WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

1. NAME OF THE MEDICINAL PRODUCT

[TB328 trade name] *

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 1000 mg kanamycin (as sulfate)

Each ampoule of 3 mL of injection contains:
4.5 mg of sodium bisulfite
6.16 mg (0.27 mmol) sodium

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for Injection

Clear colourless to slightly yellow or yellow-green solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB328 trade name] is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by kanamycin-sensitive strains of *Mycobacterium tuberculosis*. Kanamycin is only indicated as a second-line antimycobacterial drug when first-line drugs cannot be used because of resistance or intolerance (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official treatment guidelines for tuberculosis. Official guidance will normally include WHO and local health authorities' guidance.

4.2 Posology and method of administration

Posology

Adults and adolescents

Adults and adolescents 15 years or older and weighing at least 30 kg
The usual dose is 15 mg/kg once daily on 5–7 days each week (usually up to a maximum of 1 g; a higher dose can be given to a large, muscular person but with monitoring of kanamycin concentration—see section 4.4 and 5.2 for serum concentrations)

Special populations

Obese patients
Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supra-therapeutic concentrations.

For dosing, use adjusted weight as follows: Ideal body weight +40 % of excess weight.

- Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft
- Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft

One inch=2.5 cm, 5 ft=152 cm.

Kanamycin concentration should be monitored closely (see section 5.2).

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility.

The duration of kanamycin therapy is based on individual response and drug susceptibility (please refer to official treatment guidelines for tuberculosis).

Adults aged over 59 years
10 mg/kg (maximum 750 mg) once daily on 5–7 days each week, or 2–3 times each week (at roughly equal intervals throughout the week) after the initial treatment period. Alternatively, the dose can be 15 mg/kg once daily, 3 times per week, administered at roughly equal intervals throughout the week.

Patients with renal impairment
Dosage should be reduced in those with renal impairment, in whom plasma-drug concentration should be monitored. The recommended dose and frequency for patients with creatinine clearance less than30 mL/min or for patients receiving haemodialysis is 12–15 mg/kg/dose 2 or 3 times per week (not daily).

Caution should be used in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. If on dialysis, the dose should be administered after dialysis.

Hepatic impairment:

No dose adjustment is necessary.

Paediatric population
There is limited reported experience on the use of second-line drugs, including kanamycin, for extended periods in children. Kanamycin should not be used in children with clinically-diagnosed disease associated with less severe clinical or radiological manifestations (see sections 4.4 and 5.1).
The usual dose is 15–30 mg/kg (maximum 1 g) once daily on 5–7 days each week.

Method of administration

Kanamycin is normally given by the intramuscular route, but can be given intravenously when intramuscular administration is not feasible.

Intramuscular injection
Adults: The preferred site is the upper outer quadrant of the buttock, (i.e., gluteus maximus), or the mid-lateral thigh. The deltoid area should be used only if well-developed such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-third of the upper arm.

Children: It is recommended that intramuscular injections be given preferably in the mid-lateral muscles of the thigh. In infants and small children, the periphery of the upper outer quadrant of the gluteal region should be used only when necessary, in order to minimize the possibility of damage to the sciatic nerve.

For instructions on reconstitution of [TB328 trade name] before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to kanamycin. Clinically significant hypersensitivity to other aminoglycosides may contraindicate the use of kanamycin because of known cross-sensitivity of patients to drugs in this class.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Warnings
Ototoxicity: Both vestibular and auditory dysfunction can follow the administration of kanamycin. The degree of impairment is directly proportional to the dose and duration of kanamycin administration, to the age of the patient, to the level of renal function and to the amount of underlying existing auditory dysfunction. The ototoxic effects of the aminoglycosides, including kanamycin, are potentiated by the coadministration of ethacrynic acid, mannitol, furosemide and possibly other diuretics.

The use of kanamycin in patients with auditory impairment must be undertaken with great caution, and the risk of additional eighth cranial nerve impairment should be weighed against the potential benefits of treatment. Appropriate monitoring and early discontinuation of the drug may permit recovery prior to irreversible damage to the sensorineural cells.

Nephrotoxicity: Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. The drug is variably cleared by haemodialysis.

Neurotoxicity: The risk of severe neurotoxic reactions is sharply increased in patients with impaired renal function or pre-renal azotemia. These include disturbances of vestibular and cochlear function, optic nerve dysfunction, peripheral neuritis, arachnoiditis, and encephalopathy may also occur. Paraesthesia in and around the mouth is not uncommon after intramuscular injection of kanamycin, and other neurological symptoms, including peripheral neuropathies, optic neuritis, and scotoma have occasionally occurred. The incidence of clinically detectable, irreversible vestibular damage is particularly high in patients treated with kanamycin.

