IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Gentamicin 10 mg/ml solution for injection or infusion
Gentamicin
PA0281/242/001

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

This product was initially authorised under procedure number UK/H/5516/001-002/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 20th June 2018 under procedure number IE/H/0614/001-002/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/242/001-002
Marketing Authorisation Holder: Pinewood Laboratories Ltd.

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) considered that the applications for Gentamicin 10 mg/ml and 40 mg/ml Solutions for Injection or Infusion (PL 29831/0659-0660; UK/H/5516/001-02/DC), indicated in bacteraemia, urinary tract infections, chest infections, severe neonatal infections and other serious systemic infections due to susceptible organisms, in adults and children including neonates are approvable.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as the RMS and Republic of Ireland as CMS. The applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant has cross-referred to Cidomycin Paediatric Injectable 20 mg/2 m1 and CidomycinTM Adult Injectable 80 mg/2 ml, originally granted to Roussel Laboratories Ltd (PL 00109/5065R-5066R) on 24th January 1991.

Gentamicin is an aminoglycoside antibiotic extracted from *Micromonospora purpurea*. It represents a mixture of the structurally very similar homologues gentamicin C_1, C_{1a} and C_2. The gentamicin homologue C_2 is classified as the component with the highest toxicity. The antibacterial activity of gentamicin sulphate is determined both on the basis of units and also on the basis of mass (weight).

Gentamicin has bactericidal efficacy both in the proliferation and in the resting stage of bacteria. It forms a bond with the proteins of the 30S subunits of the bacterial ribosomes, which causes "misreading" of the mRNA.

No new non-clinical or clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. A bioequivalence study was not necessary to support these applications for parenteral products, containing the same active substance as the reference products.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

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.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and these are satisfactory.

The RMS and CMS agreed to grant Marketing Authorisations for the above products at the end of the procedure (Day 210 – 29th October 2014). After a subsequent national phase, the UK granted Marketing Authorisations to Edmond Pharma S.r.l. on 24 November 2014.

A change of ownership was granted on 13 January 2015 to change the Marketing Authorisation Holder to Wockhardt UK Ltd (PL 29831/0659-0660).

II. QUALITY ASPECTS

II.1 Introduction

Each ml of Solution for Injection or Infusion contains 10 mg or 40 mg gentamicin (as gentamicin sulphate) respectively. The excipients are sodium metabisulfite (E223), sulfuric acid (10%) or sodium hydroxide and Water for Injections.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The finished product is packaged in a 2 ml type I glass ampoules. The pack sizes are 5 and 10 (40 mg/ml only) ampoules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

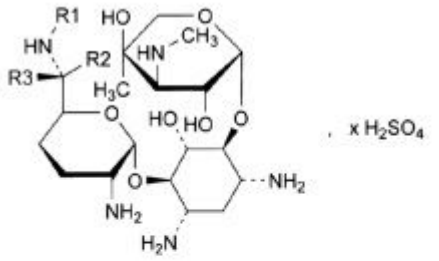
II.2 Drug Substance

Gentamicin sulphate

INN: Gentamicin sulphate

Chemical name(s): Gentamicin sulphate is a mixture of sulphates of the antimicrobic substances deriving from the Micromonospora purpurea fermentation. It is composed of 5 principal components: Gentamicin C_1, Gentamicin C_2, Gentamicin C_{1a}, Gentamicin C_{2a}, Gentamicin C_{2b}.

Structure:



Gentamicin	Mol. Formula	R1	R2	R3
C1	$C_{21}H_{43}N_5O_7$	CH_3	CH_3	H
C1a	$C_{19}H_{39}N_5O_7$	H	H	H
C2	$C_{20}H_{41}N_5O_7$	H	CH_3	H
C2a	$C_{20}H_{41}N_5O_7$	H	H	CH_3
C2b	$C_{20}H_{41}N_5O_7$	CH_3	H	H

Molecular formula: $C_{17}H_{18}FN_3O_3$

Molecular weight: 331.4 g/mol

Appearance: White or almost white hygroscopic powder.

Solubility: Gentamicin sulphate is very soluble in water and practically insoluble in alcohol.

Gentamicin sulphate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance gentamicin sulphate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain stable solution for injection or infusion containing gentamicin sulphate that could be considered as generic medicinal products of Cidomycin Paediatric Injectable 20 mg/2 m1 and CidomycinTM Adult Injectable 80 mg/2 ml (Roussel Laboratories Ltd).

Comparative impurity profiles have been provided for the proposed and originator products.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated and have shown satisfactory results. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specifications
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months with storage conditions "Do not store above 25°C", "Do not refrigerate or freeze" and "Store in the original package in order to protect from light" have been set. These are satisfactory.

The product should be used immediately once the ampoule is opened.

