1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS FOR SEFKIN 500mg/2ml INJECTION

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1. NAME OF THE MEDICINAL PRODUCT

Sefkin Injection 500mg/2ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml vial of Sefkin contains: 500mg of Amikacin (as sulphate)

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colorless solution filled in 2ml vial with dark blue flip off seal.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amikacin is indicated for treating severe infections due to susceptible strains of Gram-negative bacteria, including the following:

- Severe infections with bacteraemia (including neonatal sepsis);
- Severe hospital acquired pneumonia;
- Severe skin and soft tissue infections including burns and post-operative infections (including vascular surgery);
- Complicated urinary tract infections;
- Intra-abdominal infections, including peritonitis;
- Bacterial endocarditis caused by *Enterococcus* spp., *Staphylococcus* spp. or *Streptococcus* spp. with reduced susceptibility to penicillin, in combination with a beta-lactam or a glycopeptide antibiotic.

In order to provide adequate antimicrobial coverage for empiric treatment of infections, particularly for severe infections with risk for bacteraemia, including pneumonia, intra-abdominal-infections, neonatal sepsis, infections caused by *Listeria monocytogenes* and sepsis in immunosupressed subjects, the use of amikacin in combination with other antibiotic agents should always be considered.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

In adults, 0.25% solutions have been used for instillation in organ cavities. In patients with impaired renal function, doses should be reduced or the intervals between them prolonged.
For all patients, doses should be adjusted according to serum concentrations of amikacin. For most infections the intramuscular route is preferred, but in life-threatening infections, or in patients in whom intramuscular injection is not feasible, the intravenous route, either slow bolus (2 to 3 minutes) or infusion (0.25% over 30 minutes) may be used.

For all patients, doses should be adjusted according to serum concentrations of amikacin. Before administering treatment, weight of the patient must be known to calculate correct dosage.

Intramuscular and intravenous administration

At the recommended dosage level, uncomplicated infections due to sensitive organisms should respond to therapy within 24 to 48 hours.

If clinical response does not occur within three to five days, consideration should be given to alternative therapy.

Patients with normal kidney function:

Adults and Children over 12 years

The recommended intramuscular or intravenous dosage for adults and adolescents with normal renal function (creatinine clearance 50 ml/min) is 15 mg/kg/day which may be administered as a single daily dose or divided into 2 equal doses i.e. 7.5 mg/kg q 12 h. The total daily dose should not exceed 1.5 g. In endocarditis and in febrile neutropenic patients dosing should be twice daily, as there is not enough data to support once daily dosing.

Children 4 weeks to 12 years

The recommended intramuscular or intravenous (slow intravenous infusion) dose in children with normal renal function is 15-20 mg/kg/day which may be administered as 15-20 mg/kg, once a day; or as 7.5 mg/kg q 12 h. In endocarditis and in febrile neutropenic patients dosing should be twice daily, as there is not enough data to support once daily dosing.

Neonates

An initial loading dose of 10 mg/kg followed by 7.5 mg/kg q 12 h (see sections 4.4 and 5.2).

Premature Infants

The recommended dose in premature is 7.5 mg/kg in every 12 hours (see sections 4.4 and 5.2).

Specific recommendation for intravenous administration

In paediatric patients the amount of diluents used will depend on the amount of amikacin tolerated by the patient. The solution should normally be infused over a 30 to 60 minute period. Infants should receive a 1 to 2 hour infusion.

Elderly

Amikacin is excreted by the renal route, renal function should be assessed whenever possible and dosage adjusted as described under impaired renal function.

Life-threatening infections and/or those caused by *Pseudomonas*.

The adult dose may be increased to 500 mg every eight hours but should never exceed 1.5 g/day nor be administered for a period longer than 10 days. A maximum total adult dose of 15 g should not be exceeded.

Urinary tract infections: (other than pseudomonas infections)

7.5 mg/kg/day in two equally divided doses (equivalent to 250 mg b.i.d. in adults). As the activity of amikacin is enhanced by increasing the pH, a urinary alkalinising agent may be administered concurrently.

Impaired renal function

In patients with impaired renal function, the daily dose should be reduced and/or the intervals between doses increased to avoid accumulation of the drug. A suggested method for estimating dosage in patients with known or suspected diminished renal function is to multiply the serum creatinine concentration (in mg/100 ml) by 9 and use the resulting figure as the interval in hours between doses.

