



Public Assessment Report

National Procedure

**Gentamicin 10 mg/ml solution for
injection/infusion**

gentamicin sulfate

PLGB 44124/0059

Panpharma

LAY SUMMARY

Gentamicin 10 mg/ml solution for injection/infusion gentamicin sulfate

This is a summary of the Public Assessment Report (PAR) for Gentamicin 10 mg/ml solution for injection/infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Gentamicin in this lay summary for ease of reading.

For practical information about using Gentamicin, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Gentamicin and what is it used for?

This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU), called Garamycin 40 mg/ml solution for injection, and in the United Kingdom (UK) called Cidomycin 80 mg/2ml Solution for Injection, albeit with certain differences. In this case, Gentamicin 10 mg/ml solution for injection/infusion is for the change in strength.

This application is for a line extension of the existing product, Gentamicin 40 mg/ml, solution for injection/infusion (PL 44124/0028).

Gentamicin is used to treat severe infections with bacteria.

The medicine may be used to treat the following diseases:

- Complicated infections of the urinary tract
- Infections and inflammation within the belly
- Infections of lungs and airways occurring during hospital treatment
- Infections of lungs from cystic fibrosis
- Inflammation of the inner lining of the heart (to treat infections)
- Infections of the skin related to severe burns
- Serious infections with bacteria in the blood

Gentamicin should only be used in combination with other antibiotics except for complicated infections of the kidneys, urinary tract and bladder.

How does Gentamicin work?

Gentamicin belongs to a group of medicines called antibiotics, that is, they are used to treat severe infections with bacteria that can be killed by the active substance gentamicin.

How is Gentamicin used?

The pharmaceutical form of this medicine is a solution for injection/infusion, and the route of administration is intravenous (into a vein) or intramuscular (into a muscle) use.

This medicine is administered as an infusion over 20-30 minutes into the vein in diluted form or as an injection directly into the vein over no less than 3 minutes or administration into the muscle.

Gentamicin must *not* be administered via the inhalation route.

Individual dose will be determined by the patient's doctor according to their body weight and kidney function.

Daily doses of gentamicin are administered in a single injection. In certain situations, the dose may be given as two injections over 24 hours. The treatment course may be complete after two to three days or continued for a maximum of seven days, according to test results.

The adult dose is 3-6 mg/kg/day, depending on the duration of the course, type and severity of the bacterial infection.

Patient's doctor will monitor their blood level of Gentamicin during treatment, especially if they are elderly, newborn, obese, have renal impairment or suffer from cystic fibrosis (a serious disease affecting several organs for example the lungs and gastrointestinal system).

Use in children and adolescents

- Children and adolescent with normal kidney function will be given their daily dose 3-6 mg/kg administered in one injection. The dose may be divided into two injections over 24 hours in certain situations.
- Infants after their first month of life: 4,5-7,5 mg/kg daily administered in one injection. The dose may be divided into two injections over 24 hours in certain situations.
- Neonates and pre-term infants (aged 0-4 weeks old): 4-7 mg/kg daily administered in one injection.

The accuracy of dosing in children is very important as even minor errors may be significant. There is *no* dose recommendation for children with impaired kidney function.

For patients with impaired kidney function

First injection: 3 to 6 mg/kg/day. Other injections will be given either in the same dose or adjusted according to the patient's gentamicin blood levels.

If the patient is undergoing dialysis, they will be administered Gentamicin 2 to 4 hours before the dialysis in order to reduce the potential toxicity.

For elderly patients

The treatment with Gentamicin will be determined according to the patient's kidney function and signs of toxicity.

For obese patients

The patient will be administered the dose according to their lean body weight.

For patients with impaired liver function

No dosage adjustment is necessary.

For further information on how Gentamicin is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient or caregiver should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Gentamicin have been shown in studies?

No additional studies were needed as Gentamicin contain the same active substance as the reference medicine, and satisfactory data to justify the differences have been provided.

What are the possible side effects of Gentamicin?

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at <https://yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Gentamicin is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

Why was Gentamicin approved?

Gentamicin is a line extension of the existing product, Gentamicin 40 mg/ml, solution for injection/infusion (PL 44124/0028), some of the data and information which supported the approval decision was based on that submitted for the previously authorised products. Furthermore, the side effects observed with use of these products are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

What measures are being taken to ensure the safe and effective use of Gentamicin?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Gentamicin. The RMP details the important risks of Gentamicin, how these risks can be minimised, any uncertainties about Gentamicin (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Gentamicin.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Gentamicin are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Gentamicin

A Marketing Authorisation for Gentamicin was granted in the Great Britain (GB, consisting of England, Scotland and Wales) on 25 September 2024.

The full PAR for Gentamicin follows this summary.

This summary was last updated in October 2024.

