Public Assessment Report

UKPAR

Cidomycin 80mg/2ml Solution for Injection

(gentamicin sulphate)

UK Licence Number: PL 04425/0672

Aventis Pharma Limited
LAY SUMMARY
Cidomycin 80mg/2ml Solution for Injection
(gentamicin sulphate)

This is a summary of the Public Assessment Report (PAR) for Cidomycin 80mg/2ml Solution for Injection (PL 04425/0672). It explains how Cidomycin 80mg/2ml Solution for Injection was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use this product.

For ease of reading, this medicinal product will be referred to as Cidomycin Solution for Injection in this Lay Summary.

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

What is Cidomycin Solution for Injection and what is it used for?
This medicine is the same as Cidomycin Adult 80mg/2ml Solution for Injection (PL 04425/0181), previously authorised to the same Marketing Authorisation Holder (Aventis Pharma Limited).

Cidomycin is used to treat infections caused by bacteria. This includes infections in:

• the urinary tract (including the kidneys or bladder)
• the chest (including the lungs)
• the abdomen (including the gut)
• the brain and spinal cord
• the blood – this is sometimes called ‘bacteraemia’ or ‘septicaemia’
• Newborn babies

How is Cidomycin Solution for Injection used?
The pharmaceutical form of this medicine is a solution for injection. Cidomycin is always given as an injection by a doctor or nurse.

A doctor will decide on the dosage depending on the weight of the patient. The correct dose also depends on the type of infection and any other illnesses the patient may have, in particular diseases of the kidney.

Blood samples will be taken by a doctor or nurse to check the dose is right for a patient. The patient should not receive Cidomycin if these blood tests cannot be performed.

The patient may also need tests to check his/her hearing and balance.

Elderly or obese people, newborns, people with impaired kidney function and those with cystic fibrosis should be particularly closely monitored when having this medicine.

The usual daily dose in adults is 3-5mg for each kg of body weight. This is given either as one single dose (preferred) or split into two or three daily doses. This dose may be increased or decreased by a doctor depending on the illness and the results of the blood tests. If the patient has kidney problems a doctor may give him/her a lower dose or may prolong the interval between doses.
The usual daily dose in children and adolescents and children (aged 1 year and above) is 3-6mg for each kg of body weight. This is given either as one single dose (preferred) or split into two separate doses.

The usual daily dose in babies (aged 4 weeks to 1 year) is 4.5-7.5mg for each kg of body weight. This is given either as one single dose (preferred) or split into two separate doses.

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

Cidomycin Solution for Injection can only be obtained on a prescription from a doctor.

For further information on how Cidomycin Solution for Injection is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**How does Cidomycin Solution for Injection work?**
Cidomycin Solution for Injection contains the active ingredient gentamicin as gentamicin sulphate. This belongs to a group of antibiotics called ‘aminoglycosides’. It is used to treat infections caused by bacteria.

**What benefits of Cidomycin Solution for Injection have been shown in studies?**
Cidomycin Solution for Injection (PL 04425/0672) is considered to be identical to the previously authorised product, Cidomycin Adult 80mg/2ml Solution for Injection (Aventis Pharma Limited, PL 04425/0181), with the same benefits and risks, so no new studies have been provided for Cidomycin Solution for Injection (PL 04425/0672) but reference is made to the studies for Cidomycin Adult 80mg/2ml Solution for Injection (Aventis Pharma Limited, PL 04425/0181).

**What are the possible side effects from Cidomycin Solution for Injection?**
The most common side effects with Cidomycin Solution for Injection (may affect more than 1 in 10 people) is being sick (vomiting).

For the full list of all side effects reported with Cidomycin Solution for Injection, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why is Cidomycin Solution for Injection approved?**
No new or unexpected safety concerns arose from this application. The MHRA, therefore, considered that the benefits of Cidomycin Solution for Injection outweigh its risks; and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Cidomycin Solution for Injection?**
A satisfactory pharmacovigilance system has been provided to monitor the safety of this product.

**Other information about Cidomycin Solution for Injection**
A Marketing Authorisation was granted in the UK on 27 July 2011.

The full PAR for Cidomycin Solution for Injection follows this summary.
This summary was last updated in February 2019.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Introduction</td>
</tr>
<tr>
<td>II</td>
<td>Quality aspects</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
</tr>
<tr>
<td></td>
<td>Table of content of the PAR update</td>
</tr>
<tr>
<td></td>
<td>Annex</td>
</tr>
</tbody>
</table>
I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Aventis Pharma Limited a Marketing Authorisation for the medicinal product Cidomycin 80mg/2ml Solution for Injection (PL 04425/0672) on 27 July 2011. This is a prescription-only medicine (POM).

Gentamicin is an aminoglycoside antibiotic with broad-spectrum bactericidal activity. It is indicated to treat severe infections caused by bacteria susceptible to gentamicin such as, but not limited to:

- Urinary tract infections
- Respiratory tract infections
- Intra-abdominal infections
- CNS infections
- Severe neonatal infections

It is usually active against most strains of the following organisms: Escherichia coli, Klebsiella spp., Proteus spp. (indole positive and indole negative), Pseudomonas aeruginosa, Staphylococci, Enterobacter spp., Citrobacter spp. and Providencia spp.

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

This application was submitted as an abridged simple application, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Cidomycin Adult 80mg/2ml Solution for Injection, which was authorised to Roussel Laboratories Limited (PL 00109/5065R) on 24 January 1991. Following a change of ownership procedure the Marketing Authorisation had transferred to Aventis Pharma Limited (PL 04425/0181) on 14 July 2010.

Cidomycin 80mg/2ml Solution for Injection contains the active substance gentamicin, which is a mixture of antibiotic substances produced by the growth of micromonospora purpurea. It is bactericidal with greater antibacterial activity than streptomycin, neomycin or kanamycin.

Gentamicin exerts a number of effects on cells of susceptible bacteria. It affects the integrity of the plasma membrane and the metabolism of RNA, but its most important effects is inhibition of protein synthesis at the level of the 30s ribosomal subunit.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted cross-reference product.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a product that is identical to an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.
It is not considered that this medicinal product represents any risk to the environment. There is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The availability of this medicinal product, which is identical to the cited reference product, will not lead to any increase in environmental exposure concentrations of the active ingredient, gentamicin. An Environmental Risk Assessment (ERA) is not considered necessary.

No new data were submitted, nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) was generated for it.
II QUALITY ASPECTS

II.1 Introduction
This is a simple, informed consent application for Cidomycin 80mg/2ml Solution for Injection (PL 04425/0672) submitted under Article 10c of Directive 2001/83/EC, as amended. The reference product is Cidomycin Adult 80mg/2ml Solution for Injection, which was authorised to Roussel Laboratories Limited (PL 00109/5065R) on 24 January 1991. Following a change of ownership procedure the Marketing Authorisation has transferred to Aventis Pharma Limited (PL 04425/0181) on 14 July 2010. The proposed and reference products are identical. The application is considered valid.

II.2 Drug Substances
Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3 Medicinal Product
Name
The proposed product name is Cidomycin 80mg/2ml Solution for Injection. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack size
Each ampoule or vial (2 ml) gentamicin sulphate Ph. Eur. equivalent to 80 mg gentamicin base. The route of administration is intravenous or intramuscular.

The finished product is supplied in packs of 5 x 2ml type I colourless glass ampoules an one point cut (OPC) break system and red and green rings or in packs of 5 x 2ml type I colourless glass vials closed with a chlorobutyl rubber stopper sealed with an aluminium capsule type flip-off.