The concurrent or sequential use of other neurotoxic and/or nephrotoxic drugs with kanamycin sulfate should be avoided (see section 4.5).
The neurotoxicity of kanamycin can result in respiratory paralysis from neuromuscular blockage, especially when the drug is given soon after the use of anaesthesia or muscle relaxants.
Kanamycin should be used with caution in conditions characterised by muscular weakness, since it may aggravate muscle weakness because of its potential curare-like effect on the neuromuscular junction.
Kanamycin must be used in conjunction with adequate doses of other antituberculous drugs. The use of kanamycin alone allows rapid development of strains resistant to it. As with other antibiotics, the use of kanamycin may result in overgrowth of non-susceptible organisms. If this occurs, appropriate therapy should be instituted.
Aminoglycosides should be used with caution in premature and neonatal infants because of the renal immaturity of these patients and the resulting prolongation of serum half-life of these drugs.

Precautions
As kanamycin is potentially ototoxic, hearing (e.g. by audiometry) and vestibular function should be assessed before starting treatment and at monthly intervals during treatment.
In case of clinically significant ototoxicity or if early symptoms of vestibular toxicity appear, the dosing frequency should be decreased to 2–3 times a week and switching to capreomycin should be considered. If symptoms worsen despite dose adjustment, kanamycin should be stopped and, if possible, additional anti-TB drugs should be added to reinforce the regimen. Hearing loss and vestibular dysfunction are generally not reversible upon discontinuation of therapy.
Renal function should be tested at least monthly throughout treatment, and the dose should be reduced in patients with known or suspected renal impairment (see 'Posology and method of administration'). If feasible, therapeutic drug monitoring should be conducted in patients with renal impairment. Peak and trough plasma-kanamycin concentration should be measured at the start of treatment; and plasma kanamycin concentrations should be measured throughout treatment. Peak concentrations (30 to 90 minutes after injection) >35 μg/mL and trough concentrations (just prior to the next dose) >10 μg/mL should be avoided because of the associated risk of toxicities (for therapeutic drug concentrations see section 5.2).
Since hypokalaemia, hypocalcaemia and hypomagnesaemia may occur during kanamycin therapy, serum potassium, calcium, magnesium and other electrolyte levels should be monitored regularly.

Changes in hepatic function may occur and liver function should be tested periodically.

Excipients
Each ampoule contains sodium bisulfite, which may rarely cause hypersensitivity reactions and bronchospasm. It is however essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous administration of other antituberculous drugs which also have ototoxic and nephrotoxic potential (e.g. streptomycin, amikacin) is not recommended. Also, administration with other neurotoxic, ototoxic or nephrotoxic drugs to patients receiving kanamycin should be avoided. These include other aminoglycoside antibiotics, polymyxin, colistin, vancomycin, cephalosporins, amphotericin B, ciclosporin, cisplatin, and loop diuretics (e.g. furosemide, etacrynic acid, mannitol).

Where this is not possible, monitor carefully for neurotoxic, ototoxic or nephrotoxic effects.

In patients with severely impaired renal function, a reduction in activity of aminoglycosides may occur with concomitant use of penicillin-type drugs.

In vitro admixture of aminoglycosides with beta-lactam antibiotics (penicillins or cephalosporins) may result in significant mutual inactivation. A reduction in serum activity may also occur when an aminoglycoside or penicillin-type drug is administered in vivo by separate routes. Inactivation of the aminoglycoside is clinically significant only in patients with severely impaired renal function. Inactivation may continue in specimens of body fluids collected for assay, resulting in inaccurate aminoglycoside readings. Such specimens should be properly handled (assayed promptly, frozen, or treated with beta-lactamase).

Kanamycin may potentiate the effect of neuromuscular blocking agents administered during anaesthesia.

Renal excretion of zalcitabine may be reduced by aminoglycosides.

Concurrent use of the Botulinum Toxin and aminoglycoside antibiotics may increase the risk of toxicity due to enhanced neuromuscular block.

Concurrent use with oral anticoagulants may increase the hypothrombinemic effect.
There is an increased risk of hypocalcaemia when aminoglycosides are administered with bisphosphonates.

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

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3) and there are isolated case reports of deaf children born to women who received streptomycin in pregnancy.

There are no well-controlled studies in pregnant women. Kanamycin is suggested to cause hearing impairment when administered during pregnancy. Therefore, [TB328 trade name] should not be used during pregnancy.

Breastfeeding

Kanamycin appeared in human milk in low concentrations. Milk: plasma ratios ranging between 0.05 and 0.40 have been reported. The small dose derived from breastfeeding and the poor gastrointestinal absorption of this agent make it unlikely that neonatal toxicity would appear from milk exposure.

[TB328 trade name] can be used under caution during breast-feeding.