Serum Creatinine Concentration (mg/100 ml)		Interval between Amikacin doses of 7.5 mg/kg IM (hours)
1.5		13.5
2.0		18.0
2.5		22.5
3.0		27.0
3.1	X9=	31.5
4.0		36.0
4.5		40.5
5.0		45.0
5.5		49.5
6.0		54.0

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

Intraperitoneal use

Following exploration for established peritonitis, or after peritoneal contamination due to faecal spill during surgery, amikacin may be used as an irrigant after recovery from anaesthesia in concentrations of 0.25% (2.5 mg/ml). The intraperitoneal use of amikacin is not recommended in young children.

Other routes of administration

Amikacin in concentrations 0.25% (2.5 mg/ml) may be used satisfactorily as an irrigating solution in abscess cavities, the pleural space, the peritoneum and the cerebral ventricles.

4.3 Contraindications

Hypersensitivity to amikacin, to any of the excipients listed in section 6.1 or to any other antibiotic in the aminoglycoside group, due to cross-sensitivities to drugs in this class; Myasthenia gravis; Hypersensitivity to sulphites (present in the excipient).

4.4 Special warnings and precautions for use

Particular attention must be paid in patients with a history of vestibular and cochlear disorders.
Amikacin, just as other aminoglycosides, is potentially nephrotoxic, ototoxic and neurotoxic.
The safety of use in treatment periods greater than 14 days has not been established.
The concurrent or serial use of other ototoxic, nephrotoxic or neurotoxic drugs, either systemically, orally or topically should be avoided because of the potential for additive effects.
Other factors that may increase the risk of toxicity are advanced age and the state of dehydration of the patient.

The risk of ototoxicity due to aminoglycosides increases with the level of exposure to maximum or persistently high serum concentrations. The risk of nephrotoxicity is higher in patients with impaired renal function and in those receiving high or prolonged doses (use amikacin only when absolutely necessary and adapt the dosage based on creatinine clearance). Renal and 8th cranial nerve function should be monitored, especially at the onset of treatment in patients with known or suspected impaired renal function, or in patients who have normal renal function at the start of treatment but who develop signs of renal dysfunction during treatment. Serum concentrations of amikacin should be monitored in order to assure adequate levels and to avoid potentially toxic levels.

In cases of surgery, the recovery anaesthetist should be informed that the drug is being taken. During treatment with amikacin, it is recommended that: urinalysis be done to test the specific density, whether the excretion of proteins has increased and whether cells or casts are present. Periodic assays should be done for uraemia, serum creatinine or creatinine clearance. Serial audiograms should be done, especially in high-risk patients. If symptoms of ototoxicity (dizziness, vertigo, tinnitus, a roaring sensation in the ears or hearing loss) or nephrotoxicity appear, treatment should be discontinued or the dosage should be adjusted. Patients should be well hydrated during treatment, and renal function should be assessed prior to starting treatment and on a daily basis during the course of treatment.

Precautions in patients

Aminoglycosides should be used with caution in patients with muscular disorders, such as parkinsonism (aminoglycosides may aggravate muscle weakness because of their potential effect on neuromuscular synapses).
When patients are properly hydrated and their renal function is normal, the risk of nephrotoxic reactions is reduced if the dosage recommendations are followed.

Pregnancy

Aminoglycosides can cause harm to the foetus when administered to pregnant women. Aminoglycosides cross the placenta and there have been several reports of total, irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy.

Although serious side effects to the foetus or newborns have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists.

Premature and neonatal infants

The administration of aminoglycosides should be avoided in premature and neonatal infants because of the renal immaturity of these patients and the resulting prolongation of the serum half-life of these drugs.

Precautions for use

Amikacin should not be used concurrently with potent diuretics such as ethacrynic acid or furosemide, since the diuretics themselves may cause ototoxicity.

Aminoglycosides are rapidly and almost totally absorbed when they are applied topically, in association with surgical procedures, except to the bladder. Cases of irreversible deafness, renal failure, and death due to neuromuscular blockage have been reported following irrigation of surgical fields with aminoglycosides.

In people susceptible to sulfites, sodium metabisulfite, which in rare cases may trigger severe hypersensitivity reactions and bronchial spasms.
Amikacin (Sefkin) contains less than 1 mmol (23 mg) of sodium per vial.

