Public Assessment Report

Decentralised Procedure

Gentamicin 10 mg/ml and 40 mg/ml Solution for Injection or Infusion

(gentamicin sulphate)

Procedure No: UK/H/5516/001-2/DC

UK Licence No: PL 29831/0659-60

Wockhardt UK Ltd
LAY SUMMARY
Gentamicin 10 mg/ml and 40 mg/ml Solution for Injection or Infusion
(gentamicin sulphate)

This is a summary of the public assessment report (PAR) for Gentamicin 10 mg/ml and 40 mg/ml Solution for Injection or Infusion (PL 29831/0659-0660; UK/H/5516/001-02/D). It explains how Gentamicin 10 mg/ml and 40 mg/ml Solution for Injection or Infusion were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Gentamicin 10 mg/ml and 40 mg/ml Solution for Injection or Infusion. These medicinal products will be collectively referred to as Gentamicin Solution in this summary.

For practical information about using Gentamicin Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Gentamicin Solution and what is it used for?
Gentamicin Solution is a “generic medicine”. This means that Gentamicin Solution is similar to ‘reference medicines’ already authorised in the European Union (EU) called Cidomycin Paediatric Injectable 20 mg/2 ml and CidomycinTM Adult Injectable 80 mg/2 ml (Roussel Laboratories Ltd; PL 00109/5065R-5066R).

Gentamicin Solution is used to treat infections caused by bacteria in adults and children including new-borns. This includes infections in the:

- Urinary tract (including kidney or bladder)
- Chest (including lungs)
- Blood – this is sometimes called “bacteraemia”
- Other serious infections

How is Gentamicin Solution used?
Gentamicin Solution is given by a health professional as an injection or infusion into the muscle or vein.

The correct dose will be decided by a doctor depending on the weight, type of infection and other illness the patient may have.

The usual daily dose in adults is 3-5 mg for each kg of body weight. This is split into doses given every 6-8 hours. Patients with kidney problems may be given a lower dose. Elderly patients should be closely checked when given this medicine.

The recommended dose in children (aged 1 year and above) is 3-6 mg for each kg of body weight. In babies (aged 4 weeks to 1 year) the usual daily dose is 4.5 to 7.5 mg for each kg of body weight. These are given either as a single dose or sometimes are split into 2 separate doses.

The usual daily dose in new born babies (up to 4 weeks) is 4 to 7 mg for each kg of body weight. This is given in a single dose.

Gentamicin Solution can only be obtained with a prescription from a doctor.
For further information on how Gentamicin Solution is used, please see the Summaries of Product Characteristics or the package leaflet available on the MHRA website.

How does Gentamicin Solution work?
Gentamicin Solution contains an active ingredient called gentamicin sulphate which belongs to a group of antibiotics called aminoglycosides. It works by killing the bacteria that causes infection.

How has Gentamicin Solution been studied?
No additional studies were needed as Gentamicin Solution is a generic medicine that is given intramuscularly or intravenously and contain the same active substance and content as the reference medicines, Cidomycin Paediatric Injectable 20 mg/2 ml and CidomycinTM Adult Injectable 80 mg/2 ml (Roussel Laboratories Ltd; PL 00109/5065R-5066R).

What are the benefits and risks of Gentamicin Solution?
As Gentamicin Solution is a generic medicine and is comparable to the reference medicines, Cidomycin Paediatric Injectable 20 mg/2 ml and CidomycinTM Adult Injectable 80 mg/2 ml, its benefits and risks are taken as being the same as those of Cidomycin Paediatric Injectable 20 mg/2 ml and CidomycinTM Adult Injectable 80 mg/2 ml (Roussel Laboratories Ltd; PL 00109/5065R-5066R).

Why is Gentamicin Solution approved?
It was concluded that, in accordance with EU requirements, Gentamicin Solution has been shown to have comparable quality and to be comparable to Cidomycin Paediatric Injectable 20 mg/2 ml and CidomycinTM Adult Injectable 80 mg/2 ml. Therefore, the MHRA decided that, as for Cidomycin Paediatric Injectable 20 mg/2 ml and CidomycinTM Adult Injectable 80 mg/2 ml, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Gentamicin Solution?
A risk management plan has been developed to ensure that Gentamicin Solution is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Gentamicin Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Gentamicin Solution
The Marketing Authorisations for Gentamicin 10 mg/ml and 40 mg/ml Solution for Injection or Infusion (PL 14682/0021-22) were granted in the UK to Edmond Pharma S.r.l. on 24 November 2014.

Changes of ownership were granted on 13 January 2015 to change the Marketing Authorisation Holder to Wockhardt UK Ltd (PL 29831/0659-60).

The full PAR for Gentamicin Solution follows this summary. For more information about treatment with Gentamicin Solution, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in February 2016.
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I. INTRODUCTION

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 14682/0021-22; UK/H/5516/001-2/DC), are approvable. These prescription only medicines (POM) are indicated for bacteraemia, urinary tract infections, chest infections, severe neonatal infections and other serious systemic infections due to susceptible organisms, in adults and children including neonates.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as the RMS and Republic of Ireland as a 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 ml and CidomycinTM Adult Injectable 80 mg/2 ml, originally granted to Roussel Laboratories Ltd (PL 00109/5065R-5066R) on 24 January 1991.

