Summary of Product Characteristics

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

AMIKA 500 (Amikacin Sulfate Injection USP 500mg/2ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration

Each 2ml contains:
Amikacin Sulfate USP
Eq. to Amikacin 500 mg
Methylparaben USNF 0.08%
w/v Propylparaben USNF
0.02% w/v (As preservative)
Water for Injection USP q.s.

3. PHARMACEUTICAL FORM

Liquid Injection

Visual/ Physical description of FPP: Clear, colorless solution filled in 2 ml transparent glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amikacin Sulfate Injection USP is indicated in combination with other antituberculosis agents for the treatment of multidrug resistant tuberculosis (MDR-TB) caused by amikacin-sensitive strains of Mycobacterium tuberculosis.
Amikacin is only indicated as a second-line antimycobacterial agent when first-line medicines cannot be used because of resistance or intolerance.
Consideration should be given to current official treatment guidelines for tuberculosis (e.g., those of the WHO).

4.2 Posology and method of administration

Posology:

Amikacin Sulfate Injection USP is always given in combination with other anti-tuberculosis medicines for the treatment of MDR-TB.
The duration of amikacin therapy is based on individual response and drug susceptibility (please refer to official treatment guidelines for tuberculosis).

Dosing recommendations for patients 15 years and older:
The recommended dose is 15-20 mg/kg body weight, taken once daily,

up to a maximum dose of 1 g per day.

Weight-based	**Weight bands in patients 15 years old or older**

daily dose					
Volume of 500 mg/2 mL solution for injection*	30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg
	2.5 ml	3 ml	3-4 ml	4 ml	4 ml

* The weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. For i.v. use, the volume may be increased.

Special populations:

Renal impairment:

Amikacin Sulfate Injection USP should be used with caution in patients with renal disease because of the increased risk of both ototoxicity and nephrotoxicity, and plasma-drug concentrations should be monitored. In patients with CLCR < 50 mL/min the dose should be decreased and/or the interval between doses increased, based on plasma drug concentrations.

As renal function may change during therapy, serum creatinine should be checked frequently, and the dosage regimen modified as necessary.

In patients with severe renal impairment (CLCR < 30 ml/min or on dialysis) and those on haemodialysis, the dose should be adjusted to 12–15 mg/kg once daily, 2–3 times each week at roughly equal intervals throughout the week. In patients on haemodialysis, the dose should be given after the dialysis on the day of haemodialysis.

Hepatic impairment:

No dose adjustment is necessary.

Paediatric population:

The use of injectable agents, such as amikacin, in children should be exceptional and limited to salvage therapy because of the risk of serious toxicities (i.e. ototoxicity and nephrotoxicity), and given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school. Amikacin Sulfate Injection USP 500mg/2ml should only be used in children under strict monitoring to ensure early detection of ototoxicity.

Method of administration

Amikacin may be given intramuscularly or intravenously. Intramuscular injection:

Adults: The preferred site is the mid-lateral thigh or the upper outer quadrant of the buttock. The deltoid area (at the upper third of upper

arm) should be used only if well-developed such as in certain adults and older children.

Children: It is recommended that intramuscular injections be given preferably in the mid-lateral muscles of the thigh.

4.3 Contraindications

- Hypersensitivity to amikacin or to any of the excipients used in formulation.
- Clinically significant hypersensitivity to other aminoglycosides may contraindicate the use of amikacin because of the known cross-sensitivity of patients to medicines in this class. Special warnings and precautions for use

Amikacin should only be used to treat tuberculosis if susceptibility to amikacin is confirmed and if high quality audiometry monitoring for hearing loss can be ensured.

Neuro/ototoxicity:

The use of aminoglycosides, including amikacin, is associated with a risk of hearing impairment and renal injury resulting from its toxic effects on the auditory and vestibular branches of the eighth cranial nerve and the renal tubules. Patients with impaired renal function and those with normal renal function who receive high doses or prolonged therapy (as for the treatment of tuberculosis) are at increased risk of severe neurotoxic (mainly ototoxic) and nephrotoxic reactions. The risk of these toxic effects should be carefully weighed against the potential benefits of treatment. The use of amikacin in patients with renal insufficiency or auditory impairment must be undertaken with great caution.

