IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Zavedos 1mg/ml solution for injection
IDARUBICIN HYDROCHLORIDE
PA0822/142/005

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

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Zavedos 1mg/mL Solution for Injection , from Pfizer Healthcare Ireland on <date of authorisation> for the following indications.

Adults
For the treatment of acute non-lymphoblastic leukaemia (ANLL), 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 non-lymphoblastic leukaemia (ANLL), in combination with cytarabine, for remission induction.

For second line treatment of relapsed acute lymphoblastic leukaemia (ALL).

Zavedos may be used in combination chemotherapy regimens involving other cytotoxic agents (see section 4.2).

This application for a marketing authorisation was submitted in accordance with Article 8(3) of Directive 2001/83/EC as a line extension of the approved marketing authorisation for Zavedos 5mg and 10mg powder for solution for injection PAPA0822/142/003-4.

The Summary of Product Characteristics for (SmPC) for this medicinal product Zavedos 1mg/mL solution for injection is available on the HPRA's website at www.HPRA.ie

Name of the product	Zavedos 1mg/mL solution for injection
Name(s) of the active substance(s) (INN)	IDARUBICIN HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	L01DB06
Pharmaceutical form and strength(s)	1mg/mL
Marketing Authorisation Number(s) in Ireland (PA)	PA0822/142/005
Marketing Authorisation Holder	Pfizer Healthcare Ireland

II. QUALITY ASPECTS

II.1. Introduction

This application is for Zavedos 1 mg / ml solution for injection

II.2 Drug substance

The active substance is idarubicin hydrochloride, an established active substance described in the US 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 ml of solution contains 1 mg of idarubicin hydrochloride.

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 ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for solutions for injection, 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. requirements and 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.

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 Zavedos 1mg/ml injection for solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Zavedos powder for solution for injection on the Irish market by Pfizer. Zavedos solution for injection is a new formulation of this active substance. Cross reference is made to the preclinical data for Zavedos powder for solution for injection and no new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Adequate justification has been provided for the absence of specific studies in the environmental risk assessment. This product is a national line extension for a new formulation, intended for substitution of a previously approved product. No increase in environmental exposure to Idarubicin is anticipated.

III.3 Discussion on the non-clinical aspects

Zavedos solution for injection is a national line extension for a new formulation, the active substance is the same as that present in Zavedos powder for solution for injection on the Irish market by Pfizer. Cross reference is made to the preclinical data for Zavedos powder for solution for injection and no new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Introduction

Idarubicin was originally formulated as a lypholised powder, containing 5, 10, or 20 mg of idarubicin hydrochloride for reconstitution prior to injection, and this product is still marketed in Ireland as Zavedos®. Before administration, the vial contents of the powder formulation are reconstituted with water for injections to give a final concentration of l 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 preparations 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 to use (RTU) aqueous solutions. The indications for use, dosing regimen and target population for this new formulation are identical to the marketed product Zavedos 5mg and 10mg powder for solution for injection.

IV.2 Clinical Pharmacology

No new pharmcokinetic or pharmacodynamic data has been submitted. The pharmacokinetics and pharmacodynamics of Zavedos 1mg/ml Solution for Injection are considered identical to the marketed product Zavedos powder for solution for injection.

IV.3 Clinical Efficacy

No new clinical efficacy data has been submitted. This application cross refers to the efficacy data for Zavedos 5mg and 10mg powder for solution for injection. This is acceptable

IV.5 Clinical Safety

A safety study comparing the local safety and effect on serum osmolality of Zavedos powder for solution for injection compared with Zavedos 1mg/ml solution for injection was submitted.The study was an open, randomized, multicentre phase I study.Ninety-four adult patients with blood malignancies were enrolled Patients were randomized to receive either idarubicin RTU (Ida RTU) or freeze-dried formulation (Ida i.v.) and were stratified according to their haematological malignancies. 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. 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). Patients received various idarubicin-based regimens according to their disease. Overall, patients treated with Ida RTU and Ida i.v. received respectively 116 and 93 peripheral injections of the drug. A total of 43 patients in Ida i.v. arm and 50 patients in the Ida RTU arm were evaluable for local toxicity analysis. No local toxicity was observed in either study arms, the only exception being one patient entered the study in the Ida i.v. arm with grade 1 local toxicity and who experienced a worsening of this toxicity after the first injection of idarubicin in the same arm.One death on therapy was reported in a 37 year female patient who had received 4 days of treatment with 21 mg of Ida RTU and all-trans Retinoic Acid (ATRA).The patient developed acute respiratory distress syndrome ten days after the last administration of Ida RTU.No autopsy was performed. No relationship with study drug was reported by the Investigator. The two formulations were shown to be as equivalent with regard to the incidence of local toxicity.

During treatment, serum osmolality was measured at scheduled times with each daily administration of Ida i.v. and Ida RTU. Serum osmolality values were classified as normal, lower or upper with respect to the normal laboratory values for the Institution. 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 normalized 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 UNL for the institution in 3 and 13 patients the Ida i.v. and RTU study arm, respectively. The most likely cause for these high values was tumor-related hyperosmolality (1 pt treated with Ida RTU), supportive therapy or concomitant medications in 5 patients.In five patients the increase in osmolality was attributed to Ida RTU. In no instances the Investigators considered these values to be of clinical concern. At the end of study, serum osmolality was measured in 32 patients in the Ida i.v. arm and 35 patients in the Ida RTU arm. Comparison between pre- and post-treatment normalized values in each treatment arm did not evidence any statistically significant difference (Student t-test for paired data: $p = 0.70$ in Ida i.v. and $p = 0.58$ in Ida RTU).