4.5 Interaction with other medicinal products and other forms of interaction

Avoid concomitant use with diuretics that are highly active on Henle's loop, as well as other drugs that are equally nephrotoxic and ototoxic, such as cephalordin, paromomycin, viomycin, polymyxin B, colistin and vancomycin. Amikacin should not be used concomitantly with other aminoglycosides.
Amikacin may potentiate the action of curare, myorelaxants and general anaesthetics (risk of neuromuscular blockage attaining even respiratory paralysis).

Contraindications of concomitant use

Aminoglycosides: amikacin should not be used concomitantly with other aminoglycosides due to high risk of nephrotoxicity and neurotoxicity.

Concomitant use not recommended

Polypeptide antibiotics (Colistin, polymyxin): addition of nephrotoxic and neurotoxic effects.
Botulinum toxin: it can increase botulinum toxin effects

Precautions of concomitant use

General anaesthetics (ether, chloroform): there are studies with other aminoglycosides that it has been recorded increasing of muscle relaxants attaining even respiratory paralysis, due to

there is additive effect by competition aminoglycoside with acetylcholine at the neuromuscular junction.

Neuromuscular-blocking drug (pancuronium, tubocurarine): amikacin may potentiate their action (risk of neuromuscular-blockade effect attaining even respiratory paralysis due to there is additive effect by competition aminoglycoside with acetylcholine at the neuromuscular junction. It must be review curarization grade at the end of anesthesia.

Cephalosporin (Cephalotin): amikacin may potentiate toxicity with risk of nephrotoxicity. Mechanism of action is unknown.

Diuretics *that are highly active on Henle's loop (ethacrynic acid, furosemide, bumetanide):* the administration with aminoglycosides may potentiate ototoxicity with deafness events, especially in patients with impaired renal.

Amphotericin B: it increases the risk of nephrotoxicity.

Carboxypenicillin (Piperacillin): it has been shown inhibition to both antibiotics in patients with impairment renal.

Organoplatinum (carboplatin at increased doses, cisplatin, oxaliplatin): Addition of nephrotoxic and ototoxic effects, especially in patients with impairment renal.

Indomethacin: it may increase the plasma concentration of amikacin in by reducing the elimination of antibiotic with toxicity risk.

Immunossuppresive drugs (Cyclosporin, tacrolimus): it increases creatinine in blood and nephrotoxic effects.

Clindamicyn: addition of nephrotoxic effects showed severely impaired renal function.

Clodronic acid: there is a study that it has been recorded increase toxicity (hypocalcemia and hypomagnesaemia).

Penicillin-based antibiotics: synergistic effect.

Other antibiotics *(cephalordin, paromomycin, vancomycin, viomicin):* addition nephrotoxic and ototoxic effects.

Concurrent use with other potentially nephrotoxic or ototoxic drug substances should be avoided. Where this is not possible, monitor carefully.

Additionally, the intraperitoneal use of amikacin is not recommended in patients under the influence of anaesthetics or muscle-relaxing drugs (including ether, halothane, d-tubocurarine, succinylcholine and decamethonium) as neuromuscular blockade and consequent respiratory depression may occur.

Interaction with laboratory tests:

Amikacin could increase the following laboratory values: BUN, transaminases, alkaline phosphatase, bilirrubin, creatinine, lactate dehydrogenase, due to intrinsic toxicity.
Amikacin could reduce the following laboratory values: sodium, potassium, magnesium and calcium, due to intrinsic toxicity.

4.6 Fertility, pregnancy and lactation

Do not use during pregnancy due to potential toxicity for the cochlear-vestibular mechanism of the foetus. Because of the potential for ototoxicity and nephrotoxicity, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from amikacin therapy.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect: on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Aminoglycosides have potential effect to produce auditory otoxicity, vestibular and renal toxicity, and neuromuscular blockade (see section 4.4.). It is very common in impaired renal patients, patients with ototoxic and nephrotoxic treatments and patients treated long-time and/or with doses higher than recommended.

These reactions depend on doses, interval between doses and period of the treatment. The symptoms could appear during or at the end of the treatment.
The adverse reactions are listed by MedDRA System Organ Class bellow.

The following terminologies have been used in order to classify the occurrence of undesirable effects.
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 (cannot be estimated from the available data)

Blood and lymphatic system disorders	
Rare	Eosinophilia, anaemia, granulocytopenia, thrombocytopenia, leucopenia.

