SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

Grasil® (Amikacin Sulphate) 25mg Injection
Grasil® (Amikacin Sulphate) 50mg Injection
Grasil® (Amikacin Sulphate) 100mg Injection
Grasil® (Amikacin Sulphate) 250mg Injection
Grasil® (Amikacin Sulphate) 500mg Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Grasil® 25mg Injection	**Grasil®** 50mg Injection	**Grasil®** 100mg Injection	**Grasil®** 250mg Injection	**Grasil®** 500mg Injection
Each ml contains:	Each ml contains:	Each 2ml contains:	Each 2ml contains:	Each 2ml contains:
Amikacin Sulphate USP	Amikacin Sulphate USP	Amikacin Sulphate USP	Amikacin Sulphate USP	Amikacin Sulphate USP
eq. to Amikacin.....25mg	eq. to Amikacin.....50mg	eq. to Amikacin.....100mg	eq. to Amikacin.....250mg	eq. to Amikacin.....500mg

3. PHARMACEUTICAL FORM

Solution for Injection.

Appearance:

Grasil® 25mg/ml Injection: Clear colorless to straw coloured solution free from any visible particles.
Grasil® 50mg/ml Injection: Clear colorless to straw coloured solution free from any visible particles.
Grasil® 100mg/2ml Injection: Clear colorless to straw coloured solution free from any visible particles.
Grasil® 250mg/2ml Injection: Clear colorless to straw coloured solution free from any visible particles.
Grasil® 500mg/2ml Injection: Clear colorless to straw coloured solution free from any visible particles.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

- Amikacin is a semi-synthetic, aminoglycoside antibiotic which is active against a broad spectrum of Gram-negative organisms, including pseudomonas and some Gram-positive organisms.
- Sensitive Gram-negative organisms include; *Pseudomonas aeruginosa, Escherichia coli.*, indole-positive and indole-negative *Proteus* spp., *Klebsiella, Enterobacter* and *Serratia* spp., *Minea-Herralae, Citrobacter freundii, Salmonella, Shigella, Acinetobacter* and *Providencia* spp.
- Many strains of these Gram-negative organisms resistant to gentamicin and tobramycin show sensitivity to amikacin in vitro.
- The principal Gram-positive organism sensitive to amikacin is *Staphylococcus aureus,* including some methicillin-resistant strains. Amikacin has some activity against other Gram-positive organisms including certain strains of *Streptococcus pyogenes, Enterococci* and *Diplococcus pneumoniae.*
- Amikacin is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including *Pseudomonas* species. Although amikacin is not the drug of choice for infections due to staphylococci, at times it may be indicated for the treatment of known or suspected staphylococcal disease. These situations include:
  - the initiation of therapy for severe infections when the organisms suspected are either Gram-negative or staphylococci,
  - patients allergic to other antibiotics, and mixed staphylococcal/Gram-negative infections.

Therapy with amikacin may be instituted prior to obtaining the results of sensitivity testing. Surgical procedures should be performed where indicated.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Amikacin sulphate injection may be given intramuscularly or intravenously. Amikacin should not be physically premixed with other drugs, but should be administered separately according to the recommended dose and route. The patient's pre-treatment bodyweight should be obtained for calculation of correct dosage. The status of renal function should be estimated by measurement of the serum creatinine concentration or calculation of the endogenous creatinine clearance rate. The blood urea nitrogen (BUN) is much less reliable for this purpose. Reassessment of renal function should be made periodically during therapy. Whenever possible, amikacin concentrations in serum should be measured to assure adequate, but not excessive levels. It is desirable to measure both peak and trough serum concentrations intermittently during therapy. Peak concentrations (30-90 minutes after injection) above 35mcg/ml and trough concentrations (just prior to the next dose) above 10mcg/ml should be avoided. Dosage should be adjusted as indicated. In patients with normal renal function, once-daily dosing may be used; peak concentrations in these cases may exceed 35mcg/ml. 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.

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. If required, suitable diluents for intravenous use are: Normal saline, 5% dextrose in water. Once the product has been diluted the solution must be used as soon as possible and NOT STORED.

Adults and Children over 12 years: The recommended intramuscular or intravenous dosage for adults and adolescents with normal renal function (creatinine clearance ≥ 50ml/min) is 15mg/kg/day which may be administered as a single daily dose or divided into 2 equal doses i.e. 7.5mg/kg q 12h. The total daily dose should not exceed 1.5g. 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 15-20mg/kg/day which may be administered as 15-20mg/kg, once a day; or as 7.5mg/kg q 12h. 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 10mg/kg followed by 7.5mg/kg q 12h.