Neurotoxicity is manifested by bilateral auditory toxicity and sometimes by vestibular ototoxicity, both of which may be permanent. Loss of high frequency perception usually occurs before there is noticeable clinical hearing loss and can be detected by audiometric testing. There may not be clinical symptoms to warn of developing cochlear damage. Vertigo may occur and there may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions.

The risk of hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations and continues to progress after drug withdrawal.

Because of the risk of hearing impairment, the use of amikacin in children, especially in very young children and children with mild disease as determined by the absence of malnutrition, serious forms of

extrapulmonary disease, cavitation on chest radiography or HIV infection should be avoided. Hearing loss can have a permanent impact on the acquisition of language and the ability to learn at school. If amikacin is used in children, regular audiometry is critical. Amikacin should be avoided in patients who may have subclinical renal or eighth nerve damage induced by prior use of nephrotoxic and/or ototoxic agents such as amphotericin B, streptomycin, dihydrostreptomycin, gentamicin, tobramycin, kanamycin, neomycin, polymyxin B, colistin, cephaloridine, vancomycin or viomycin, as toxicity may be additive. If its use is unavoidable, these patients should be monitored closely for neurotoxic and nephrotoxic reactions.

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 medicines.

Neuromuscular toxicity:

Neuromuscular blockade and respiratory paralysis have been reported following aminoglycoside use. The possibility of respiratory paralysis should be considered if aminoglycosides are administered by any route, especially in patients receiving anaesthetics or neuromuscular blocking agents or in patients receiving massive transfusions of citrate-anticoagulated blood. If neuromuscular blockade occurs, mechanical respiratory assistance may be necessary. Amikacin 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.

Resistance:

Amikacin must be used in conjunction with adequate doses of other antituberculous drugs. The use of amikacin alone allows rapid development of strains resistant to it.

As with other antibiotics, the use of amikacin may result in overgrowth of non-susceptible organisms. If this occurs, appropriate therapy should be instituted.

Precautions:

As amikacin 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. If symptoms worsen despite dose adjustment, amikacin should be stopped and, if possible, additional anti-TB medicines should be added to reinforce the regimen.

Hearing loss and vestibular dysfunction are generally not reversible upon discontinuation of therapy.

Patients should be well hydrated during treatment. Renal function should be tested at least monthly throughout treatment, and the dose should be reduced in patients with known or suspected renal impairment. If serum creatinine continues to rise, amikacin should be stopped.

If feasible, therapeutic drug monitoring should be conducted in patients with renal impairment. Peak and trough plasma-amikacin concentration should be measured at the start of treatment, and plasma-amikacin 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.

Elderly patients may have reduced renal function. Monitoring of renal function in elderly patients during treatment with aminoglycosides is particularly important.

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

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous administration of other antituberculous medicines which also have ototoxic and nephrotoxic potential (e.g. streptomycin, kanamycin) is not recommended. Also, other neurotoxic, ototoxic or nephrotoxic medicines should not be administered to patients receiving amikacin. These include other aminoglycoside antibiotics, polymyxin B, colistin, cephalosporins, amphotericin B, ciclosporin, cisplatin, methoxyflurane and diuretics (e.g. furosemide, etacrynic acid, mannitol). Where this is not possible, neurotoxic, ototoxic or nephrotoxic effects should be carefully monitored for.

Neuromuscular blockade and respiratory paralysis may occur from administration of aminoglycosides to patients under the influence of anaesthetics or muscle-relaxing medicines (including ether, halothane, dtubocurarine, succinylcholine, decamethonium, atracurium, rocuronium, vecuronium or in patients receiving massive transfusions of citrate-anticoagulated blood).

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

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).

Indomethacin may increase the plasma concentration of amikacin in neonates. Indomethacin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may also enhance the nephrotoxicity of amikacin.

There is an increased risk of hypocalcaemia when aminoglycosides are administered with bisphosphonates.

A reduction in the effect of neostigmine or pyridostigmine occurs with concomitant administration of aminoglycoside antibiotics.

Concomitantly administered thiamine (vitamin B1) may be destroyed by the reactive sodium metabisulfite component of the amikacin sulfate formulation.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Studies in animals have shown reproductive toxicity.