Gentamicin is an aminoglycoside antibiotic extracted from Micromonospora purpurea. It represents a mixture of the structurally very similar homologues gentamicin C₁, C₁₄ and C₂. The gentamicin homologue C₂ 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 – 29 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 procedure was granted on 13 January 2015 to change the Marketing Authorisation Holder to Wockhardt UK Ltd (PL 29831/0659-60).
II QUALITY ASPECTS

II.1 Introduction
Each ml of Solution for Injection or Infusion contains 10 mg or 40 mg gentamicin (as gentamicin sulphate) as the active ingredient. 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 or 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 antimicrobial substances deriving from the Micromonospora purpurea fermentation. It is composed of 5 principal components: Gentamicin C₁, Gentamicin C₂, Gentamicin C₁a, Gentamicin C₂a, Gentamicin C₂b.

Structure:

Molecular formula: C₁₇H₁₈FN₃O₃
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 a generic medicinal product of Cidomycin Paediatric Injectable 20 mg/2 ml 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.

After first opening: from the microbiological point of view, the product should be used immediately.
After dilution: when diluted with 0.9% sodium chloride or 5% glucose solution, gentamicin is stable for 24 hour 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:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity &amp; anaphylaxis.</td>
<td>Specific statement in section 4.3 of SmPC and correspondent</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>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 &amp; ether.</td>
<td>Specific statement in section 4.3 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of renal impairment in approximately 10% of patients treated with gentamicin.</td>
<td>Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of ototoxicity (e.g. vestibular damage).</td>
<td>Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of antibiotic-associated diarrhoea and pseudomembranous colitis after use of gentamicin.</td>
<td>Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of antibiotic-associated diarrhoea and pseudomembranous colitis after use of gentamicin.</td>
<td>Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk to fetus if used during pregnancy &amp; to newborn if used during breastfeeding.</td>
<td>Specific statement in section 4.4 and 4.6 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of severe hypersensitivity reactions and bronchospasm given the presence of sodium metabisulphite as excipient.</td>
<td>Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of cross resistance and hypersensitivity to aminoglycosides.</td>
<td>Specific statement in section 4.4 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of nephrotoxicity and ototoxicity when concomitant administration with other nephrotoxic and ototoxic drugs (e.g. some cephalosporins, amphotericin B, loop diuretics, cisplatin, ciclosporin).</td>
<td>Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
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</tr>
<tr>
<td>Risk of increased anticoagulant effect when concomitant administration with oral anticoagulants.</td>
<td>Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of severe nephropathies when concurrent administration with methoxyflurane.</td>
<td>Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of hypocalcaemia in case of concurrent use of bisphosphonates.</td>
<td>Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Serious blood dyscrasias (including thrombocytopenia, leucopenia, granulocytopenia)</td>
<td>The reactions are listed in section 4.8 of SmPC and in section 4 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Serious dermatological effects (including erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome)</td>
<td>The reactions are listed in section 4.8 of SmPC and in section 4 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Risk of lack of efficacy due to non-sensitive or resistant species to gentamicin.</td>
<td>Specific statement in section 5.1 of SmPC</td>
<td>None</td>
</tr>
<tr>
<td>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</td>
<td>Specific statement in section 6.2 of SmPC</td>
<td>None</td>
</tr>
<tr>
<td>Risk of elevated plasma gentamicin concentrations if used with indomethacin in neonates.</td>
<td>Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
<tr>
<td>Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or</td>
<td>Specific statement in section 4.5 of SmPC and correspondent statement in section 2 of PIL</td>
<td>None</td>
</tr>
</tbody>
</table>
Safety concern | Routine risk minimisation measures | Additional risk minimisation measures
--- | --- | ---
pyridostigmine.

IV.7 Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

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, as amended. The language used for the purpose of user testing the PIL was English.

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
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.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website. The current approved UK labelling is available in Annex 1.
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

The following table lists a non-safety update to the Marketing Authorisations for these products that has been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure numbers</th>
<th>Product information affected</th>
<th>Date of start of procedures</th>
<th>Date of end of procedures</th>
<th>Approval / non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>UK/H/5516/001-2/1B/003</td>
<td>SmPCs, PIL and labelling</td>
<td>19/11/2015</td>
<td>17/01/2016</td>
<td>Approved</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 29831/0659-0008; PL 29831/0660-0008

Product: Gentamicin 10 mg/ml and 40 mg/ml Solution for Injection or Infusion

Marketing Authorisation Holder: Wockhardt UK Limited

Active Ingredient: Gentamicin sulphate

Reason:
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 the Patient Information Leaflet (PIL) and labelling have been amended.

Supporting evidence
The applicant has submitted an updated Section 4.2 of the SmPCs, PIL and labelling.

Evaluation
The amended section of the SmPCs, PIL and labelling are satisfactory.

Conclusion
The proposed changes are acceptable. The updated SmPCs, PIL and labelling have been submitted and are acceptable.

In accordance with Directive 2010/84/EU, the current granted UK SmPCs, PIL and labelling are available on the MHRA website.

Decision
Grant

Date: 17 January 2016