Table 1. Osmolality: Descriptive Statistics on the Highest Difference Between Pre and Post Treatment Evaluation Whenever it Occured

		Pre-Treatment	Post-Treatment	Difference
Treatment				
Ida i.v.	N	39	39	39
	Mean	285.9	285.3	-0.5
	SD	7.1	12.6	8.7
	Median	285.9	285.1	0.6
	T value*			-0.39
	P value			0.700
Ida RTU	N	49	49	49
	Mean	288.0	289.1	1.2
	SD	11.4	15.8	14.8
	Median	287.0	285.9	-2.1
	T value*			0.56
	P value			0.581

Abbreviation: N: Number of patients; SD: Standard Deviation
* T Value-Student's T test for paired Data
Between Treatment Comparison: Cochran's T test T=0.64 p=0.50

Serum osmolality was not significantly affected after i.v. injection of both idarubicin formulations. The presence of glycerol in the RTU formulation does
not appear to exert a clinically relevant effect on this parameter.

The published literature has been reviewed for relevant clinical safety information as part of the PSUR process June 1997 for previously unreported relevant clinical safety information concerning idarubicin RTU formulation. The marketing authorisation holder states that no new clinical data were reported that would alter the benefit/risk profile of idarubicin**.**

The marketing authorisation holder also conducted a review of its safety database up to 8th October 2015. A total of 168 idarubicin solution cases (294 adverse events) were identified and a total of 180 idarubicin powder formulation cases (354 adverse events) were identified. The System Organ Class (SOCs) containing the greatest number of adverse events for the idarubicin solution were Infections and infestations (73), Blood and lymphatic system disorders (51), Gastrointestinal disorders (38) and General disorders and administration site conditions (24). The SOCs containing the greatest number of adverse events for the idarubicin powder formulation were Blood and lymphatic system disorders (84), Infections and infestations (51), Gastrointestinal disorders (36), General disorders and administration site conditions (29) and Investigations (29). Selected AEs of medically confirmed idarubicin cases are presented in Table 2.

Table 2 Adverse Event Reporting Proportion- Idarubicin- (PT)

SOC and PT	Number of Events Idarubicin Solution	Percentage (%) Idarubicin Solution	Number of Events Idarubicin Powder Formulation	Percentage (%) Idarubicin Powder Formulation
Blood and lymphatic system disorders	**51**		**84**	
Anaemia	/	/	5	2.8%
Bone marrow failure	5	3.0%	10	5.6%
Febrile neutropenia	33	19.6%	23	12.8%
Leukopenia	1	0.6%	10	5.6%
Neutropenia	2	1.2%	11	6.1%
Pancytopenia	5	3.0%	3	1.7%
Thrombocytopenia	3	1.8%	16	8.9%
Cardiac disorders	**19**		**20**	
Cardiac failure	3	1.8%	6	3.3%
Cardiomyopathy	1	0.6%	4	2.2%
Gastrointestinal disorders	**38**		**36**	
Diarrhoea	8	4.8%	2	1.1%
Neutropenic colitis	7	4.2%	3	1.7%
Stomatitis	4	2.4%	5	2.8%
Vomiting	2	1.2%	4	2.2%
General disorders and administration site conditions	**24**		**29**	
Disease progression	/	/	6	3.3%
Hyperpyrexia	5	3.0%	1	0.6%
Pyrexia	6	3.6%	7	3.9%
Hepatobiliary disorders	**9**		**6**	
Hepatic function abnormal	/	/	4	2.2%
Infections and infestations	**73**		**51**	
Infection	6	3.6%	2	1.1%
Pneumonia	9	5.4%	4	2.2%
Sepsis	17	10.1%	11	6.1%
Septic shock	2	1.2%	4	2.2%
Investigations	**12**		**29**	
Haemoglobin decreased	1	0.6%	4	2.2%
White blood cell count decreased	/	/	6	3.3%

User Consultation

To comply with the requirements of article 59(3) of Council Directive 2001/83/EC the parent patient leaflet (PL) (Zavedos® 5 mg and 10 mg Capsules) and the proposed daughter PL (Zavedos® 1mg/mL Solution for Injection) were compared in the Zavedos Bridging Study Group (BSG). Minor differences were identified in the indications, route of administration and handling instructions. The leaflets are nearly identical in all basic bridging criteria. The identified differences were not considered to be significant. The results indicate that the package leaflet is structured and written in a patient friendly manner.

Pharmacovigilance System

The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan (RMP)

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities designed to identify, characterise, prevent or minimise risks relating to Zavedos 1mg/ml solution for injection.

The summary of safety concerns is presented below:

Summary of safety concerns	
Important identified risks	§ Acute cardiotoxicity (arrhythmias) § Cardiomyopathy

Summary of safety concerns	
	§ Severe myelosuppression, increases susceptibility to severe infections and haemorrhages § Secondary leukaemia § Gastrointestinal haemorrhage/ perforation
Important potential risks	§ Increased toxicity in patients with hepatic impairment § Increased toxicity in patients with renal impairment
Missing information	§ None

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.
Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

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.

IV.6 Discussion on the clinical aspects

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 may occur. Idarubicin has been formulated as RTU aqueous solutions to reduce this risk. No new efficacy or safety concerns have been identified with this new ready to use formulation of Zavedos 1mg/ml solution for injection. Clinical experience to date with this product has not raised any new safety or efficacy concerns.

V. OVERALL CONCLUSIONS

The benefit risk assessment for this product is considered to be positive.

VI. REVISION DATE

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE