GENTAMICIN

INJECTION, 10 MG/ML IN 2 ML VIAL (AS SULFATE) AND 40 MG/ML IN 2 ML VIAL (AS SULFATE)

GENERAL PRODUCT INFORMATION

Gentamicin injection is recommended by WHO for the treatment of neonatal meningitis and also for severe community acquired bacterial pneumonia in children (co-prescribed with amoxicillin, ampicillin or benzylpenicillin), severe or mild-moderate peritonitis (co-prescribed with ampicillin), severe or mild-moderate peritonial abscess (co-prescribed with ampicillin), complicated severe acute malnutrition in infants, children or adolescents (co-prescribed with ampicillin or benzylpenicillin), and sepsis without septic shock (co-prescribed with amoxicillin, ampicillin or benzylpenicillin). Gentamicin injection is the recommended by WHO for the treatment of gonococcal infection following treatment failure of other antibiotics and for other specified prophylactic measures. It is also considered an essential medicine for child health by the UN Commission on Life-Saving Commodities.

Gentamicin for injection is presented as an aqueous solution of gentamicin sulfate, mostly available in 2-mL vials or ampoules in two concentrations (10 mg/mL or 40 mg/mL). Gentamicin is also available in eye drops for ophthalmological infections, in ear drops for ear infections, and as a topical ointment for skin infections.

The scope of this manual includes only the presentation described in the WHO Essential Medicines List for Children (EMLc) that is gentamicin injection 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers whose gentamicin injection has been approved by an SRA or accepted by the United Nations Children's Fund (UNICEF), and those with a proven record of quality products.

2. Procurers need to focus on product quality to ensure that it is safe for patient use.

3. Cases of adverse drug reactions (ADRs) relating to gentamicin-containing solutions for injections were reported in different countries due to the presence of histamine in the drug product. Investigations have revealed elevated levels of histamine in gentamicin API linked to a fish peptone raw material that is utilized in the fermentation process . Therefore, if the API is obtained by fermentation, the drug substance and drug product manufacturers need to ensure the appropriate control of the raw materials as part of their auditing strategy. Additionally, the following considerations should be considered:

   - The source of peptone used (e.g. animal or vegetable origin) should be clearly declared by the API manufacturer.
   - If fish peptone is used in the manufacture of the active substance, histamine should be specified and controlled for as an impurity in the specifications.

KEY QUALITY CONSIDERATIONS

Product specification

The product must comply with the quality specifications as detailed in the Annex.

Packaging and labeling

Gentamicin injection should be procured in vial presentations as per the WHO EMLc recommendation of 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial. For typical neonatal dosages, approximately two doses could be obtained from a 10-mg/mL vial and up to eight doses from a 40 mg/mL vial. Note that some SRA-approved products may be presented in ampoules. For ampoules, any medicine not immediately used would have to be discarded, as it cannot be resealed.

The container-closure system (vial and rubber stopper) must be sufficient to preserve sterility during the shelf life of the product.

While pediatric ampoules exist for the intramuscular injections to newborns, the volumes are smaller if the 80 mg/2 ml ampoule is used (it is less painful for the patient). In this situation, syringes and needles of the right sizes for newborns should be considered in the procurement.

Note: Due to the calculations needed to determine the dose volume by weight of the infant, health workers at the primary care level may have difficulty accurately determining the correct amount of drug they should administer. A custom-marked syringe would be best, as a 1-mL syringe with 0.2 increment markings is most relevant for gentamicin administration, so it may be that a regularly marked 1-mL syringe can be used effectively by health care workers for this purpose. Based on a literature review, the syringe specifications shown in the table below are optimal for IM delivery of gentamicin in neonates[1].

ITEM	OPTIMAL RANGE
Gauge	22–25 G
Needle length	16–25 mm
Gradations	< 0.1 mL
Volume	≥1 mL

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Procurers need to verify with manufacturers that there are satisfactory stability data to support shelf life and storage conditions.

Gentamicin injection does not need to be maintained in the cold chain, but should be stored below 25°C.

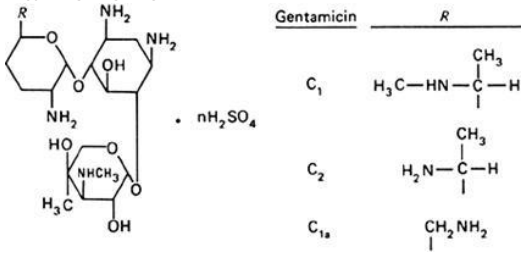
Procurers must ensure that the product is stored safely so that the vial cannot break or leak, which would compromise its sterility.

