the market, no increase in environmental exposure is anticipated and no ERA is required.

III.2 Discussion on the non-clinical aspects

This product is a line extension to Zavedos, powder for solution for injection 5 mg and 10 mg, which is available on the European market. No new non-clinical data on the pharmacodynamics, pharmacokinetic and toxicological properties of the active substance idarubicin hydrochloride have been submitted. Reference is made to the non-clinical data of Zavedos, powder for solution for injection 5 mg and 10 mg.

IV. CLINICAL ASPECTS

IV.1 Introduction

In this procedure, no new pharmacokinetic, pharmacodynamic or efficacy studies have been conducted. Instead, reference is made to Zavedos, powder for solution for injection 5 mg and 10 mg. Given the fact that the route of administration and the dosing have not changed, and no quality issues have been found, the above mentioned data are not considered necessary.

A local toxicity report on the proposed product has been included.

IV.2 Clinical safety

Study 94-OIDR-001 was an open, randomised, multicentre phase I study. Patients were randomised to receive either idarubicin RTU (Ida RTU) or freeze-dried formulation (Ida i.v.) and stratified according to their haematological malignancies, i.e. acute myeloid leukaemia, acute lymphoblastic leukaemia, acute promyelocytic leukaemia, lymphoma and myeloma.

Both drugs were administered as 15' i.v. infusion through a peripheral venous access device during one treatment course and according to the treatment plan defined for each patient by the treating physician. Follow-up for any local toxicity was carried out for 48 hours after the last idarubicin administration.

The objectives of this trial were to survey the acute local toxicity of the new formulation of idarubicin RTU as compared with the freeze-dried form and to monitor serum osmolality changes. Serious adverse events were collected up to 30 days after completion of the course of therapy under study, or until start of a second treatment course (whichever occurred first).

Local toxicity

Ninety-four adult Caucasian patients with blood malignancies were enrolled between June 1995 and May 1997 in ten Italian Institutions. Of these patients 50 subjects received idarubicin ready to use formulation and 44 received idarubicin freeze dried (Ida i.v.) formulation. Mean age was 49.8 ± 14.3 years (range: 18-74; median: 49) in the Ida RTU arm and 46.3 ± 14.2 years (range: 19-74; median: 48) in the Ida i.v. arm. Gender was equally distributed between the two arms.

One patients experienced grade 1 local toxicity with the Ida RTU formulation, which worsened after the first injection (in the same arm). In the freeze dried formulation group, no local toxicity was observed.

One patient with acute promyelocytic leukaemia died of acute respiratory distress syndrome. This patient received Ida RTU in combination with all-trans-retinoic acid and death was not considered related to the study medication.

Osmolality

Serum osmolality ranged from 265.8 to 350.4 mOsm/kg in the Ida i.v. arm and from 261.9 to 357.9 mOsm/kg in the Ida RTU arm. The largest differences between post- and pre-treatment normalised values were: -20.3 (day 2, 3 hr) to +35.2 mOsm/kg (day 2, 30 min) in the Ida i.v. arm and -24.6 (day 3, 30 min) to +69.3 mOsm/kg (day 1, 30 min) in the Ida RTU arm.

Osmolality was found to be above the upper limit of normal values in 3 patients in the Ida i.v. and in 13 patients in the Ida RTU i.v. arm, respectively. These values were not considered clinical relevant. After study completion, the difference between pre- and post-dose osmolality was not different between the two groups.

Post marketing reports for toxicity from the MAH's safety database through October 2015 were analysed. For the intravenous idarubicin solution, a total of 168 idarubicin cases and 294 adverse events were identified. Number of fatal (24 vs 25) events and not recovered events (8.95 vs 7.2) were comparable between the RTU formulation and the powder for solution formulation. Haematological and infectious adverse events were most prevalent and generally equally distributed between the two formulations.

IV.3 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 Zavedos.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> - Acute cardiotoxicity (arrhythmias) - Cardiomyopathy - Myelosuppression and increased susceptibility to infections - Secondary leukaemia - Mucositis/Stomatitis/Esophagitis (complications including gastrointestinal haemorrhage/perforation) - Tumour lysis syndrome
Important potential risks	None
Missing information	<ul style="list-style-type: none"> - Use in patients with hepatic impairment - Use in patients with renal impairment

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

Except for a clinical safety study, no new clinical studies were conducted. Local tolerability of the ready to use formulation of idarubicine is considered sufficient and not different from the powder for solution formulation. No additional safety data have been reported. Risk management is adequately addressed.

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 test consisted of two rounds with 10 participants each. 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

Zavedos, 1 mg/ml solution for injection has a proven chemical-pharmaceutical quality and is an approvable line extension to Zavedos, powder for solution for injection 5 mg and 10 mg. Zavedos, powder for solution for injection 5 mg and 10 mg is a well-known medicinal product with an established favourable efficacy and safety profile.

Except for a clinical safety study, no new clinical studies were conducted. Local tolerability of Zavedos, 1 mg/ml solution for injection is considered sufficient and not different from the powder for solution formulation.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Zavedos, 1 mg/ml solution for injection was authorised in the Netherlands on 15 May 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
AT/H/xxxx/WS/056	revision of product informations and - where applicable - DHC-letters with regard to replacement of ' idarubicin' by ' idarubicin hydrochloride' in order to avoid dosage error	Yes	17-09-2018	Approved	-