Fertility

No human data on the effect of [TB328 trade name] on fertility are available. Animal studies indicate no effects of kanamycin on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for symptoms of vestibular toxicity (see sections 4.4 and 4.8) while taking kanamycin and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

The following undesirable effects have been recorded but reliable information on the frequency of occurrence is not available.

The major toxic effects associated with kanamycin therapy are ototoxicity and nephrotoxicity. Kanamycin is considered one of the more toxic aminoglycosides. The risks are higher for patients with renal impairment (especially if haemodialysis is required) or a history of renal impairment, for those receiving concomitant or sequential treatment with other ototoxic or nephrotoxic drugs or rapid acting diuretic agents given intravenously, and for patients treated for longer periods and with higher doses than recommended.

Other adverse reactions reported are anaphylaxis, hypersensitivity reactions, rash, anaemia, blood dyscrasias, purpura, headache, nausea, vomiting, diarrhoea, stomatitis, antibiotic–associated colitis, electrolyte

disturbances, and effects on liver function. The "malabsorption syndrome" characterized by an increase in faecal fat, decrease in serum carotene, and fall in xylose absorption, has occurred with prolonged therapy.

Nephrotoxicity

Renal side effects have included albuminuria, haematuria, azotaemia, oliguria, and increased serum creatinine and BUN. Acute renal failure may occur occasionally.

Ototoxicity and vestibular toxicity

Ototoxicity resulting in loss of vestibular function secondary to hair cell damage, and irreversible or partially reversible bilateral hearing loss has been observed. Nystagmus, vertigo, nausea, vomiting, and acute Meniere's syndrome are signs of vestibular dysfunction. Cochlear damage may be asymptomatic and may initially manifest as minor changes in audiometric test results at higher frequencies.

Neurotoxicity

Nervous system side effects have included neuromuscular blockade. Aminoglycosides have been associated with acute muscular paralysis, apnoea, peripheral neuropathy and encephalopathy (numbness, paraesthesia, muscle twitching, seizures), and myasthenia gravis-like syndrome. Neurotoxicity may occur after intrapleural, intraperitoneal, or parenteral administration. Patients with renal impairment may be at a higher risk.

Injection-site reactions

Local reactions have included pain at the injection site after intramuscular injection.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

In case of overdosage, there is a general risk for nephro-, oto- and neurotoxic (neuromuscular blockage and respiratory paralysis) reactions (see 'Special warnings and special precautions for use').

If kanamycin is ingested, toxicity is unlikely because less than 1% of the amount taken is absorbed from an intact gastrointestinal system.

Treatment

Symptomatic and supportive therapy is recommended.

Fluid balance, electrolytes and creatinine clearance should be monitored. Haemodialysis or peritoneal dialysis is effective in the removal of kanamycin from the blood. In the newborn infant, exchange transfusion may also be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminoglycoside antibacterials, ATC Code J01GB04

Kanamycin is an aminoglycoside antibiotic and is active against *Mycobacterium tuberculosis*.

Mode of action

Aminoglycosides are taken up into sensitive bacterial cells by an active transport process. Within the cell, they bind to the 30S, and to some extent to the 50S subunits of the bacterial ribosome, inhibiting protein synthesis and generating errors in the transcription of the genetic code.

Mechanisms of resistance

The most common mechanism is inactivation of aminoglycosides by a family of enzymes named aminoglycoside-modifying enzymes (AMEs). Also, aminoglycoside resistance can be achieved by mutations of the ribosome target and by enzymatic modification of the ribosome by ribosomal methyltransferase enzymes. Furthermore, there may be active transport of aminoglycosides out of the cell by efflux pumps.

5.2 Pharmacokinetic properties

Pharmacokinetics of Kanamycin

General	
	Kanamycin is almost not absorbed after oral administration
Absorption	
Oral bioavailability	Not Applicable
Food effect	Not Applicable
Distribution	
Volume of distribution (mean)	19.6 L
Plasma protein binding *in vitro*	None.
Tissue distribution	**CSF**: Concentrations in normal infants are approximately 10 to 20 percent of serum levels and may reach 50 percent when the meninges are inflamed. In normal adult patients, only trace levels of kanamycin present in spinal fluid. No data are available on adults with meningitis **Uterine tissue:** Significant levels appear in cord blood and amniotic fluid. **Other tissue:** Peritoneal fluid, bile and synovial fluid.
Metabolism	
	Little, if any metabolic transformation
Elimination	
Elimination half life	2.5 h
Mean systemic clearance (Cl/F)	Renal clearance 4.6 L/h
% of dose excreted in urine	Almost completely excreted unchanged
% of dose excreted in faeces	NA*
General	
	Kanamycin is almost not absorbed after oral administration
Absorption	
Oral bioavailability	Not Applicable
Food effect	Not Applicable