Not all pack sizes may be marketed.

The proposed shelf-life is 3 years for the medicinal product “Do not store above 25°C” and “Do not refrigerate or freeze” are identical to the details registered for the cross-reference product.

The proposed packaging, shelf-life and storage conditions are consistent with the details registered for the cross-reference product.

Legal status
This product is prescription-only medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Aventis Pharma Limited, One Onslow Street, Guildford, Surrey, GU1 4YS, UK

Or trading as-
Sanofi-aventis or Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS, UK

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory Curriculum Vitae (CV) has been provided.
Manufacturer
The proposed manufacturing site is consistent with that registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

TSE Compliance
None of the excipients contain materials of animal or human origin. This is consistent with the cross-reference product.

Bioequivalence
No bioequivalence data are required to support this simple abridged application as the proposed product is manufactured to the same formula utilising the same process as the cross-reference product, Cidomycin Adult 80mg/2ml Solution for Injection (PL 04425/0181).

Expert Report
The applicant cross-refers to the data for Cidomycin Adult 80mg/2ml Solution for Injection (PL 04425/0181), to which this application is claimed to be identical. This is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
Introduction
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Environmental Risk Assessment (ERA)
A suitable justification has been provided for not submitting an environmental risk assessment. As the application is identical version of already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.
IV CLINICAL ASPECTS

Introduction
This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referring to the Marketing Authorisation for Cidomycin Adult 80mg/2ml Solution for Injection (PL 04425/0181).

No new clinical data have been supplied with the application, and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.

Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

V User consultation
PIL user testing has been accepted based on a bridging statement provided by the applicant making reference to the successful user-testing of the PIL for the reference product, Cidomycin Adult 80mg/2ml Solution for Injection (PL 04425/0181). The text, content and layout of the proposed PIL are essentially identical to the approved PIL for the reference product. The bridging is accepted.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant’s product identical to the reference product. The benefit-risk assessment is, therefore, considered to be positive.
**Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels**

The Summary of Product Characteristics and Patient Information Leaflet (PIL) are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Cidomycin 80mg/2ml Solution for Injection is presented below:
Table of content of the PAR update

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

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/09/2017</td>
<td>Type II</td>
<td>To update sections 4.2 and 4.4 of the SmPC to introduce a preferred `once daily dosing' (ODD) schedule for adults in addition to the previously approved ODD paediatric schedule. To update section 4.8 of the SmPC due in particular to new quality, non-clinical, clinical or pharmacovigilance data.</td>
<td>Approved on 11/01/2019</td>
</tr>
</tbody>
</table>

The change to update section 4.8 of the SmPC was rejected during assessment of the initial variation application (PL 04425/0672-0022). A separate variation application (PL 04425/0376-0024) was submitted to include the updates recommended in the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report on the PSUR for gentamicin. The MAH has also restructured sections 4.4 and 4.8 of the SmPC.
Annex 1

Reference: PL 04425/0672-0022

Product: Cidomycin 80mg/2ml Solution for Injection

Marketing Authorisation Holder: Aventis Pharma Limited

Active Ingredient: Gentamicin sulphate

Type of Procedure: National

Submission category: Type II Variation

Reason:
To update sections 4.2 and 4.4 of the SmPC to introduce a preferred 'once daily dosing' (ODD) schedule for adults in addition to the previously approved ODD paediatric schedule.
To update section 4.8 of the SmPC due in particular to new quality, non-clinical, clinical or pharmacovigilance data.

The change to update section 4.8 of the SmPC was rejected during assessment of the initial variation application (PL 04425/0672-0022). A separate variation application (PL 04425/0376-0024) was submitted to include the updates recommended in the PRAC assessment report on the PSUR for gentamicin. The MAH has also restructured sections 4.4 and 4.8 of the SmPC.

Supporting evidence
For sections 4.2 and 4.4

Once daily dosing
The applicant stated that according to current guidelines, once daily dosing (ODD) or extended interval dosing is favoured over conventional (multiple daily) dosing for several reasons: (i) concentration dependent bacterial killing, (ii) toxicity linked to trough levels, (iii) post antibiotic effect, and (iv) adaptive resistance.

Concentration-dependent killing:
Gentamicin exhibits concentration-dependent bacterial killing against Gram-negative bacteria and partially concentration-dependent bacterial killing against Gram-positive strains, meaning that a minimum peak level must be achieved to obtain bactericidal activity, and that killing efficiency is amplified by increases in peak concentration. Higher peak concentrations are achieved with ODD where the total daily dose is administered in a single infusion.

Toxicity linked to trough levels:
Toxicity of gentamicin administered once daily was not found to be more nephrotoxic or ototoxic than the same daily dose given in two to three infusions. Some studies showed lower nephrotoxicity with ODD as compared to conventional dosing, which might be due to the fact that nephrotoxicity correlates with $C_{\text{min}}$ (trough level) and treatment duration, but not $C_{\text{max}}$. Indeed, aminoglycosides are mainly eliminated via glomerular filtration. A fraction is reabsorbed in the proximal tubule, and aminoglycosides accumulate within lysosomes. This mechanism is saturable meaning that higher peak concentrations do not increase accumulation. However, during repetitive dosing, lysosomes continuously take up a fraction of the drug, leading to size increase, disruption and liberation of
proteolytic enzymes into the cell cytosol, which ultimately leads to cell necrosis and renal failure (1). For either dosing regimen, treatment duration is directly linked to toxicity and should be limited to 5-7 days.

**Post-antibiotic effect:**
Aminoglycoside antibiotics exhibit a post-antibiotic effect (PAE), which means that bacterial growth is suppressed for a period of time after administration of the antibiotic. Bacteria in the PAE are more susceptible to intracellular killing and phagocytosis by leukocytes.

**Adaptive resistance:**
Finally, aminoglycosides are subject to adaptive resistance, generally due to down-regulation of drug uptake into bacteria. However, in case of some bacteria, such as *P. aeruginosa*, adaptive resistance has been shown to be due to aminoglycoside efflux rather than decreased drug uptake. Adaptive resistance is reversible and ideally requires full clearance of the drug prior to subsequent dosing.

Therefore, optimal aminoglycoside dosing regimens are those achieving high C_{max} levels, optimizing bacterial killing, and low trough levels (C_{min}) minimizing toxicity. For a 90% clinical response, the peak concentration should be 8 to 10 times the mean inhibitory concentration of the target organism while trough levels should be below recommended toxicity thresholds for gentamicin (< 0.5-1 g/ml). ODD is favoured over conventional dosing in most clinical situations, as it uses the entire duration of the PAE and leaves a long enough dosing interval to minimize adaptive resistance and recover full susceptibility to aminoglycosides.

Recommended starting doses of gentamicin range between 3 and 7mg/kg/day with the aim to reach a peak level of 4 to 10mg/L. It should however be noted that for some organisms with higher MICs, such as *P. aeruginosa*, higher peak level might be needed.

In order to allow an evaluation of the optimization of bacterial activity and minimization of toxicity following once daily dosing regimens compared to multiple dosing regimens, the publications summarized in this section are those providing pharmacokinetic data on gentamicin peak and trough concentrations. Some examples are included below:

Elderly male patients were randomized to receive gentamicin or tobramycin as 4 mg/kg once daily dosing or as 2 mg/kg dose every 12 hours infused over 1 hour. In the multiple daily dosing group, dosing was adjusted based on the individual pharmacokinetic data to achieve a serum peak concentration of 6 to 10 mg/L and a trough concentration below 1.5 mg/L. Mean first/maximum peak concentrations were 11.5/12.0 mg/L and 6.6/7.8 mg/L following ODD or MDD, respectively. Mean first/maximum trough concentrations were 0.74/0.77 mg/L and 0.99/1.12 mg/L following ODD or MDD, respectively.

Postpartum women with endometritis were randomized to receive gentamicin 5 mg/kg as a once daily dose or 1.75 mg/kg every 8 hours infused over 30 minutes. All patients receiving the once daily dose regimen had an initial peak serum concentration above 5.0 mg/L (mean: 16.8 mg/L), whereas 37% of patients (37%) receiving the 8-hour dosing regimen had initial peak serum concentrations less than 5.0
mg/L (mean: 5.2 mg/L) and required dose adjustment. Mean trough levels were 0.02 μg/mL and 0.57 μg/mL following once daily and the 8-hour dosing regimens, respectively.


Patients with a suspected or documented Gram-negative infection were randomized to receive gentamicin 4.5 mg/kg once daily or 1.5 mg/kg every eight hours infused over 20 minutes. The mean (range) peak level of gentamicin following the once daily dose regimen was significantly higher than that in the thrice daily dose regimen, 8.7 (3.1-14.8) mg/L versus 4.6 (2.8-4.8) mg/L (p < 0.005), and the trough level significantly lower, 0.7 (0.1-1.9) mg/l versus 1.1 (1.0-2.4) mg/L (p < 0.005).

A review of literature has been performed in Embase and Medline with emphasis on clinical trials and systematic reviews comparing gentamicin or aminoglycoside once daily dosing regimen versus multiple dosing regimens in adults. Articles published from 1990 onwards in English language were considered. Some of the summaries presented are included below:


The aim of this randomised study was to investigate the effects of once versus twice daily gentamicin dosing on renal function and measures of infectious disease in a population with infective endocarditis (IE). Seventy-one IE patients needing gentamicin treatment according to guidelines were randomized to either once (n = 37) or twice daily (n = 34) doses of gentamicin. Kidney function (glomerular filtration rate, GFR) was measured with an isotope method ((51)Cr-EDTA) at the beginning of treatment and at discharge. Treatment efficacy was assessed by C-reactive protein (CRP) time to half-life, mean CRP and leukocytes. Baseline GFR was similar in the two groups. Both groups displayed a significant fall in GFR from admission to discharge. The mean decrease in GFR was as follows: with once daily gentamicin, 17.0% (95% confidence interval 7.5-26.5), and with twice daily gentamicin, 20.4% (95% confidence interval 20.2-28.8). However, there was no significant difference in the GFR decrease between the once and twice daily regimens (p = 0.573). No difference in infection parameters was demonstrated between the two dosing regimens.

The authors concluded that a twice daily gentamicin dosing regimen is neither less nephrotoxic nor more efficient than a once daily regimen in the treatment of IE patients. When indicated, gentamicin may therefore also be administered as a single-dose regimen in the treatment of IE patients.


The primary purpose of this clinical trial was to assess the safety and efficacy of once-a-day compared with three-times-a-day gentamicin in patients with serious infections who had protocol determined peak serum aminoglycoside concentrations.

A total of 249 hospitalized patients with suspected or proven serious infections were randomised in a 2:2:1 ratio to gentamicin given three times a day with ticarcillin-clavulanate (TC), gentamicin once a day with TC, or ticarcillin-clavulanate (TC) alone between 1991 and 1994 in two participating centers in the US. The gentamicin once-a-day dosage for patients with estimated creatinine clearance values of > or =80 mL/min was 5.1 mg/kg. With lower creatinine clearance estimates, the mg/kg dosage of gentamicin was decreased, and the dosage intervals (once daily or three times a day) were maintained. Evaluability required documentation of achievement of protocol-defined peak serum gentamicin levels. Most frequent diagnoses were mucosa invasion in febrile neutropenic cancer patients,
pneumonia or empyema, peritonitis or intra-abdominal abscess, pyelonephritis, and skin and subcutaneous tissue infections. A total of 40 (23%) patients had a positive blood culture. Of the total 175 evaluable patients, there were no significant differences found between treatment regimens with respect to clinical or microbiologic efficacy. Based on the traditional increase in serum creatinine values from baseline values, no difference in renal toxicity between the treatment groups was identified. When changes in renal function were re-analysed based on maintaining, as opposed to worsening, of renal function, preservation of renal function was better in the gentamicin once-a-day patients as opposed to the gentamicin three-times-a-day patients (p <0.01). The authors concluded that gentamicin once a day plus TC, gentamicin three times a day plus TC, and TC alone had similar effects in seriously ill hospitalized patients. The incidence of nephrotoxicity was similar in the three treatment groups. Using a non-validated post-hoc analysis, renal function was better preserved in gentamicin once-a-day + TC and TC-only patients as opposed to gentamicin three-times-a-day + TC.


The objective of the study was to evaluate the efficacy of gentamicin and clindamycin given once daily versus the more common 8-hour dosing regimen for the treatment of postpartum endometritis. In a prospective, placebo-controlled, double-blinded study, patients who had postpartum endometritis diagnosed were randomly selected to receive 1.5 mg/kg gentamicin and 900 mg clindamycin phosphate administered every 8 hours versus gentamicin 5 mg/kg and clindamycin phosphate 2700 mg administered as a single-daily dose. The single-dose group received an infusion of gentamicin and clindamycin, followed by an administration of intravenous placebo 8 and 16 hours later to maintain blinding. Treatment success was defined as absence of fever 72 hours after initiation of antibiotic therapy.

One hundred ten patients were enrolled. The daily-dose group (n = 55) and the thrice-daily dose group (n = 55) were similar with respect to age, gravidity, parity, gestational age, and maternal weight. Clinical characteristics (including maximum temperature, presence of pre-delivery chorioamnionitis, white blood cell count, and mode of delivery) were also similar. There was no difference in the mean time from initiation of therapy until becoming afebrile in the daily-dose group (27.4 +/- 24.9 hours) compared with the thrice-daily dose group (32.9 +/- 26.3 hours). Forty-five of 56 (82%) patients in the daily-dose group and 38 of 55 (69%) patients in the thrice daily dose group had treatment success (p=0.12).

The authors concluded that once-daily dosing with gentamicin and clindamycin in women with postpartum endometritis has a similar success rate as the standard every 8-hour dosing schedule.

**Prins JM, Büller HR, Kuiper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. Lancet. 1993; 341(8841):335-9.**

Aminoglycosides are usually given in two or three divided doses. The authors hypothesized that a once-daily regimen might be more effective and less toxic and the goal of this study was to investigate this hypothesis. The authors conducted a randomized trial in consecutive patients with serious infections for whom an aminoglycoside seemed warranted. Exclusion criteria were neutropenia or severely impaired renal function. For efficacy analysis only those patients were considered in whom treatment with the aminoglycoside was not stopped within 72 hours (n = 67); toxicity was analysed on patients receiving aminoglycosides for more than 48 hours and not using other nephrotoxic medication (n = 85).