The safety of amikacin in pregnancy has not yet been established. Amikacin should be administered to pregnant women and neonatal infants only when clearly needed and under medical supervision.

There are limited data on the use of aminoglycosides in pregnancy. Aminoglycosides can cause fetal harm.

Aminoglycosides cross the placenta and there have been reports of total, irreversible, bilateral congenital deafness in children whose mother received streptomycin during pregnancy. Adverse effects on the fetus or newborns have been reported in pregnant women treated with other aminoglycosides, therefore the potential for harm exists. If amikacin is used during pregnancy or if the patient becomes pregnant while taking this medicine, the patient should be appraised of the potential hazard to the fetus.

Breast-feeding:

Amikacin 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 Amikacin Sulfate

Injection USP 500mg/2ml make it unlikely that neonatal toxicity would appear from milk exposure.
Amikacin can be used under caution during breastfeeding.

Fertility:

There are no data on the effects of amikacin on human male or female fertility. Animal studies indicate no effects of amikacin on male or female fertility

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for symptoms of vestibular toxicity while taking amikacin and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

The majority of available safety data on amikacin has been generated in patients with other conditions than tuberculosis in studies using shorter treatment durations (mostly up to 10 days) than recommended for tuberculosis treatment.
The major toxic effects associated with amikacin therapy are ototoxicity and nephrotoxicity. The risks are higher for patients with renal impairment 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/or with higher doses than recommended.
The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), 'not known' (frequency cannot be estimated from the available data). Note that the frequencies relate to short-term therapy (<1 month).

Infections and infestations

Uncommon: Superinfections or colonisation with resistant bacteria or yeast

Blood and lymphatic system disorders

Rare: anaemia, eosinophilia, thrombocytopenia, granulocytopenia

Immune system disorders

Not known: hypersensitivity reactions, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction

Metabolism and nutrition disorders

Rare:

Hypomagnesaemia

Nervous system disorders

Common: vertigo

Rare: paresthesia, tremor, balance disorders, headache Not known: paralysis

Ear and labyrinth disorders

Common: hearing loss, tinnitus

Not known: deafness, sensory deafness

Vascular disorders

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders

Not known: Apnoea, bronchospasm

Gastrointestinal disorders

Uncommon: Nausea, vomiting

Hepatobiliary disorders

Rare elevated transaminases

Skin and subcutaneous tissue disorders

Uncommon:

Rash Rare:

Pruritus,

urticaria

Musculoskeletal, connective tissue and bone disorders

Rare: Arthralgia, muscle twitching **Renal and urinary disorders** Common

nephrotoxicity, oliguria

Not known: increased serum creatinine, albuminuria, azotaemia, haematuria, acute renal failure

General disorders and administration site conditions

Rare: Pyrexia.

Reporting of suspected adverse reactions:

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

4.9 Overdose

Symptoms:

In case of overdosage there is a general risk of nephro, oto and neurotoxic (neuromuscular blockade and respiratory paralysis) reactions.

Treatment:

Symptomatic and supportive therapy is recommended. Neuromuscular blockade with respiratory arrest needs appropriate treatment. Artificial respiration may be required in the event of respiratory paralysis.
Fluid balance, electrolytes and creatinine clearance should be monitored. Haemodialysis or peritoneal dialysis is effective in the removal of amikacin from the blood. In the newborn infant, exchange transfusion may also be considered.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group & ATC-Code: Aminoglycoside antibacterials.
ATC Code: J01GB06.

Mechanism of action:

Amikacin is a semi-synthetic aminoglycoside antibiotic derived from kanamycin A. It is a bactericidal agent, most likely acting through inhibition of protein synthesis by binding to the 30S ribosomal subunits.

Mechanisms of resistance:

Various mechanisms may underlie resistance against aminoglycosides. The most common mechanism is inactivation of aminoglycosides by aminoglycoside-modifying enzymes (acetyltransferases, phosphotransferases or nucleotidyl transferases). Resistance can also be caused by modification of the ribosome target through mutations or by ribosomal methyl transferase enzymes. In addition, decreased permeability of the bacterial cell wall and active expulsion of aminoglycosides out of the cell by efflux pumps contribute to resistance.
There is partial cross-resistance of amikacin with other aminoglycoside antibiotics.