Distribution	
Volume of distribution (mean)	19.6 L
Plasma protein binding *in vitro*	None.
Tissue distribution	**CSF**: Concentrations in normal infants are approximately 10 to 20 percent of serum levels and may reach 50 percent when the meninges are inflamed. In normal adult patients, only trace levels of kanamycin present in spinal fluid. No data are available on adults with meningitis **Uterine tissue:** Significant levels appear in cord blood and amniotic fluid. **Other tissue:** Peritoneal fluid, bile and synovial fluid.
Metabolism	
	Little, if any metabolic transformation
Elimination	
Elimination half life	2.5 h
Mean systemic clearance (Cl/F)	Renal clearance 4.6 L/h
% of dose excreted in urine	Almost completely excreted unchanged
% of dose excreted in faeces	NA*

NA*-Information not available

Special populations

Renal impairment
Clearance is decreased in patients with renal impairment

5.3 Preclinical safety data

General toxicity

Intravitreal dosages of 200 mg/kg/day in pregnant rats and pregnant guinea pigs led to hearing impairment in the offspring.

Guinea pigs dosed intramuscularly with kanamycin up to 400 mg/kg bodyweight/day for 4 weeks showed reduction of pinna reflex and slight loss of cochlea cells resulting in ototoxicity at 200 mg/kg bodyweight and above.

Nephrotoxic effects were seen in rats and rabbits at 50 mg/kg bodyweight. In rabbits at 50 mg/kg bodyweight dosed intramuscularly effects included proximal tubular nephropathy.

Genotoxicity

Kanamycin has been tested for mutagenicity. The tests indicate that kanamycin is not an in vivo mutagen.

Carcinogenesis

No carcinogenicity studies have been performed.

Reproductive toxicity

Reproductive studies have been performed in rats and rabbits and have revealed no evidence of impaired fertility or teratogenic effects. Dosages of 200 mg/kg/day in pregnant rats and pregnant guinea pigs led to hearing impairment in the off-spring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bisulfite
Sodium citrate
Sulfuric acid
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Un-opened: 24 months

Following dilution with the infusion solutions, chemical and physical in-use stability has been demonstrated for 8 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C. Avoid freezing.

6.5 Nature and contents of container

5 mL glass ampoule made of neutral borosilicate colourless glass ampoule (USP Type I). 10 ampoules are packed in a carton.

6.6 Instructions for use and handling and disposal

Reconstitution of [TB328 trade name]

The solution for intravenous use is prepared by adding the contents of a 1000 mg ampoule to 200 to 400 mL of sterile diluent such as Normal Saline or 5 % Dextrose in Water. The appropriate dose is administered over a 30 to 60 minutes period. Single use only. Discard unused portion.

For administration of a 1000 mg dose, the entire contents of the vial should be given. For doses lower than 1000 mg, the following dilution table may be used.

DILUTION TABLE

Diluent Added to 1000 mg, 10 mL Vial	Volume of Kanamycin Sulfate Solution	Concentration (Approx)
3 mL	3.8 mL	263.2 mg/mL
4 mL	4.9 mL	204.1 mg/mL

*Equivalent to kanamycin activity. Approximated concentration takes into account the retention volume.

Disposal

Reconstituted and further diluted solutions that show discoloration, haziness, visible particulate matter or precipitation should not be used.

7 SUPPLIER

Livzon (Group) Pharmaceutical Factory
No.38, Chuangye Road North,
Jinwan District, Zhuhai,
Guangdong, 519045, P. R. China

Tel: 0086-756-8135859

E-mail: overseas@livzon.com.cn

8 WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB328

9 DATE OF PREQUALIFICATION

06 February 2019

10 DATE OF REVISION OF THE TEXT

September 2019

References

WHO treatment guidelines for drug-resistant tuberculosis (2016 update, October 2016 revision). WHO 2016. Available at: http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. WHO 2014. Available at: http://www.who.int/tb/publications/pmdt_companionhandbook/en/

Brayfield A (ed), *Martindale: The Complete Drug Reference*. [online] London: Pharmaceutical Press [accessed 19 September 2018]

Label Kanamycin Injection, available at: https://www.drugs.com/pro/kanamycin.html [accessed September 2019]

SmPC Cidomycin 80mg/2ml Solution for Injection available at : https://www.medicines.org.uk/emc/product/1264/smpc [accessed September 2019]

TB261Capreomycin (as sulfate) 1 g powder for injection: https://extranet.who.int/prequal/sites/default/files/TB261Part4v1.pdf [accessed September 2019]

Garneau-Tsodikovaa S. and Labby KJ. Mechanisms of Resistance to Aminoglycoside Antibiotics: Overview and Perspectives. Medchemcomm. 2016 Jan 1; 7(1): 11–27.

Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/ .