Gentamicin 4 mg/kg every day (ODD) or gentamicin 1.33 mg/kg three times daily (MDD) (with dose-reduction in case of renal dysfunction) were given intravenously. Overall, 123 patients were enrolled; 59 were assigned to the ODD and 64 patients to the MDD group. In almost all patients IV amoxycillin 1 g every 6 hours was also started. Baseline characteristics were
comparable in both arms. A good clinical response was observed in 32/35 (91%) of the ODD and in 25/32 (78%) in the MDD group (difference 13%, 95% confidence interval -6.4% to +26.9%). Two patients in each group died with uncontrolled infection. An insufficient bacteriological response (persistent positive cultures, resistance, or superinfection) was observed in two patients with ODD and three patients with MDD. In patients treated for more than 48 h duration of therapy and mean doses were 7.0 days (1590 mg) and 7.4 days (1672 mg) in ODD and MDD, respectively. Mean first serum trough/peak levels were 0.6/10.2 mg/L and 1.4/5.2 mg/L. Nephrotoxicity (a rise in serum creatinine of 45 μmol/L or more) developed in 2/40 (5%) in ODD and 11/45 (24%) in MDD (p = 0.016). Risk factors for nephrotoxicity were duration of therapy and baseline creatinine clearance rate. High-tone audiometry was performed when possible; no significant differences were found in hearing loss (3/12 and 3/11) or prodromal signs of ototoxicity (5/12 and 4/11).

The authors concluded that a once-daily dosing regimen of gentamicin was at least as effective as multiple dosing and appeared less nephrotoxic than more frequent dosing.


The objective of this study was to compare efficacy and safety of intravenous gentamicin administered once daily versus thrice daily was evaluated in adults.

Patients over 16 years of age with a suspected or documented gram-negative infection were randomly divided into two groups: one group received gentamicin intravenously 4.5 mg/kg once daily (n = 48), and the other received 1.5 mg/kg every eight hours (n = 52).

Baseline characteristics were comparable in the two groups. The mean peak level of gentamicin in the once daily group was significantly higher than that in the thrice daily group, 8.7 +/- 2.3 mg/l versus 4.6 +/- 1.2 mg/l (p <0.005), and the trough level lower, 0.7 +/- 0.3 mg/l versus 1.1 +/- 0.9 mg/l (p <0.005).

The clinical cure rate was significantly higher in the once daily group, 42 of 48 (87.5%) versus 36 of 52 (69.2%). The microbiological cure rate was also better in the once daily group than in the thrice daily group (31 of 36 versus 28 of 38 patients evaluated), although this difference was insignificant. Nephrotoxicity was not observed in either group, but ototoxicity was present in three of the patients treated thrice daily. The authors concluded that a once daily dosing regimen of gentamicin is more effective and less ototoxic than a thrice daily regimen.


Once-daily dosing has been suggested as an alternative method of dosing aminoglycosides that would reduce their toxicity while maintaining efficacy. There have been no studies published to date comparing once-daily dosing and pharmacokinetic dosing of aminoglycosides.

The authors conducted a randomised, non-blinded, controlled trial comparing the safety and effectiveness of 4 mg/kg IV once-daily dosing of gentamicin or tobramycin with a pharmacokinetic dosing method using an initial dose of 2 mg/kg IV every 12 hours.

Ninety-six patients were randomly assigned to either the once-daily dosing group (4 mg/kg) or the pharmacokinetic dosing group (initial dose of 2 mg/kg every 12 hours). In the once-daily dosing group, the dosing interval was extended by 12 to 24 hours to maintain a serum trough concentration <1.5 mg/L regardless of the peak concentration. Dosing in the other group was adjusted based on the individual pharmacokinetic data to achieve a serum peak concentration of 6 to 10 mg/L and a trough concentration below 1.5 mg/L. The patients studied were predominantly elderly males (mean age 69 years). All patients were assessed for treatment efficacy and nephrotoxicity.

There was no significant difference between the two groups with regard to clinical and bacteriologic efficacy (clinical efficacy: 70.6% vs 75%; bacteriological efficacy: 75% vs 81.8%, respectively). Incidence of nephrotoxicity was 24% in the once-daily group and 14% in the pharmacokinetic dosing group but the difference was not statistically significant (P = 0.13). The authors found a correlation
between high serum peak concentration and incidence of nephrotoxicity in the once-daily dosing group. Nephrotoxicity developed in six out of 10 patients (60%) with an initial serum peak concentration greater than 12.0 mg/L compared to two out of 24 patients (8.3%) with an initial peak concentration less than 12.0 mg/L (P < 0.001) in the once daily group. Serum peak concentrations in the pharmacokinetic dosing group were not correlated with nephrotoxicity. The authors concluded that once-daily dosing and pharmacokinetic dosing of aminoglycosides appear to have equal efficacy and toxicity. However, in the elderly population, high serum peak concentrations that occur with once-daily aminoglycoside dosing may increase the risk of nephrotoxicity.

Administration time
As summarized in Table 2, gentamicin in patients is mainly administered intravenously over 30 minutes to 1 hour. No obvious differences in peak and trough gentamicin concentrations were observed between 30-minute and 1-hour infusion in adults.

Renal impairment
Gentamicin is predominantly excreted as unchanged compound via the kidneys through glomerular filtration. Consistently, creatinine clearance was identified as a significant covariate impacting gentamicin pharmacokinetics in patients. Several nomograms have been published to support dosage adjustment in patients with renal insufficiency following extended interval dosing (see examples in Table 5). These nomograms were developed to adapt dosing interval according to renal function status in order to optimize the peak/MIC ratio and to reach a trough concentration below 1 μg/mL. Usually, it is recommended to
monitor gentamicin level within 6 to 14 hours after first dose and to adapt dosing interval according to nomograms (see Hartford nomogram in Figure 1 as an example).

Table 5 – Examples of gentamicin nomograms for extended-interval dosing in patients with renal insufficiency

<table>
<thead>
<tr>
<th>Nomogram (Reference/ Guideline)</th>
<th>Dose (mg/kg)</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Clcr ≥60 mL/min</td>
</tr>
<tr>
<td>Hartford (1)</td>
<td>7</td>
<td>24 hours</td>
</tr>
<tr>
<td>Ramos-Jewish Hospital (2)</td>
<td>5</td>
<td>24 hours</td>
</tr>
<tr>
<td>Stanford (3)</td>
<td>6-7</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

Note: creatinine clearance (Clcr) estimated by Cockcroft-Gault equation.

Evaluation (Sections 4.2 and 4.4)

1. Once daily dosing
The applicant provided a summary of pharmacokinetic (PK) studies comparing once daily dosing with twice or three times daily dosing in patients with various infections, which confirm that – as may be expected – 
$C_{\text{max}}$ is higher when the same daily dose is given as a single dose compared to divided doses.

The applicant elaborates that “optimal aminoglycoside dosing regimens are those achieving high $C_{\text{max}}$ levels, optimizing bacterial killing, and low trough levels ($C_{\text{min}}$) minimizing toxicity, which is agreed. Providing PK/PD data substantiating the PK/PD target for gentamycin would have been helpful. A summary of studies in the published literature comparing once daily dosing to multiple daily doses was submitted. Some of the studies were conducted with doses other than those proposed and cannot be considered very helpful. Most of the studies were small and included a range of infections. There is
some heterogeneity in the results, but overall the data suggest that once daily dosing of gentamycin is similarly effective as multiple daily dosing and may reduce nephrotoxicity. The mechanism of nephrotoxicity, with saturable uptake of gentamycin into the renal cells, makes this observation biologically plausible. With regards to efficacy, the data submitted similarly suggest that once daily dosing is at least as efficacious as multiple daily dosing. This observation is also supported by PK/PD data suggesting that gentamycin with its concentration-dependent mode of action should be more efficacious if concentrations reached are high (>4) multiples of the MIC. Accordingly, once daily dosing has been used in clinical practice for some time now.

In summary the proposed changes relating to the preference for once daily dosing, are supported by data from the published literature. Equivalent wording has already been approved for other gentamycin containing solutions for injection or infusion in the UK.

The following points were raised by MHRA

MHRA Question 1.1:
The wording of the paragraph in section 4.2 should be further amended, the following is proposed:

**Posology**

**Adults**
The recommended dose in adults with normal renal function is 3–5mg/kg/day depending on the severity of the infection, administered as one single dose (preferred) or in two divided doses. The dose should be adjusted according to clinical response and serum concentration levels (see below).

**Urinary tract infections:** In patients with normal renal function 160 mg once daily may be used.

**MAH Response:**
The MAH acknowledges and accepts MHRA text proposal. The MAH also proposes to add the populations especially concerned by dose adjustment (elderly and patients with renal impairment). The SmPC has been amended consequent:

**Adults**
The recommended dose in adults with normal renal function is 3 – 5 mg/kg/day depending on the severity of infection, administered as one single dose (preferred) or in two divided doses. The dose should be adjusted according to clinical response and serum concentration levels, especially in the elderly and patients with impaired renal function (see below).

MHRA Question 1.2:
At present, once daily dosing is not recommended in all cases of endocarditis, enterococcal or HACEK endocarditis. An appropriate statement should be added to this section: e.g. Once daily dosing is not recommended in all cases of endocarditis. National guidance on treatment with gentamicin and plasma level monitoring in endocarditis should be followed.

**MAH Response:**
The MAH acknowledges MHRA question and confirmed that MHRA comment on endocarditis is fully supported by the clinical overview submitted with the variation. Therefore, MHRA text proposal
is accepted with minor changes to reflect that the decision must be based on the responsible pathogen. The SmPC has been amended consequently:

Once daily dosing is not recommended in cases of endocarditis, depending on the responsible pathogens. National and local guidance on treatment with gentamicin and serum level monitoring in endocarditis should be followed.

Assessment of response
This is accepted.

MHRA Question 1.3:
The statement “A dosing frequency of more than twice daily may be adopted for some specific pathogens, as clinically indicated.” is not supported by the data provided. Please provide a reference demonstrating the benefit of more than twice daily dosing for specific pathogens, detailing what pathogens are concerned. It should be discussed if this effect is related to the pathogen or to the type/site of infection. (See question 1.2).

MAH Response
The MAH acknowledges MHRA question and confirmed that the sentence “A dosing frequency of more than twice daily may be adopted for some specific pathogens, as clinically indicated” refers mainly to endocarditis. However, as mentioned in the Clinical Overview, in some guidelines especially from the US, a multiple dose daily regimen is also recommended for the treatment of bacterial meningitis due to Listeria monocytogenes or Streptococcus agalactiae or for intravascular catheter related infections due to Enterococci or in case of Methicillin-Resistant Staphylococcus aureus. This explains why this sentence was added. As guidelines may evolve or change, the choice was made not to be too specific on the sites of infection or the pathogens for which a multiple dose regimen may be recommended. As a consequence, the MAH proposes to refer to local/national guidelines instead of being more specific on sites of infection or pathogens. The SmPC has been amended consequently.

A dosing frequency of more than twice daily may be adopted for some specific pathogens or some sites of infection as recommended in national and local guidance.

Assessment of response
This is accepted.

2. Method of administration

MHRA Question 2.1:
Please discuss if multiple daily dosing should be administered preferentially via the intravenous route, taking into account the target population for treatment with gentamycin.

MAH Response
The aim of the provided data was to assess the once a day dose regimen (ODD) in adults as it was done for children in 2010 in the context of Article 45. Gentamicin is an antibiotic registered since 1969 and therefore used for years with multiple daily doses (MDD).

When looking at the mode of administration for ODD, it appears that only IV infusion was used. This makes sense as a higher dose is administered with the ODD than with the MDD regimen of administration. Injected dose can be therefore diluted and not directly injected via a bolus or intramuscular route. High dosages are expected to be better tolerated when diluted overview mentioned
another route of administration than IV infusion. No comparison between routes of administration was therefore possible. As far as MDD is concerned, there has been no indication that the known clinical practices regarding the routes of administration have to be modified. In textbooks, as in the labelling documents, modes of administration for MDD include IV infusion, IV bolus or IM. The choice between IV or IM route then refers to usual clinical practices and medical knowledge (volume to be injected, risk of local bleeding in patients with coagulation disorders or treated with anticoagulants, young children etc.). The SmPC has been amended to reflect further clarity:

**Method of administration**
The recommended dose and precautions for IM and IV administration are identical. Gentamicin when given intravenously should be injected directly into a vein or into the drip set tubing over no less than three minutes. If administered by infusion, this should be over 20 – 30 minutes for a multiple daily dosing regimen and over 60 minutes for a once daily dosing regimen, and in no greater volume of fluid than 100 ml. Once daily dosing should only be administered through the intravenous route.

**Assessment of response**
The revised wording is accepted.

**MHRA Question 2.2:**
Please justify the proposed change in infusion time. As $C_{\text{max}}$ is considered relevant for efficacy, an increase of the presently proposed infusion time from 20 to 30 – 60 minutes is not understood. Table 2 presented in the clinical overview does not justify or support the need for a change in infusion time. The data are very limited and include interstudy comparisons, making interpretation very difficult. However, it is acknowledged that most clinical studies use infusion times of 30 – 60 minutes. It may be preferable to recommend an infusion time of 20 – 30 minutes unless there are concerns relating to $C_{\text{max}}$. Please clarify.

**MAH Response**
The MAH acknowledges that comparative PK data after 20, 30 and 60 minute infusions are limited. However, the available data, summarised in Table 1, show no major difference in $C_{\text{max}}$ whatever the infusion duration. In addition, $C_{\text{trough}}$ was below 1 mg/mL independently of the infusion duration.

<table>
<thead>
<tr>
<th>Table 1 - Gentamicin $C_{\text{max}}$ or $C_{\text{trough}}$ in healthy subjects and patients by dose level and infusion duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population (n)</td>
</tr>
<tr>
<td>Healthy subject(12)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/mL)</td>
</tr>
<tr>
<td>$C_{\text{trough}}$ (mg/mL)</td>
</tr>
</tbody>
</table>

Exposures are expressed as Mean or Mean (SD)
Min: minutes; NA: not applicable; Pts: patients; $^a$: 24 on gentamicin and 10 on tobramycin; $^b$: first maximum $C_{\text{max}}$ or $C_{\text{trough}}$. 

23
Due to limited PK data, the MAH cannot accept the MHRA proposal. The MAH proposes to align to the administration guidance in the British National Formulary January 2018 (20 – 30 minutes for MDD and 60 minutes for ODD) as shown in the following table. The SmPC has been amended consequently.

**Assessor’s comment**

The applicant asks for a change of infusion times from 20 minutes to 20-30 or 60 minutes while arguing that there is no difference in PK parameters regardless of what time is used. It is unclear why the infusion time should be doubled for no reason. The data as presented suggest an infusion time of 20-60 minutes is acceptable for both once and multiple daily dosing. Without any reason, a mandatory doubling of the infusion time for ODD is not justified. Longer infusion times are inconvenient for patients and may complicate drug administration for healthcare professionals.

The following would be acceptable:

If administered by infusion, this should be over 20 – 30 minutes and in no greater volume of fluid than 100 ml. Longer infusion times of up to 1 hour may be used, in particular for a once daily dosing regimen.

**MHRA Question 4:**

**Monitoring of peak plasma concentration – The proposed changes may be acceptable in principle but require further substantiation. Please provide more detailed data specific to the monitoring of peak plasma concentration. (e.g. timing of sample after dose and method of subsequent dose adjustment).**

**MAH Response**

There is no UK national guidance available that describes therapeutic drug monitoring (TDM) of gentamicin in the treatment of systemic infection. Guidance is provided by the British Antimicrobial Chemotherapy Society (1) specific to the treatment of infective endocarditis which describes the principles of TDM that can be extended to other indications. Otherwise, monitoring advice and requirements are routinely provided by the local microbiology/pathology laboratories and/or antimicrobial pharmacy services in the locations where treatment with gentamicin is undertaken, and this is tailored to practice at each location. A review of a variety of local UK guidance has been undertaken (2)(3)(4)(5), which confirmed a uniform approach across the UK. Two principles are common to the selection of local guidelines reviewed:

**Trough (Pre-Dose) Level**

After administration of the appropriate weight-adjusted dose, trough levels are measured to ensure that the correct interval between doses is being observed. The principle is to avoid the subsequent dose until serum gentamicin levels have dropped to a level that safely allows further administration without risking dose accumulation and associated toxicity.

- For multiple daily dosing, serum gentamicin levels should be obtained 30 minutes prior to the next dose is due. The next dose should only be given once the trough level is confirmed to be < 2mg/L.

- For once daily dosing, serum gentamicin levels should be obtained 18-24 hours after the previous dose (i.e. in the 6 hours before the subsequent dose is due). The next dose should only be given once the trough level is confirmed to be < 1mg/L.
Peak (Post Dose) Level
Peak levels are not routinely required, but may be valuable in situations where it is beneficial to know that the dose is delivering an adequate bactericidal serum concentration, or to ensure that the toxic concentrations are not being reached (for example in the elderly, very young and those with renal impairment). A serum gentamicin level should be obtained 60 minutes after an IM or IV dose, or 30 minutes (6)(7) after the end of a dose administered by infusion (unless local guidance directs otherwise). A value in the range 4 – 10 mg/L confirms adequacy of the dose; levels below/above this range indicate that the dose is insufficient/excessive respectively and appropriate adjustment is required. Changes in dose need to be accompanied by repeat monitoring of both peak and trough levels to both confirm dose adequacy and detect any change that needs to be made to the dose interval. The monitoring advice paragraph has been revised to reflect this information. The SmPC has been amended consequently.

2 Nottingham University Hospitals NHS Trust. Gentamicin Prescribing Guideline For Adult Patients; 3 NHS Lothian. Treatment Guidance for gentamicin in adults (age ≥16 years); Accessed January 2018
6 Koo J. Comparison of once-daily versus pharmacokinetic dosing of aminoglycosides in elderly patients. American Journal of Medicine 1996 101: 2 (177-183) (Ref 9 of original ODD CO)

Monitoring advice
Serum concentration monitoring of gentamicin is recommended, especially in the elderly, newborns and in patients with impaired renal function. Local monitoring and dose adjustment guidelines should be followed where these are available, and advice taken from the local microbiology/pathology service for situations that fall outside of local guidance.

Pre-dose (“trough level”) monitoring should be used to ensure that the interval between doses is correct. Local guidance should be followed where this is available. Trough levels are measured at the end of a dosing interval and should not exceed 1 mg/L for a once daily dose or 2 mg/L for multiple daily dosing. Levels in excess of these indicate the need to extend the interval between doses, not reduce the dose.

Post dose (“peak levels”) are not routinely required, but may be used to check the adequacy of a dose or to ensure that it is not excessive and likely to cause toxicity. Local guidance should always be followed where this is available. Peak levels should be measured 1 hour after an IV or IM bolus dose, or 30 minutes after the end of an infusion. A concentration < 4mg/L indicates that the dose is likely to be inadequate and a dose increase should be considered; > 10mg/L indicates potential for toxicity and a dose reduction should be considered. Any change in dose should be re-assessed with pre- and post-dose levels to confirm the adequacy of the new dose and the appropriateness of the dose interval.

Assessment of responses
There are differences in the recommendations for gentamycin TDM in the published literature and there is no UK National guidance covering all aspects of TDM. NICE has issued guidance for aminoglycoside monitoring, however this is mainly applicable to multiple daily dosing: “Serum-aminoglycoside concentrations should be monitored in patients receiving parenteral aminoglycosides
and must be determined in the elderly, in obesity, and in cystic fibrosis, or if high doses are being given, or if there is renal impairment. For multiple daily dose regimens, blood samples should be taken approximately 1 hour after intramuscular or intravenous administration (‘peak’ concentration) and also just before the next dose (‘trough’ concentration). If the pre-dose (‘trough’) concentration is high, the interval between doses must be increased. If the post-dose (‘peak’) concentration is high, the dose must be decreased. For once daily dose regimens, consult local guidelines on serum concentration monitoring.

The following is considered acceptable:

**Monitoring advice**
Serum concentration monitoring of gentamicin is recommended for all patients and especially in the elderly, newborns, obesity and in patients with impaired renal function as well as patients with cystic fibrosis.

There are no universally accepted guidelines for TDM of gentamicin. Local monitoring and dose adjustment guidelines should be followed where available. The following is commonly recommended: Pre-dose (“trough level”) monitoring should be used to ensure that the interval between doses is correct. Trough levels are measured at the end of a dosing interval and should not exceed 1 mg/L for a once daily dose or 2 mg/L for multiple daily dosing. Levels in excess of these indicate the need to extend the interval between doses, not a reduction of the dose.

Post dose (“peak levels”) should be used to check the adequacy of a dose or to ensure that it is not excessive and likely to cause toxicity. Local guidance should be followed where this is available. Peak levels should be measured 1 hour after an IV or IM bolus dose, or 30 minutes after the end of an infusion. A concentration < 4mg/L indicates that the dose is likely to be inadequate and a dose increase should be considered; plasma concentrations > 10mg/L indicates an increased risk for toxicity, particularly ototoxicity, and a dose reduction should be considered. Any change in dose should be re-assessed with pre- and post-dose levels to confirm the adequacy of the new dose and the appropriateness of the dose interval.

**MHRA Question 5:**
Changes to posology in renal impairment – The proposed changes to the posology in renal impairment requires further justification. The presently approved posology allows use of gentamycin even in patients with significant renal impairment, while the proposed new posology for extended interval dosing excludes patients with CLcrea of less than 30 ml/minute from treatment with gentamycin. It is acknowledged and agreed that the use of gentamycin in these patients is best avoided wherever possible, but to our knowledge no new data have been generated that would preclude its use in this population entirely. The applicant should clarify.

For patients with less severe renal impairment, the proposed doses (per 24hour) are generally considerably higher than the presently approved doses. The use of a nomogram may be acceptable in principle; however validation data are required. The company should provide PK and if available PK/PD data supporting the proposed revised posology based on the nomogram.