TABLE OF CONTENTS

I	INTRODUCTION	7
II	QUALITY ASPECTS	9
III	NON-CLINICAL ASPECTS.....	11
IV	CLINICAL ASPECTS.....	11
V	USER CONSULTATION	12
VI	OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION	12
	TABLE OF CONTENTS OF THE PAR UPDATE	13

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Gentamicin 10 mg/ml solution for injection/infusion(PLGB 44124/0059) could be approved.

The product is approved for the following indications:

Treatment of the below infections in adults and children from birth when less toxic antimicrobial agents are not effective.

Under these conditions, Gentamicin 10 mg/ml solution for injection/infusion is indicated in the treatment of the following infections:

- Complicated urinary tract infection (cUTI), including acute pyelonephritis
- Complicated intra-abdominal infection (cIAI)
- Hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP)
- Broncho-pulmonary infections in patients with cystic fibrosis
- Infective endocarditis
- Burn wound infections
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Gentamicin 10 mg/ml solution for injection/infusion should for all indications, except complicated urinary tract infections, only be used in combination with other relevant antibiotics (predominantly together with a beta-lactam antibiotic or with an antibiotic effective against anaerobic bacteria).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The active substance, gentamicin is an aminoglycoside antibiotic extracted from *Micromonospora purpurea*. It represents a mixture of the structurally very similar homologues gentamicin C1, C1a 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 a bactericidal effect on both the proliferation and latency of bacteria. It forms a bond with bacterial 30S ribosomal subunits, which causes misreading of mRNA.

This application was approved under Regulation 52A of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Garamycin 40 mg/ml solution for injection and Cidomycin 80 mg/2ml Solution for Injection, that has been licensed for a suitable time in the EU and UK respectively, in line with the legal requirements. This application is for a line extension of the existing product, Gentamicin 40 mg/ml, solution for injection/infusion (PL 44124/0028) to add a new dose strength.

No new non-clinical studies were conducted, which is acceptable given that the application is for a hybrid medicinal product of a suitable reference product.

A biowaiver was submitted with this application which was accepted. A bioequivalence study was not necessary to support this application for a parenteral product and the applicant

submitted none. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

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

A national marketing authorisation was granted in the Great Britain (GB, consisting of England, Scotland and Wales) on 25 September 2024.

II QUALITY ASPECTS

II.1 Introduction

The active substance is gentamicin.

Each ampoule of 2 ml contains either 20.0 mg or 80.0 mg of gentamicin as gentamicin sulfate.

In addition to gentamicin sulfate, this product also contains the following excipients: disodium edetate, sodium chloride, sulfuric acid (for pH adjustment) and water for injections.

The finished product is packaged in glass type I ampoules and are available in a pack-size of 5 ampoules in each box.

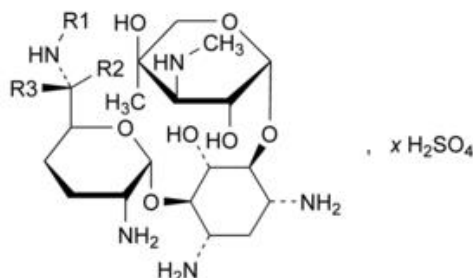
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: gentamicin sulfate

Chemical Name: Gentamicin sulfate is a mixture of the sulfates of antimicrobial substances produced by *Micromonospora purpurea*, the main components being gentamicins C1, C1a, C2, C2a and C2b.

Structural Formula:



Gentamicin	Mol. Formula	R1	R2	R3
C1	C ₂₁ H ₄₃ N ₅ O ₇	CH ₃	CH ₃	H
C1a	C ₁₉ H ₃₉ N ₅ O ₇	H	H	H
C2	C ₂₀ H ₄₁ N ₅ O ₇	H	CH ₃	H
C2a	C ₂₀ H ₄₁ N ₅ O ₇	H	H	CH ₃
C2b	C ₂₀ H ₄₁ N ₅ O ₇	CH ₃	H	H

Appearance: White or almost white, hygroscopic powder.

Solubility: Freely soluble in water, practically insoluble in ethanol (96 per cent).

Gentamicin sulfate is the subject of a European Pharmacopoeia monograph.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life 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

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the storage conditions 'Store below 30°C', and 'Do not freeze', is acceptable. After opening, the product must be used immediately.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C when diluted with the infusion fluids.

Chemical and physical in-use stability has also been demonstrated for 3 hours at 25°C, after 24 hours at 2-8°C when diluted with the infusion fluids.

From a microbiological point of view, 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 and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution have taken place in controlled validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of gentamicin sulfate is well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

In accordance with the regulatory requirements, the applicant has provided a suitable biowaiver. No bioequivalence or therapeutic equivalence studies have been submitted with this application.

IV.2 Pharmacokinetics

No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application, and none were required. The safety profile for this product is considered to be the same as Garamycin 40 mg/ml Solution for Injeciton and Cidomycin 80 mg/2ml Solution for Injection.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

In accordance with legal requirements, the current approved versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N