Immune System Disorders	
Rare	Hypersensitivity reactions
Very rare	Anaphylactic shock (isolated cases)
Nervous system disorders	
Very common	Neurotoxicity-neuromuscular blockade: muscular paralysis and apnoea, stiffness, tingling, muscular spasms and convulsions.
Uncommon	Headache, shaking
Ear and labyrinth disorders	
Very common	Neurotoxicity-ototoxicity (VIIIth cranial nerve disorders): deafness, tinnitus, vertigo, cochlear nerve damage (including deafness to high frequencies) and this often occurs before it can be detected by audiometric tests.
Infections and Infestation	
Rare	Superinfection or colonization (resistant microorganisms or fungus of type yeasts)
Cardiac disorders	
Rare	Hypotension, hypomagnesaemia
Gastrointestinal disorders	
Uncommon	Dizziness, vomiting
Skin and subcutaneous tissue disorders	
Uncommon	Rash
Musculoskeletal and connective tissue disorders	
Uncommon	Paresthesia, arthralgia
Renal and urinary disorders	
Very common	Nephrotoxicity: increased serum creatinine, albuminuria, present in urine of casts, leucocytes and erithrocytes, azotemia and oliguria
General disorders and administration site conditions	
Very common	Drug fever
Eye disorders	
Uncommon	Nystagmus, Macular ischaemia with visual loss by intravitreal administration of Amikacin

4.9 Overdose

Recourse to hemodialysis or peritoneal dialysis for the removal of amikacin from the blood in the event of overdosage or toxic reaction.

In neonates, exchange transfusion may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials; Aminoglycosides;
ATC Code: J01GB06

Mode of action:

Amikacin is a semi-synthetic aminoglycoside antibiotic derived from Kanamycin A. Aminoglycoside antibiotics are bactericidal in action. Although the exact mechanism of action has not been fully elucidated, the drugs appear to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S ribosomal subunits, causing misreading of t-RNA, leaving the bacterium unable to synthesize proteins vital to its growth.

PK/PD relationship

Efficacy mainly depends on the relation between the maximum concentration in serum (Cmax) and the minimum inhibitory concentration (MIC) of amikacin for a bacterial pathogen.

A ratio Cmax/MIC of 8:1 or 10:1 is considered efficient in bacterial killing and in recidive prevention of bacterial growth. Amikacin demonstrates a post-antibiotic in vitro and in vivo effect. The post-antibiotic effect allows that the dosage interval may be extended without loss of efficacy against the majority of Gram-negative bacteria.

Mechanism of resistance:

Three mechanisms of bacterial resistance have been identified:

- Alteration of the cellular transport system which effectively blocks the drug transport into the cell, resulting in decreased intracellular accumulation of the amynoglycoside.
- Alteration in the ribosomal target site of aminoglycoside attachment results in the inability of the drug to bind to the ribosome.
- Elaboration of enzymes which activate aminoglycoside.

Breakpoints

MIC breakpoints for amikacin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility breakpoints (µg/ml)	
	Susceptible	Resistant
Enterobacteriaceae1	≤ 8	16 >
Pseudomonas spp.1	≤ 8	16 >
Acinetobacter spp.1	≤ 8	16 >
Staphylococcus aureus2	≤ 8	16 >
Coagulase-negative staphylococci2	≤ 8	16 >

Non-species related breakpoints3	≤ 8	16 >

[1]Aminoglycoside breakpoints are based on once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents.
[2]Resistance to amikacin is most reliably determined by testing with kanamycin (zone diameter breakpoints under development).
[3]EUCAST breakpoints apply to intravenous amikacin dosage of 15 mg/kg/day. In the absence of Pk/Pd data these have been determined mainly on the basis of Pk data and pre-existing breakpoints.