**MAH Response**
The nomogram was provided as an example but, as the dose regimen in patients with normal renal function may be given once, twice or thrice a day, it is difficult to provide a single nomogram covering the 3 regimen according to the degree of renal failure. Consequently, the MAH proposes to delete the nomogram and to remind that:
- in patients with impaired renal function, a dosing interval of 24 hours is preferred;
- the interval should be extended according to the severity of the renal failure and serum gentamicin monitoring results;
- local guidance should be followed where this is available. The renal impairment paragraph has been to reflect this information. The SmPC has been amended consequently.

**Assessment of responses**

The applicant submitted dosing and monitoring guidelines from several NHS trusts as supportive evidence. These documents represent the interpretation and opinion of the respective institutions of the PK (and PD) of gentamycin, and while of interest, are not suitable on their own for regulatory purposes. The difference between some of the recommendations illustrate the difficulties in identifying the correct posology and monitoring recommendations for aminoglycosides in particular in renal impairment. Despite the longstanding use of these agents, there appears to be a lack of relevant data. The applicant has not provided sufficient data justifying the proposed changes of the posology in renal failure and not answered the question relating to subjects with severe renal impairment.

The current proposal does not include any recommendation regarding the initial dose for renally impaired subjects. If the standard dose is used, and the dose interval adjustment as per the proposed table, the resulting daily doses of gentamycin in subjects with renal impairment will exceed the currently approved dosing significantly. There is insufficient data to justify this change. It is acknowledged that the applicant aims to include a posology for subjects with renal impairment who would receive once daily dosing if their renal function were normal. The posology currently included in the SmPC for patients with renal impairment recommends multiple daily dosing and stems from a time when that was the standard way of using gentamycin and other aminoglycosides. It is evident from local guidelines and literature data that extended interval dosing in subjects with (moderate) renal impairment at least is commonly used. However, as explained, the proposed changes are not supported by adequate data and are hence not approvable.

The currently approved posology should remain in the SmPC; however, it may be appropriate to add an additional comment on the posology in renal failure for subjects who would receive once daily dosing of gentamycin if their renal function were normal. The applicant made no proposal regarding the initial dose in subjects with renal failure. There are reports (e.g. Nayak-Rao, 2010) indicating similarity to other polar drugs that mainly distribute in the ECF, there may be a reduction in Vd when renal function is impaired, which implies that the initial dose should be reduced. Study data by Kim et al (Int Med J 2015 doi:10.1111/imj.12684) suggest that including kidney function in the calculation of the calculating initial dosing, but insufficient information is available as to how to reduce this first dose. For subsequent doses, an increase in dose interval may be considered an appropriate means of reducing the total (average) daily dose in renal failure. This type of dose adjustment may allow maintaining peak plasma concentrations associated with efficacy. TDM recommendations already included in the SmPC would allow identifying the time for the next dose.

Currently approved wording:

**RENAL IMPAIRMENT:**

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function. Gentamicin is excreted by simple glomerular filtration and therefore reduced dosage is necessary where renal function is impaired. Nomograms are available for the calculation of dose, which depends on the patient’s age, weight and renal function. The following table may be useful when treating adults.
Blood Urea | Creatinine clearance (GFR) | Dose & frequency of administration
--- | --- | ---
(mg/100ml) | (mmol/l) | (ml/min)
< 40 | 6 - 7 | > 70 | 80mg* 8 hourly
40 - 100 | 6 - 17 | 30 - 70 | 80mg* 12 hourly
100 - 200 | 17 - 34 | 10 - 30 | 80mg* daily
> 200 | > 34 | 5 - 10 | 80mg* every 48 hours
Twice weekly intermittent haemodialysis | < 5 | 80mg* after dialysis

*60mg if body weight <60kg. Frequency of dosage in hours may also be approximated as serum creatinine (mg%) x eight or in si units, as serum creatinine (μmol/l) divided by 11. If these dosage guides are used peak serum levels must be measured. Peak levels of gentamicin occur approximately one hour after intra muscular injection and intravenous injection. Trough levels are measured just prior to the next injection. Assay of peak serum levels gives confirmation of adequacy of dosage and also serves to detect levels above 10mg/l, at which the possibility of ototoxicity should be considered. One hour concentrations of gentamicin should not exceed 10mg/l (but should reach 4mg/l), while the pre dose trough concentration should be less than 2mg/l.

Applicant’s revised proposed wording

Renal impairment

In impaired renal function the interval between two injections should be at least 24 hours and extended according the degree of renal impairment and the results of serum gentamicin monitoring.

The table below provides suggested dose intervals in renal failure. Local guidance should always be followed where this is available:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Example of dosing interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 ml/min</td>
<td>24</td>
</tr>
<tr>
<td>59 – 40 ml/min</td>
<td>36</td>
</tr>
<tr>
<td>30 – 39 ml/min</td>
<td>48</td>
</tr>
<tr>
<td>&lt; 30 ml/min</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

The serum gentamicin concentration and renal function must be monitored regularly. The serum gentamicin concentration must not exceed 10 mg/L, and it must not exceed 1 mg/L prior to the next given dose in once daily dosing.

In patients with significant renal impairment, serum gentamicin levels should be obtained 24 hours after the start of treatment, and repeated every other day (or at other intervals as required according to the measured serum gentamicin level and/or local guidance).

The following would be acceptable:

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function. This can be achieved by reducing the dose and/or the dose interval.

In all patients with renal impairment, serum gentamicin peak and trough concentration and renal function must be monitored frequently (see below). Local guidance should be adhered to.
Nomograms are available for the calculation of dose, which depends on the patient’s age, weight and renal function. The following table may be useful when treating adults on multiple dose regimens.

<table>
<thead>
<tr>
<th>Blood Urea (mg/100ml)</th>
<th>Creatinine clearance (GFR) (ml/min)</th>
<th>Dose &amp; frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>6 - 7</td>
<td>&gt; 70</td>
</tr>
<tr>
<td>40 - 100</td>
<td>6 - 17</td>
<td>30 - 70</td>
</tr>
<tr>
<td>100 - 200</td>
<td>17 - 34</td>
<td>10 - 30</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>&gt; 34</td>
<td>5 - 10</td>
</tr>
<tr>
<td>Twice weekly intermittent haemodialysis</td>
<td>&lt; 5</td>
<td>80mg* after dialysis</td>
</tr>
</tbody>
</table>

*60mg if body weight <60kg.

No clear recommendation can be made for once daily dosing, dosing should be guided by plasma concentration levels. The following may be useful: In patients with moderate renal impairment, in whom once daily dosing would be considered appropriate if their renal function were normal, the dose interval should be at least 24 hours and extended according to the degree of renal impairment and the results of serum gentamicin monitoring. Extended interval dosing is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min).

The company was contacted regarding data requirements for changes to renal posology. After re-evaluation of the available data and a discussion of the questions relating to the posology in renal failure, the company submitted a revised section 4.2.

4.2 Posology and method of administration

**Posology**

**Adults**
The recommended dose in adults with normal renal function is 3 – 5 mg/kg/day, depending on the severity of infection, administered as one single dose (preferred) or in two divided doses. The dose should be adjusted according to clinical response and serum concentration levels (see below). A dosing frequency of more than twice daily may be adopted for some specific pathogens or some sites of infection as recommended in national and local guidance.

Once daily dosing is not recommended in cases of endocarditis, depending on the responsible pathogens. National and local guidance on treatment with gentamicin and serum level monitoring in endocarditis should be followed.

In patients with normal renal function, 160 mg once daily may be used for the treatment of urinary tract infections.

**Paediatric population**
The daily dose recommended in children (aged 1 year and above) and adolescents with normal renal function, is 3 – 6 mg/kg/day as one single dose (preferred) or two divided doses.