After dilution: when diluted with 0.9% sodium chloride or 5% glucose solution, gentamicin is stable for 24 h at 25°C.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.
From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of Marketing Authorisations is recommended.

III. NON-CLINICAL ASPECTS

III.1 Introduction
No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed products are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of these products from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
In accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), a bioequivalence study is not required if the test product is a solution containing the same active substance as the reference product. As these products are solution at the time of administration, no bioequivalence studies have been submitted and none are required.

IV.2 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

IV.3 Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data have been submitted and none are required for these applications.

IV.5 Clinical safety
No new safety data have been submitted and none are required for these applications.

IV.6 Risk Management Plan (RMP)
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 Gentamicin 10 mg/ml and 40 mg/ml Solution for Injection or Infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity & anaphylaxis.	Specific statement in section 4.3 of SmPC and correspondent statement in section 2 of PIL	None
Risk of neuromuscular blockade resulting in severe muscle weakness if used in patients with myasthenia gravis, other neuromuscular disorders (e.g. Parkinson's disease), concurrently with botulinum toxin and anaesthesia with curare-type muscle relaxants & ether.	Specific statement in section 4.3 of SmPC and correspondent statement in section 2 of PIL	None
Risk of renal impairment in approximately 10% of patients treated with gentamicin.	Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL	None
Risk of ototoxicity (e.g. vestibular damage).	Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL	None
Risk of antibiotic-associated diarrhoea and pseudomembranous colitis after use of gentamicin.	Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL	None
Risk of antibiotic-associated diarrhoea and pseudomembranous colitis after use of gentamicin.	Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL	None
Risk to fetus if used during pregnancy & to newborn if used during breastfeeding.	Specific statement in section 4.4 and 4.6 of SmPC and correspondent statement in section 2 of PIL	None
Risk of severe hypersensitivity reactions and bronchospasm given the presence of sodium metabisulphite as excipient.	Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL	None
Risk of cross resistance and hypersensitivity to aminoglycosides.	Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL	None
Risk of nephrotoxicity and ototoxicity when concomitant administration with other nephrotoxic and ototoxic drugs (e.g. some cephalosporins, amphotericin B, loop diuretics, cisplatin, ciclosporin).	Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL	None
Risk of increased anticoagulant effect when concomitant administration with oral anticoagulants.	Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL	None
Risk of severe nephropathies when concurrent administration with	Specific statement in section 4.5 of SmPC and correspondent statement in	None

methoxyflurane.	section 2 of PIL	
Risk of hypocalcaemia in case of concurrent use of bisphosphonates.	Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL	None
Serious blood dyscrasias (including thrombocytopenia, leucopenia, granulocytopenia)	The reactions are listed in section 4.8 of SmPC and in section 4 of PIL	None
Serious dermatological effects (including erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome)	The reactions are listed in section 4.8 of SmPC and in section 4 of PIL	None
Risk of lack of efficacy due to non-sensitive or resistant species to gentamicin.	Specific statement in section 5.1 of SmPC	None
Risk of inactivation of gentamicin if mixed with other medicinal products, such as beta-lactam antibiotics, erythromycin, lipiphysan, diazepam, furosemide, flecainide acetate, heparin sodium, amphotericin B, cephalothin sodium, nitrofurantoin sodium, sulfadiazine sodium and tetracyclines. Addition of gentamicin to solutions containing bicarbonate may lead to the release of carbon dioxide	Specific statement in section 6.2 of SmPC	None
Risk of elevated plasma gentamicin concentrations if used with indomethacin in neonates.	Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL	None
Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine.	Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL	None

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended.

V. OVERALL CONCLUSIONS

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, as amended. 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*.

OVERALL CONCLUSION, BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

Quality

The important quality characteristics of Gentamicin 10 mg/ml and 40 mg/ml Solutions for Injection or Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

In accordance with the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), bioequivalence studies were not conducted and none are required for these type of products.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with gentamicin sulphate is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

VI. REVISION DATE

August 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
To update section 4.2 (posology and administration) of the SmPC in line with the innovator products, Cidomycin Paediatric 20 mg/2 ml Solution for Injection and Cidomycin 80 mg/2 ml Solution for Injection. As a consequence of the Patient Information Leaflet (PIL) and labelling have been amended	UK/H/5516/001-002/ 1B/003	SmPC, PIL andLabelling	19/11/2015	17/01/2016	Approved
RMS Transfer	From UK/H/5516/001-002/ DC to IE/H/0614/001-002/D C	N/A	N/A	N/A	Approved 20/06/2018
MA Transfer	CRN009Z0V	SmPC, Leaflet Old MA holder: Wockhardt UK Limited New MA Holder: Pinewood Laboratories Ltd OLD PA number: PA1339/065/001-002 New PA number: PA0281/242/001-002	31/12/2020	31/12/2020	Approved