Additional information about the gentamicin finished product storage requirement can be found in the "Storage, Stability and Degradation" section.

Other considerations

Gentamicin injection must be manufactured in a sterile facility.

[1] Viability of customized, marked syringes for gentamicin delivery for the outpatient treatment of neonatal sepsis. Available at http://www.path.org/publications/files/PATH_dt_cust_syringe_br.pdf

Name of the Medicinal Product	Gentamicin injection
Chemical Name	Gentamicin sulfate Gentamicin sulfate is the sulfate salt of gentamicin fractions C_1, C_2, and C_{1a} produced by the growth of *Micromonospora purpurea*.
Chemical Structure	$C_{60}H_{125}N_{15}O_{25}S$ 
Pharmaceutical Form	Sterile solution for injection A clear, colorless solution
Qualitative and Quantitative Composition	Gentamicin injection is a sterile solution of gentamicin sulfate in water for injection. – Gentamicin injection 10 mg/mL: each vial (2 mL) contains gentamicin sulfate equivalent to 20 mg of gentamicin base. – Gentamicin injection 40 mg/mL: each vial (2 mL) contains gentamicin sulfate equivalent to 80 mg of gentamicin base. List of typical excipients[2]: – Sodium chloride – Water for injection – Sulfuric acid and/or sodium hydroxide, for pH adjustment Some formulations may contain the following excipients: – Methylparaben (preservative) – Propylparaben (preservative) – Sodium metabisulfite (antioxidant) – Edetate disodium (chelating agent)
Packaging and Presentation	The WHO EMLc includes two presentations for gentamicin injections: 10 mg/mL and 40 mg/mL in 2-mL vials. However, some manufacturers sell it packaged in glass ampoules.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

[2] Based on the formulation of an innovator product, Cidomycin®.

WHO-prequalified products

Gentamicin is not included in the WHO PQP. Therefore, no WHO-prequalified gentamicin products are available.

SRA-approved products

As of June 2022, few products are SRA-approved product for Gentamicin sulfate, as shown in table G-1.

Table G-1. Examples of SRA-Approved Gentamicin Injection 10 mg; 40 mg (as sulfate)/mL in 2-mL Vial or Ampoule

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Gentamicin sulfate EQ 40 mg base/mL EQ 10 mg base/mL	US FDA	Fresenius Kabi, USA	ANDA #062366	10 mg/mL: single-dose vials; 2 mL 40 mg/mL: multiple-dose flip-top vials; 2 mL	Not specified	Store at 20–25˚C. [See USP, Controlled room temperature.]
Gentamicin sulfate EQ 40 mg base/mL EQ 10 mg base/mL	US FDA	Hospira, USA	ANDA #062420	Single-dose flip-top vials; 2 mL	Not specified	Store at 20–25˚C. [See USP, Controlled room temperature.]
Cidomycin® 80 mg/2 mL solution for injection	UK MHRA	Aventis Pharma (Sanofi-Aventis) Ltd, UK	PL 04425/0672	Colorless glass ampoules (type I) or colorless glass vials (type I) closed with chlorobutyl rubber stopper sealed with an aluminum capsule	3 years	Do not store above 25°C. Do not refrigerate or freeze.
Gentamicin 10 mg/mL solution for injection or infusion	UK MHRA	Wockhardt UK Ltd, UK	PL 29831/0659	Type I glass ampoules; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze. Store in the original package to protect from light.
Gentamicin 40 mg/mL solution for injection or infusion	UK MHRA	Wockhardt UK Ltd, UK	PL 29831/0660	Type I glass ampoules; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze. Store in the original package to protect from light.
Gentamicin 40 mg/mL injection	UK MHRA	Hospira UK Ltd,	PL 04515/0037	Clear, type I glass vials; 2 mL	3 years	Do not store above 25°C.
Gentamicin 40 mg/mL solution for injection	UK MHRA	Amdipharm UK	PL 20072/0056	Colorless, type I glass ampoules; 2 mL	4 years	Do not store above 25°C. Do not freeze.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Gentamicin pediatric 20 mg/2 mL solution for injection	UK MHRA	Ennogen Pharma Ltd, UK	PL 40147/0042	Clear glass ampoules; 2 mL	2 years	Store below 25°C. Protect from light.
Gentamicin pediatric 20 mg/2 mL solution for injection	UK MHRA	Zentiva Pharma UK Ltd, UK	PL 17780/0507	Vials; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze.
Gentamicin 40 mg / mL Solution for injection / infusion	UK MHRA	Noridem Enterprises Limited Cyprus	PL 24598/0069	Type I, clear glass ampoules; 2 mL	3 years	This medicinal product does not require any special storage conditions. Do not refrigerate or freeze.
Gentamicin 40 mg / mL Solution for injection / infusion	UK MHRA	Panpharma France	PL 44124/0028	Colorless ampoules (glass type I); 2 mL	3 years	Store below 30°C.
Gentamicin 40 mg / mL Solution for injection / infusion	UK MHRA	Panpharma UK	PL 44789/0001	Colorless ampoules (glass type I); 2 mL	3 years	Store below 30°C.
Gentamicin injection USP 10 mg/mL	Health Canada	Hikma Canada Limited, Canada	02470462	Single-use ampoules; 2 mL	Not specified	Store between 15–30°C. Protect from light.
Gentamicin injection USP 40 mg/mL	Health Canada	Hikma Canada Limited, Canada	02457008	Single-use ampoules; 2 mL	Not specified	Store between 15–30°C. Protect from light.
Gentamicin injection USP 10 mg/mL	Health Canada	Sandoz Canada Incorporated	02242652	Single-use vials; 2 mL	Not specified	Store between 15–30°C. Protect from light.
Gentamicin injection USP 40 mg/mL	Health Canada	Sandoz Canada Incorporated	02268531	Single-use vials; 2 mL	Not specified	Store between 15–30°C. Protect from light.
Gentamicin injection BP 80 mg/2 mL	TGA (Australia)	Pfizer Australia Pty Ltd, Australia	AUST R 11376	LDPE ampoules; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze. Store in the original package to protect from light.
DBL Gentamicin 10mg/1mL(as sulfate) Injection	TGA (Australia)	Pfizer Australia Pty Ltd, Australia	AUST R 16339	Ampoule; 2 mL	3 years	Store below 25 degrees Celsius
Hospira Gentamicin Injection BP 80 mg/2 mL vial	TGA (Australia)	Hospira Australia Pty Ltd, Australia	AUST R 34197	Glass Type I Clear vials; 2 mL	36 months	Store below 25°C.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
DBL Gentamicin 80mg/2mL Injection BP	TGA (Australia)	Pfizer Australia Pty Ltd, Australia	AUST R 47268	Ampoule; 2 mL	3 years	Store below 25°C.
Gentamicin 80 mg/2 mL Injection BP	TGA (Australia)	Pfizer (Perth) Pty Ltd	AUST R 278535	LDPE ampoules; 2 mL	2 years	Store below 25°C. Protect from light.

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming that the FPP (including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information) will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may crosscheck the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- UK MHRA: https://products.mhra.gov.uk/
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA, Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Related products

Other formulations of gentamicin that exist in the market include the following products.

- Gentamicin 1 mg/mL solution for injection
- Gentamicin 3 mg/mL solution for infusion
- Gentamicin eye/ear drops 0.3% w/v
- Gentamicin intrathecal 5 mg/mL solution for injection
- Implants—each chain consists of 10, 30, or 60 beads (each bead contains 7.5 mg gentamicin sulfate)
- Gentamicin 0.3% w/v and hydrocortisone acetate 1% w/v ear drops
- Gentamicin 1 mg (as 1.67 mg gentamicin sulfate) and betamethasone 0.5 mg (as 0.64 mg betamethasone dipropionate) cream

It is important to note that the WHO EMLc recommends gentamicin injection 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial for the treatment of community-acquired pneumonia (severe), complicated severe acute malnutrition, and sepsis in neonates and children. Therefore, the procurement agency must focus on procurement of those presentations as per the WHO EML.

STORAGE, STABILITY, AND DEGRADATION

Gentamicin injection is stable at room temperature and does not require cold chain storage.

Shelf life: 2–4 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage conditions: Do not store above 25°C. Do not refrigerate or freeze. Protect from light.

The shelf life and storage condition of each SRA-approved product can be found in Table G-1.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the US Pharmacopoeia and British Pharmacopoeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the two pharmacopoeias are similar, except the assay limits and the composition of gentamicin sulfate (required only in the BP).

Table G-2. US Pharmacopeia Specifications for Gentamicin

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter.	Visual inspection
Identification (TLC)	The intensities and Rf values of the three principal spots obtained from the test solution correspond to those obtained from the standard solution.	USP<621>
pH	3.0–5.5	USP<791>
Assay	90.0–125.0%	USP<81>
Bacterial endotoxins	Not more than 0.71 USP endotoxin unit/mg of gentamicin	USP<85>
Particulate matter	Meet the requirements for small-volume injections	USP<788>
Extractable volume	Comply	USP<1>
Sterility	Sterile	USP<71>

Table G-3. British Pharmacopeia Specifications for Gentamicin

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter.	Visual inspection
Identification a) TLC	The three principal spots in the chromatogram obtained with solution (1) correspond to the three principal spots in the chromatogram obtained with solution (2).	Appendix III A
Identification b) Liquid chromatography	The retention times of the four principal peaks in the chromatogram obtained with solution (1) correspond to those of the four principal peaks in the chromatogram obtained with solution (2).	Appendix III D
pH	3.0–5.5	Appendix V L
Assay	The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. Calculate the content of gentamicin in the injection taking each 1,000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated content.	Appendix XIV A
Composition of gentamicin sulfate (liquid chromatography)	The proportions are within the following limits: C1 25.0–50.0% C1a' 10.0–35.0% C2 plus C2a' 25.0–55.0%	Appendix III D
Bacterial endotoxins	Below 7.1 IU per mL	Appendix XIV C
Sterility	Sterile	Appendix XVI A
Extractable volume	Comply	Appendix XII C5
Particulate matter	Comply	Appendix XIII A

GENTAMICIN ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Gentamicin is an aminoglycoside antibiotic used in the treatment of various bacterial infections. It is recommended by WHO for the treatment of neonatal meningitis and also for severe community acquired bacterial pneumonia (co-prescribed with amoxicillin, ampicillin or benzylpenicillin), severe or mild-moderate peritonitis (co-prescribed with ampicillin or benzylpenicillin), severe or mild-moderate peritoneal abscess (co-prescribed que ampicillin), complicated severe acute malnutrition in infants, children or adolescents (co-prescribed with ampicillin), and sepsis without septic shock (co-prescribed with amoxicillin, ampicillin or benzylpenicillin). Gentamicin injection is the second-line drug recommended by WHO for the treatment of gonococcal infection and for other specified prophylactic measures.

Posology, method, and duration of administration[1,2]

Severe cases of community-acquired pneumonia in children

- Neonates: gentamicin (IV/IM) 5 mg/kg dose given once a day, with ampicillin (IV/IM) 50 mg/kg dose given every 12 hours (1st week of life) or every 8 hours (>1st week of life), for 5 days (consider longer treatment if the patient is not clinically stable at day 5). Ampicillin can be replaced by amoxicillin (IV/IM) 50 mg/kg dose given every 12 hours (1st week of life) or every 8 hours (>1st week of life). Ampicillin can be also replaced by benzylpenicillin (IV) 50.000 IU/kg (30 mg/kg) given every 8 hours.
- Children: gentamicin (IV/IM) 7.5 mg/kg dose given once a day with ampicillin (IV/IM) 50 mg/kg dose given every 8 hours for 5 days (consider longer treatment if the patient is not clinically stable at day 5). Ampicillin can be replaced by amoxicillin (IV/IM) 50 mg/kg dose given every 8 hours. Ampicillin can be also replaced by benzylpenicillin (IV) 50.000 IU/kg (30 mg/kg) given every 8 hours.
- If no clinical response to ampicillin and gentamicin after 48-72 hours, change to second line treatment with cefotaxime (IV/IM) 50mg/kg dose given every 8 hours or ceftriaxone (IV/IM) 80 mg/kg dose given once a day.
- If HIV-positive and greater than 1 month of age (Pneumocystis jirovecii pneumonia is a risk), add empiric sulfamethoxazole + trimethoprim: 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole, given every 8 hours for 3 weeks.
- Severe pneumonia in school age children, may be caused by *Mycoplasma pneumoniae* (rare occurrence), which is unresponsive to beta-lactams. In this case, macrolides (e.g. clarithromycin) are options for treatment.

Community-acquired sepsis of bacterial origin in neonates and children

- Hospitalized patients

[1] WHO Essential Medicines List Antibiotic Book – Infographics. Draft for public comment. Version 1.1 (Nov 15, 2021).
[2] The WHO Essential Medicines List Antibiotic Book – Draft for public comment. November 18, 2021.

- Neonates: gentamicin (IV) 5 mg/kg dose given once a day, with ampicillin (IV) 50 mg/kg dose given every 12 hours (1st week of life) or every 8 hours (>1st week of life), for 7 days (14 days in case of meningitis). Ampicillin can be replaced by benzylpenicillin (IV) 50.000 IU/kg dose (30 mg/kg dose) given every 8 hours.
- Children: gentamicin (IV) 7.5 mg/kg dose given once a day with ampicillin (IV) 50 mg/kg dose given every 12 hours (1st week of life) or given every 8 hours (>1st week of life) for 7 days (14 days in case of meningitis). Ampicillin can be replaced by benzylpenicillin (IV) 50.000 IU/kg/dose (30 mg/kg dose) given every 8 hours.

■ Referral to hospital not possible
  - Neonates:
    Gentamicin (IM) 5 mg/kg dose given once a day, with amoxicillin (oral) 50 mg/kg dose given every 12 hours, for 7 days (14 days in case of meningitis).

    Consider giving ampicillin and gentamicin prophylactically for 2 days if there are significant risk factors for infection as follows:

    – Membranes ruptured > 18 hours before delivery
    – Mother had fever > 38°C before delivery or during labor
    – Amniotic fluid was foul smelling or purulent

  - Children:
    Gentamicin (IM) 7.5 mg/kg dose given once a day, with amoxicillin (oral) 50 mg/kg dose given every 12 hours, for 7 days (14 days in case of meningitis).

Community-acquired sepsis of bacterial origin in adults

Clinical sepsis of unknown origin

■ Gentamicin (IV) 5 mg/kg given once a day, with ceftriaxone (IV) 2 g given once a day or cefotaxime (IV) 2 g given every 8 hours, for 7 days (but duration depends on the patient's underlying disease, the causative pathogen (if any identified later on) and clinical progression).

  In case of meningitis the treatment should be given for 10 days (may differ in epidemics and with different pathogens). For lower respiratory tract infections, the treatment should be provided for 5 days.

  Gentamicin retains activity against ESBL-producing strains and can be considered as a carbapenem-sparing option.

Bacterial meningitis in neonates (< 2 months)

■ 1st week of life: gentamicin (IV) 5 mg/kg given once a day, with ampicillin (IV) 50 mg/kg dose given every 12 hours. Ampicillin can be replaced by ceftriaxone (IV) 100 mg/kg given once a day, or by cefotaxime (IV) 50mg/kg dose given every 12 hours.

■ > 1st week of life: 7.5 mg/kg given once a day, with ampicillin (IV) 50 mg/kg dose given every 8 hours. Ampicillin can be replaced by ceftriaxone (IV) 100 mg/kg given once a day, or by cefotaxime (IV) 50mg/kg/dose given every 6 hours.

■ Total treatment duration:
  - Unconfirmed pathogen: 3 weeks
  - Confirmed *pneumococcal meningitis*: 10–14 days
  - Confirmed *meningococcal meningitis*: 5–7 days
  - Confirmed *Listeria meningitis*: 21 days

Acute cholecystitis or cholangitis in children

Mild and Severe cases

- Neonates: gentamicin (IV) 5 mg/kg given once daily, with ampicillin (IV) 50 mg/kg dose given every 12 hours (first week of life) or every 8 hours (beyond first week of life), and with metronidazole oral/IV 7.5 mg/kg dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg).
- Children: gentamicin (IV) 7.5 mg/kg given once daily given with ampicillin (IV) 50 mg/kg dose given every 8 hours and with metronidazole oral/IV 7.5 mg/kg dose given every 8 hours. Oral weight bands for metronidazole:
  - 3 < 6 kg: 30 mg given every 8 hours
  - 6 < 10 kg: 50 mg given every 8 hours
  - 10 < 15 kg: 100 mg given every 8 hours
  - 15 < 20 kg: 150 mg given every 8 hours
  - 20 < 30 kg: 200 mg given every 8 hours
  - ≥ 30 kg: use adult dose
- Treatment duration:
  - Acute Cholecystitis:
    - Uncomplicated Cases: Antibiotics can be stopped once gallbladder is removed
    - Complicated Cases: 5 days is adequate in most cases with good clinical recovery and source control
  - Acute Cholangitis:
    - All Cases: Give antibiotics until biliary drainage procedures are performed and continue for a total of 5 days after successful source control

If signs and symptoms persist, abdominal imaging is suggested or an alternative extra-abdominal source of infection should be considered.

Antibiotic treatment for acute appendicitis

Mild and Severe cases

- Neonates: gentamicin (IV) 5 mg/kg given once daily, with ampicillin (IV) 50 mg/kg dose given every 12 hours (first week of life) or every 8 hours (beyond first week of life), and with metronidazole oral/IV 7.5 mg/kg dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg).
- Children: gentamicin (IV) 7.5 mg/kg given once daily, with ampicillin (IV) 50 mg/kg dose given every 8 hours and with metronidazole oral/IV 7.5 mg/kg dose given every 8 hours.
- Treatment duration:
  - Uncomplicated Cases: Antibiotics can be stopped once surgery has been performed and child is well.
  - Complicated Cases: Antibiotics can be continued for a total of 5 days provided that symptoms are resolved, and the source of infection was eliminated with surgery.
  - If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

Upper urinary tract infections

Severe cases

- Neonates: gentamicin (IV) 5 mg/kg dose given once a day. It may be prescribed with ceftriaxone (IV/IM) 80 mg/kg dose given once a day or cefotaxime (IV/IM) 50mg/kg dose given every 8 hours.
- Children: gentamicin (IV) 7.5 mg/kg dose given once a day. It may be prescribed with ceftriaxone (IV/IM) 80 mg/kg dose given once a day or cefotaxime (IV/IM) 50mg/kg dose given every 8 hours.

- Adults: gentamicin (IV): 5 mg/kg given once a day. It may be prescribed with ceftriaxone (IV/IM) 1 g given every 24 hours or cefotaxime (IV/IM) 1 g given every 8 hours.
- Treatment duration: clinical improvement is usually evident within 48-72 hours of starting treatment; if signs and symptoms persist, consider and investigate a possible complication (e.g. abscess) and review the results of the urine culture to verify that the pathogen is susceptible to the antibiotic used.

Consider gentamicin or amikacin where ESBL-producing isolates are highly prevalent.

In very sick patients, gentamicin (or amikacin) can be given in combination with ceftriaxone (or cefotaxime).

Antibiotic prophylaxis before surgical procedures

Contaminated procedure (2nd choice):

- Neonates: gentamicin (IV) 5 mg/kg single dose and metronidazole (IV) 7.5 mg/kg single dose.
- Children: gentamicin (IV) 7.5 mg/kg single dose and metronidazole (IV) 7.5 mg/kg single dose.
- Adults: gentamicin (IV) 5 mg/kg single dose and metronidazole (IV) 500 mg single dose.

Gentamicin should be given in combination with metronidazole and not as a stand-alone option in contaminated surgical procedures because, if given alone, it provides insufficient coverage of anaerobic bacteria.

Urologic procedures (2nd choice)

- Neonates: gentamicin (IV) 5 mg/kg single.
- Children: gentamicin (IV) 7.5 mg/kg single dose.
- Adults: gentamicin (IV) 5 mg/kg single dose.

Gonococcal infection

- Retreatment after treatment failure: gentamicin 240 mg IM combined with azithromycin 2 g oral.
- Genital and Anorectal Infections (2nd choice): gentamicin 240 mg IM

The 2021 EML lists gentamicin however, this option is not recommended in the WHO 2016 guidelines. Only use single therapy if local resistance data confirm susceptibility to the antibiotic.

Pyogenic liver abscess

- Severe Cases in neonates: gentamicin (IV) 5 mg/kg every 24 hours, combined with ampicillin (IV) 50mg/kg dose every 12 hours (before first week of life) or every 8 hours (beyond first week of life) and with metronidazole (IV/oral) 7.5 mg/kg dose every 12 hours (for IV loading dose 15 mg/kg).
- Severe Cases: gentamicin (IV) 7.5 mg/kg every 24 hours combined with ampicillin (IV) 50mg/kg dose every 12 hours (before first week of life) or every 8 hours (beyond first week of life) and with metronidazole (IV/oral) 7.5 mg/kg dose given every 8 hours.

For metronidazole:

  - 3 < 6 kg: 30 mg given every 8 hours
  - 6 < 10 kg: 50 mg given every 8 hours

- 10 < 15 kg: 100 mg given every 8 hours
- 15 < 20 kg: 150 mg given every 8 hours
- 20 < 30 kg: 200 mg given every 8 hours
- ≥ 30 kg: use adult dose

- Treatment duration: usually long (at least 4 weeks) depending on adequate source control with drainage procedures. Follow up imaging can help defining antibiotic treatment duration.

Other infections

Adults

- Serious infections: If renal function is not impaired, 5mg/kg/daily in divided doses at 6- or 8-hourly intervals. The total daily dose may be subsequently increased or decreased as clinically indicated.
- Systemic infections: If renal function is not impaired, 3–5 mg/kg/day in divided doses according to severity of infection, adjusting according to clinical response and body weight.
- Urinary tract infections: As for "Systemic infections," above. Or, if renal function is not impaired, 160 mg once daily may be used.

Pediatric patients

- The daily dose recommended in children aged 1 year and above and adolescents with normal renal function, is 3–6 mg/kg body weight per day as 1 dose (preferred) or up to 2 single doses.
- The daily dose in infants after the first month of life is 4.5–7.5 mg/kg body weight per day as 1 (preferred) up to 2 single doses.
- The daily dose in neonates and preterm infants (aged 0–4 weeks old) is 4–7 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in 1 single dose.

The elderly

- There is some evidence that elderly patients may be more susceptible to aminoglycoside toxicity, whether secondary to previous eighth-nerve impairment or to 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 must be decreased and adjusted according to renal function.
- Gentamicin is excreted by simple glomerular filtration; a reduced dosage is therefore necessary where renal function is impaired.

Contraindications

Hypersensitivity to gentamicin or to any of the excipients, pregnancy, and myasthenia gravis.

Special warnings and precautions for use

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinine, creatinine clearance), control of function of vestibule and cochlea, and hepatic and laboratory parameters is recommended.

Ototoxicity has been recorded following the use of gentamicin. Groups at special risk include patients with impaired renal function, infants, and possibly the elderly. Consequently, renal, auditory, and vestibular functions, as well as gentamicin serum levels, should be monitored in these patients to avoid peak concentrations above 10 mg/L and troughs above 2 mg/L when administering gentamicin twice daily and 1 mg/L for a once-daily dose. 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 usually reverts to normal during or following cessation of therapy. It is important to adjust the frequency of dosing according to the degree of renal function.

Gentamicin should be used in pregnancy only if considered essential by the physician (see section "Pregnancy and lactation" of this annex).

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

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

Interaction with other medicinal products and other forms of interaction

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. Potent diuretics such as etacrynic acid and furosemide are believed to enhance the risk of ototoxicity, and amphotericin B, cisplatin and ciclosporin are potential enhancers of nephrotoxicity.

Any potential nephrotoxicity of cephalosporins, and in particular cephaloridine, may also be increased in the presence of gentamicin. Consequently, if this combination is used, monitoring of renal function is advised.

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anesthesia.

Indomethacin possibly increases plasma concentrations of gentamicin in neonates.

Concurrent use with oral anticoagulants may increase the hypothrombinemic effect.

Concurrent use of bisphosphonates may increase the risk of hypocalcemia.

Concurrent use of the botulinum toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.

Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine.

Pregnancy and lactation

There are no proven cases of intrauterine damage caused by gentamicin. However, in common with most drugs known to cross the placenta, usage in pregnancy should be considered only in life-threatening situations where expected benefits outweigh possible risks. In the absence of gastrointestinal inflammation, the amount of gentamicin ingested from the milk is unlikely to result in significant blood levels in breast-fed infants.

Effects on ability to drive and use machines

Not known.

Undesirable effects

Side effects include vestibular damage or hearing loss, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction. Nephrotoxicity (usually reversible) and acute renal failure, hypersensitivity, anemia, blood dycrasias, purpura, stomatitis, convulsions, and effects on liver function occur occasionally.

Rarely, hypomagnesemia on prolonged therapy and antibiotic–associated colitis have been reported.

Nausea, vomiting, and rash have also been reported.

Central neurotoxicity, including encephalopathy, confusion, lethargy, mental depression, and hallucinations, has been reported in association with gentamicin therapy but is extremely rare.

Peripheral neuropathy: frequency not known.