The daily dose in infants after the first month of life is 4.5 – 7.5 mg/kg/day as one single dose (preferred) or two divided doses.
The daily dose in neonates and pre-term infants (aged 0 – 4 weeks old) is 4 – 7 mg/kg/day. Due to the longer half-life, newborns are given the required daily dose in one single dose.

**Elderly**

There is some evidence that elderly patients may be more susceptible to aminoglycoside toxicity whether secondary to previous auditory/vestibular impairment or borderline renal dysfunction. Accordingly, therapy should be closely monitored by frequent determination of gentamicin serum levels, assessment of renal function and signs of ototoxicity.

**Renal impairment**

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function. This can be achieved by reducing the dose and/or increasing the dose interval.

In all patients with renal impairment, serum gentamicin peak and trough concentration and renal function must be monitored frequently (see below).

Nomograms are available for the calculation of dose, which depends on the patient’s age, weight and renal function. Local guidance should be followed where available.

No clear recommendation can be made for once daily dosing; dosing should be guided by plasma concentration levels. In patients with moderate renal impairment, in whom once daily dosing would be considered appropriate if their renal function were normal, the dose interval should be at least 24 hours and extended according to the degree of renal impairment and the results of serum gentamicin monitoring. Extended interval dosing is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min).

The following table may be useful when treating adults on multiple dose regimens:

<table>
<thead>
<tr>
<th>Blood Urea (mg/100 ml)</th>
<th>Creatinine clearance (GFR) (ml/min)</th>
<th>Dose &amp; frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 – 7</td>
<td>&gt; 70</td>
<td>80 mg* 8 hourly</td>
</tr>
<tr>
<td>6 – 17</td>
<td>30 – 70</td>
<td>80 mg* 12 hourly</td>
</tr>
<tr>
<td>17 – 34</td>
<td>10 – 30</td>
<td>80 mg* daily</td>
</tr>
<tr>
<td>&gt; 34</td>
<td>5 – 10</td>
<td>80 mg* every 48 hours</td>
</tr>
<tr>
<td>Twice weekly intermittent haemodialysis</td>
<td>&lt; 5</td>
<td>80 mg* after dialysis</td>
</tr>
</tbody>
</table>

*60 mg if body weight < 60 kg.

**Monitoring advice**

Serum concentration monitoring of gentamicin is recommended for all patients, and especially in the elderly, newborns, obesity and in patients with impaired renal function, as well as patients with cystic fibrosis.

There are no universally accepted guidelines for therapeutic drug monitoring of gentamicin. Local monitoring and dose adjustment guidelines should be followed where available.

Pre-dose (“trough level”) monitoring is recommended to ensure that the interval between doses is correct. Trough levels are measured at the end of a dosing interval and should not exceed 1 mg/L for
once daily dosing or 2 mg/L for multiple daily dosing. Levels in excess of these indicate the need to extend the interval between doses, not reduction of the dose.

Post-dose (“peak level”) monitoring is recommended to check the adequacy of a dose or to ensure that it is not excessive and likely to cause toxicity. Peak levels should be measured one hour after an intravenous bolus or intramuscular bolus dose, or 30 minutes after the end of an infusion. A plasma concentration < 4 mg/L indicates that the dose is likely to be inadequate and a dose increase should be considered; plasma concentrations > 10 mg/L indicate an increased risk for toxicity, particularly ototoxicity, and a dose reduction should be considered.

Any change in dose should be re-assessed with pre- and post-dose levels to confirm the adequacy of the new dose and the appropriateness of the dose interval.

Method of administration
The recommended dose and precautions for intramuscular and intravenous administration are identical. Gentamicin when given intravenously should be injected directly into a vein or into the drip set tubing over no less than three minutes. If administered by infusion, this should be over 20 – 30 minutes and in no greater volume of fluid than 100 ml. Longer infusion times of up to 60 minutes may be used, in particular for a once daily dosing regimen. Once daily dosing should only be administered through the intravenous route.

Assessment of responses
This was acceptable.

As the changes to section 4.2, specifically the preference for once daily dosing and the amendments to the dose in renal impairment, together with the strengthening of the recommendations for TDM for gentamicin have implications at a National level, the case was discussed with and Expert Advisory Group of renal and infectious diseases experts and subsequently at CHM.

Advice from an Expert advisory group
The proposals for section 4.2 were discussed in a teleconference on 27 July 2018 by an ad hoc EAG including infectious diseases and renal experts. The expert group agreed with the proposed changes for section 4.2 in principle but recommended the following amendments:

The current wording recommending TDM for all patient groups should be strengthened: a comment should be added stating that gentamicin should not be prescribed unless gentamicin serum concentrations can be monitored.

The following should be deleted: “External interval dosing is not recommended in patients with severe renal impairment (Creatinine clearance < 30ml/min).” It is the view of the group that extended interval dosing can be used in severe renal impairment.

Additional statement to highlight symptoms of ototoxicity should be added to section 4.4: “Symptoms include loss of balance and hearing loss.”

MAH Response
Section 4.2
The MAH accepted the majority of the wording proposed by the CHM, but proposed to make an adjustment to the wording proposal for renal impairment in section 4.2 to be clearer and more
transparent about the amount of data available for dosing in severe renal impairment, and maintain consistency with the table provided to assist in multiple daily dosing for renal impairment.

Addition of the following sentence “Limited data are available in patients with severe renal impairment (creatinine clearance < 30 ml/min) after once daily dose administration.” instead of complete deletion of statement “External interval dosing is not recommended in patients with severe renal impairment (Creatinine clearance < 30ml/min).”

This wording adjustment was discussed and agreed with MHRA assessor on 19 November 2018.

MAH Response
Section 4.4
The following consequential amendments to section 4.4 are proposed and considered approvable (approved as part of subsequent variation (0024)):

4.4 Special warnings and precautions for use
Ototoxicity and nephrotoxicity
Ototoxicity has been reported following the use of aminoglycosides, including gentamicin. Symptoms include loss of balance and hearing loss, which may be irreversible (see section 4.8). Important risk factors include renal impairment, high doses, prolonged duration of treatment and age (neonates/infants and possibly the elderly). Due to the potential for ototoxicity and nephrotoxicity, monitoring of vestibule, cochlea and renal function is recommended before, during and shortly after treatment (see section 4.8). Serum levels are determined so as to avoid peak concentrations above 10 mg/L and troughs above 1 mg/L when administering gentamicin once daily and 2 mg/L when administering gentamicin twice daily.

As there is some evidence that risk of both ototoxicity and nephrotoxicity is related to the level of total exposure, duration of therapy should be the shortest possible compatible with clinical recovery. In some patients with impaired renal function there has been a transient rise in blood-urea-nitrogen which has usually reverted to normal during or following cessation of therapy. It is important to adjust the frequency of dosage according to the degree of renal function.

To avoid adverse events, continuous monitoring (before, during and after treatment) of hepatic and laboratory parameters is also recommended.

Gentamicin should only be used in pregnancy if considered essential by the physician (see section 4.6).

Gentamicin should be used with care in conditions characterised by muscular weakness.

In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered.

Conclusion
The changes proposed reflect the available data and their limitations and are considered acceptable.

The changes to sections 4.2 and 4.4 are approvable.

The updated SmPC fragments has been incorporated into this Marketing Authorisation. The proposed change is acceptable.
Decision: Grant
Date: 11 January 2019