Table of susceptibility

Susceptible microbial agents
Aerobic Gram-positive microorganisms
Staphylococcus aureus (MSSA)
Coagulase-negative staphylococci (MSCNS)
Aerobic Gram-negative microorganisms
Aeromonas spp.
Campylobacter spp.
Acitenobacter anitratus
Acitenobacter baumannii
Acitenobacter calcoaceticus
Acitenobacter Iwoffii
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Francisella tularensis
Haemophilus influenzae
Klebsiella oxytoca
Morganella morganii
Klebsiella pneumoniae
Proteus mirabilis
Proteus spp
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella enterica

Serratia liquefaciens
Serratia marcescens
Shigella spp.
Yersinia enterocolitica
Yersinia pseudotuberculosis
Atypical bacteria
Mycobacterium spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus (MRSA)
Coagulase-negative staphylococci (MSCNS)
Aerobic Gram-negative microorganisms
Acitenobacter spp.
Enterobacter aerogenes
Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa
Serratia marcescens
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus spp.1
Streptococcus Groups A, B, C and G
Streptococcus pneumoniae
Aerobic Gram-negative microorganisms
Burkholderia cepacia
Stenotrophomonas maltophilaii
Anaerobic microorganisms
Bacteroides spp.
Clostridium perfringens
Clostridium difficile
Prevotella spp.
Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum
1Amynoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and beta-lactam agents against enterococci without acquired aminoglycosides resistance mechanisms.

MSSA: Methicillin Susceptible Staphylococcus Aureus MRSA: Methicillin Resistant Staphylococcus Aureus MSCNS: Methicillin Susceptible Coagulase Negative Staphylococci

5.2 Pharmacokinetic properties

Absorption

Following intramuscular injection of one 500 mg vial of amikacin sulphate, serum peaks are found corresponding to 20 µg of amikacin per ml after one hour, decreasing to 2 µg/ml ten hours after the injection.

After a 500 mg intravenous infusion for 30 minutes, serum concentrations of 38 µg/ml have been found, decreasing to 18 µg/ml an hour later. Repeated infusions do not produce drug accumulation in adults with normal renal function. However, decreased renal function will lead to accumulation.

Distribution

Twenty per cent or less is bound to serum protein and serum concentrations remain in the bactericidal range for sensitive organisms for 10 to 12 hours.

Amikacin has been found in the various tissues and fluids of the body following injection: it crosses the placenta but does not rapidly enter spinal fluid.

In patients with normal renal function, a serum half-life of around two hours has been reported.

Metabolism:

Amikacin is not metabolized.

Excretion

Most of the dose is excreted in the urine, by glomerular filtration. More than 90% of the dose injected is found in the urine within 24 hours. In adults with normal renal function the plasma elimination half-life of amikacin is usually 2-3 hours. 94 - 98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours. Urine concentrations of amikacin average 563 µg/ml in the first 6 hours following a single 250 mg IM dose and 163 µg/ml over 6-12 hours. Following a single 500 mg IM dose urine concentrations average 832 µg/ml in adults with normal renal function. Along with elimination in the urine, there is slight elimination via the biliar route.

Newborns

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 birthweights (< 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 about 7 hours. In this group, the initial volume of distribution and volume of distribution at

steady state was 0.3 ml/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

Studies in guinea pigs to assess the ototoxicity of the 4 antibiotics in the aminoglycosides group most often used clinically (amikacin, tobramycin, gentamicin and sisomycin) have led to the conclusion that amikacin and tobramycin, besides presenting a lower serum concentration and a lower concentration of cochlear lymph following the administration of equivalent chromic doses of all 4 drugs, showed lower ototoxicity than did gentamicin and sisomycin.

We can thus conclude that, in addition to having greater antimicrobial action than the other antibiotics in the group, as shown in a number of studies, and especially in Klebsiella, Proteus, Pseudomonas and Enterobacter infections resistant to gentamicin and tobramycin, amikacin shows a lower resistance rate and lower ototoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Soidum Citrate
- Sodium Metabisulphite
- Sulphuric Acid
- WFI

6.2 Incompatibilities

Do not mix Amikacin NORMON in the same syringe with other drugs, especially: penicillin's, cephalosporin's, amphotericin, heparin, nitrophurantoin, phenytoin, thiopental, warfarin, tetracyclines, D-group vitamins, Vitamin C, potassium chloride.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C

Protect from heat and light.

6.5 Nature and contents of container

Type 1 colorless glass vial containing 2ml of amikacin solution at doses of 500mg.

Pack sizes:

1 vial in a Unit carton.

6.6 Special precautions for disposal and other handling

No special requirements.

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

6.7 Dispensing Requirements:

Sefkin 500mg/2ml injection is dispensed only on the prescription of registered medical practitioner only.

7. MARKETING AUTHORISATION HOLDER

Saffron Pharmaceuticals (Pvt.) Ltd.
19 Km. Sheikhupura Road, Faisalabad-Pakistan.