Overdose

Hemodialysis and peritoneal dialysis will both aid in removing gentamicin from the blood, but the former is probably more efficient. Calcium salts given intravenously have been used to counter the neuromuscular blockade caused by gentamicin.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of gentamicin injection products. When assessing the complete quality/CMC documentation, assessors should particularly consider the following information on gentamicin injection.

API

Gentamicin is not included in the WHO PQP. Therefore, no WHO-prequalified gentamicin API exists.

Only two manufacturers of gentamicin sulfate API have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming their suitable quality for use in medicinal products.

Table G-4. Manufacturers of Gentamicin API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Gentamicin sulfate (monograph number 331)	LEK Pharmaceuticals D.D. SI 1526 Ljubljana, Slovenia	R1-CEP 2005-121-Rev 01	2/3/2016	Chemica
Gentamicin sulfate (monograph number 331)	Fujian Fukang Pharmaceutical Co, Ltd, CN 350 002 Fuzhou, China	R1-CEP 1998-155-Rev 10	2/18/2019	Chemica

Other manufacturers of gentamicin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines[3].

Gentamicin API must meet pharmacopoeia specifications such as those of the International Pharmacopoeia, European Pharmacopoeia, and US Pharmacopoeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Due to the risk of adverse drug reactions (ADRs) from the presence of histamine in gentamicin API, the source of peptone used (e.g. animal or vegetable origin) should be clearly declared by the API manufacturer. If fish peptone is used in the manufacture of the active substance, the histamine should be specified and controlled for as an impurity in the specifications.

[3] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.

Excipients

Gentamicin injection may contain suitable buffers, preservatives, and sequestering agents, unless it is intended for intrathecal use, in which case it contains only suitable tonicity agents.

The typical excipients of gentamicin injection include sodium chloride, water for injection, and sulfuric acid and/or sodium hydroxide, for pH adjustment. There are no special concerns with the excipients. No excipient with the risk of transmitting TSE/BSE is used.

The quality of all excipients should be compliant with recognized pharmacopoeias (Ph.Int., Ph.Eur./BP, or USP).

Some formulations may contain methylparaben and propylparaben as preservatives when the product is intended for multiple-dose use. Where methylparaben and propylparaben are included in the formulation as antimicrobial preservatives, their assays (preservative contents) should be included in the FPP specifications. If the lower limit for the proposed acceptance criterion for the assay of parabens is below 90.0%, its effectiveness should be established by appropriate studies (e.g., USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP containing a concentration of methylparaben and propylparaben corresponding to the lower proposed acceptance criterion.

Where sodium metabisulfite is included in the formulation as an antioxidant, the effectiveness of the proposed concentration should be justified and verified by appropriate studies.

Manufacturing process

Gentamicin injection is a straightforward drug to manufacture, but the main quality concerns are the sterilization process and the sterility of the facility where it is made.

The manufacturing process of gentamicin injection is a standard process conducted under appropriate aseptic conditions, and includes the steps of preparation of the solution with adjustment of pH, prefiltration and sterile filtration, and filling and sealing of the ampoules. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacturing.

The filters used in sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of absorption of the API or any of the components. The headspace of the vials should be replaced with nitrogen during the filling process to prevent oxidation of the API.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production-scale batches should be submitted.

Notes:

- *The risk for potential presence of elemental impurity in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc,), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*

- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.*[4, 5]

Packaging

Neutral type I glass vials should be used.

Suitability of container should be demonstrated, including the following properties:

Safety

- Glass vials must meet compendial requirements such as USP<660> and USP<1660>.
- Rubber stoppers must meet compendial requirements such as USP<381> and USP<87>/<88>. Composition of the rubber stopper along with a declaration from the supplier that the material is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines should be provided.
- Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
  - One-time test reported as part of product development
  - Routine leak testing performed as part of product manufacture

Compatibility

- Extractables/leachables data of the rubber stoppers should be provided.
- Accelerated and long-term stability data on vials stored in inverted orientation should be submitted to further support absence of leachables as well as absorption.
- Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers may also need to be demonstrated.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously, or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and with the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Cidomycin® (gentamicin injection 80 mg/2 mL solution for injection 40 mg/mL, Sanofi-Aventis), gentamicin sulfate injection 10 mg/mL, 40 mg/mL (Fresenius Kabi, USA), and gentamicin sulfate injection 10 mg/mL, 40 mg/mL (Hospira, USA). The composition of the proposed product should be the same as the comparator product.

[4] https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities
[5] https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update