5.2 Pharmacokinetic properties

Absorption:

Rapid absorption after intramuscular injection.
Peak serum levels of approximately 11 mg/L and 23 mg/L are reached one hour after intramuscular doses of 250 mg and 500 mg respectively.

Peak serum concentration of 38 mg/L are reached at the end of a 30-min intravenous infusion of 500 mg.
Oral Bioavailability:
~100% Food effect: Not applicable Tmax: 1–2 hours

Distribution:
Volume of distribution (mean):
24 L Plasma protein binding in vitro: <20% Tissue distribution:
Amikacin has been found in cerebrospinal fluid, pleural fluid, amniotic fluid and in the peritoneal cavity following parenteral administration. It accumulates in the renal cortex and inner ear fluid and is only slowly eliminated from these deep compartments.
Amikacin passes the placental barrier and is excreted in human milk. Concentrations reaching 20% of those in the mother have been found in fetal blood and in the amniotic fluid.

Metabolism:
Amikacin is not metabolised.

Elimination:
Plasma half-life 2 to 3 hours. Elimination is via the kidneys, mainly by glomerular filtration, as unchanged drug.
Mean serum clearance: 100 mL/min
Mean renal clearance: 94 mL/min (in subjects with normal renal function)
% of dose excreted in urine: 94–98%

Special populations:
Renal impairment:
Amikacin is excreted primarily by glomerular filtration. Elimination is decreased in patients with impaired renal function, resulting in an increased elimination-half-life. This may lead to accumulation of amikacin.

Hepatic impairment:
Drug concentrations are not affected by hepatic disease.

Paediatric patients:
Data from dosing studies on a daily basis show that levels in CSF in normal children are around 10 to 20% of serum concentrations and may reach 50% in meningitis.
In neonates and particularly in premature babies, the renal elimination of amikacin is reduced. In a single study in newborns (1-6 days of post-natal age) grouped according to birth weights (<2000, 2000-3000 and

>3000 g). Amikacin was administered intramuscularly and/or intravenously at a dose of 7.5 mg/kg.
Clearance in neonates >3000 g was 0.84 mL/min/kg and terminal half-life was about 7 hours. In this group, the initial volume of distribution and volume of distribution at steady state was 0.3mL/kg and 0.5 mg/kg, respectively. In the groups with lower birth weight clearance/kg was lower and half-life longer. Repeated dosing every 12 hours in all the above groups did not demonstrate accumulation after 5 days.

5.3 Preclinical safety data

Neuromuscular blockade and muscular paralysis have been demonstrated in laboratory animals given high doses of amikacin.
In repeat-dose toxicity studies, the main effects were nephrotoxicity and ototoxicity.
Amikacin has been tested for mutagenicity. The tests indicate that amikacin is not an in vivo mutagen. No carcinogenicity studies have been performed.
In studies on reproduction toxicity, amikacin caused dose-related nephrotoxicity in pregnant rats and their fetuses. Reproductive toxicity studies in offspring of mice, rats and rabbits revealed increased fetal death rates. Intravitreal dosages of 200 mg/kg/day in pregnant rats and pregnant guinea pigs led to hearing impairment in the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sr. No.	Excipients
1.	Methylparaben
2.	Propylparaben
3.	Trisodium Citrate (Sodium Citrate)
4.	Sodium Metabisulfite
5.	Water for Injection

6.2 Incompatibilities

None Known.

6.3 ShelfLife

36 Months

6.4 Special Precautions for Storage

Store below 30°C in a dry place, protect from light.

6.5 Nature and Contents of Container

2 ml clear glass vial is packed in a carton along with leaflet.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Syner-Med Pharmaceuticals (Kenya)
Limited Address: Gayatri House ICD Road,
Off Mombasa Road, Nairobi KENYA

MANUFACTURING SITE ADDRESS

Scott-Edil Pharmacia Ltd.
56, EPIP, Phase-I, Jharmajri, Baddi-173205, (HP), INDIA

8. MARKETING AUTHORISATION NUMBER

20483

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/07/2006

10. DATE OF REVISION OF THE TEXT

24/07/2026