Premature Infants: The recommended dose in premature is 7.5mg/kg in every 12 hours .The usual duration of treatment is 7 to 10 days. The total daily dose by all routes of administration should not exceed 15-20mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin sulphate injection should be re-evaluated and, if continued, renal, auditory, vestibular function should be monitored, as well as serum amikacin levels. If definite clinical response does not occur within 3 to 5 days, therapy should be stopped and the antibiotic susceptibility pattern of the invading organism should be rechecked. Failure of the infection to respond may be due to resistance of the organism or to the presence of septic foci requiring surgical drainage.

Intravenous administration: The solution is administered to adults over a 30 to 60 minute period.

Specific recommendation for intravenous administration: In pediatric 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 500mg every eight hours but should never exceed 1.5g/day nor be administered for a period longer than 10 days. A maximum total adult dose of 15g should not be exceeded.

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

Impaired Renal Function: In patients with renal impairment reflected by creatinine clearance less than 50mL/min, administration of the recommended total daily dose of amikacin in single daily doses is not desirable since these patients will have protracted exposure to high trough concentrations. For patients with impaired renal function receiving usual twice or three times daily dosing, whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures. Doses should be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at fixed intervals. Both methods are based on the patient's creatinine clearance or serum creatinine values since these have been found to correlate with aminoglycoside half-lives in patients with diminished renal function. These dosage schedules must be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary, including modification when dialysis is being performed.

Normal Dose at Prolonged Intervals Between Dosing: If the creatinine clearance rate is not available and the patient's condition is stable, a dosage interval in hours for the normal single dose (ie, that which would be given to patients with normal renal function on a twice daily schedule, 7.5mg/kg) can be calculated by multiplying the patient's serum creatinine by nine; e.g., if the serum creatinine concentration is 2mg/100mL, the recommended single dose (7.5mg/kg) should be administered every 18 hours.

Serum Creatinine Concentration (mg/100ml)		Interval between Amikacin doses of 7.5mg/kg IM (hours)
1.5	x9=	13.5
2.0		18.0
2.5		22.5
3.0		27.0
3.5		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.

Reduced Dose at Fixed Time Intervals Between Dosing: When renal function is impaired and it is desirable to administer amikacin sulfate injection at a fixed time interval, dose must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration and to avoid excessive serum concentrations. If serum assay determinations are not available, and patient's condition is stable, serum creatinine and creatinine clearance values are the most readily available indicators of the degree of renal impairment to use as a guide for dosage. First initiate therapy by administering a normal dose, 7.5 mg/kg, as a loading dose. This dose is the same as the normally recommended dose which would be calculated for a patient with a normal renal function as described on left side.

To determine the size of maintenance doses administered every 12 hours, the loading dose should be reduced in proportion to the reduction in the patient's creatinine clearance rate:

Maintenance dose every 12 hours = $\frac{\text{observed CrCl in mL min x calculated loading dose in mg}}{\text{normal CrCl in mL min}}$

(CrCl = creatinine clearance rate)

An alternate rough guide for determining reduced dosage at 12-hour intervals (for patients whose steady state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine. The above dosage schedules are not intended to be rigid recommendations, but are provided as guides to dosage when the measurement of amikacin serum levels is not feasible.

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

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

4.3. CONTRAINDICATIONS:

- Amikacin sulphate injection is contraindicated in patients with known allergy to amikacin.
- A history of hypersensitivity or serious toxic reactions to aminoglycosides may contraindicate the use of any aminoglycoside because of the known cross sensitivities of patients to drugs in this class.
- Aminoglycosides may impair neuromuscular transmission, and should not be given to patients with myasthenia gravis.
- Hypersensitivity to the active substance or to any of the excipients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Patients should be well hydrated during amikacin therapy. Caution should be applied to patients with pre-existing renal insufficiency, pre-existing hearing or vestibular damage and diminished glomerular filtration. Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established. If therapy is expected to last seven days or more in patients with renal impairment, or 10 days in other patients, a pre-treatment audiogram should be obtained and repeated during therapy.

Renal Toxicity: Aminoglycosides are potentially nephrotoxic. Renal toxicity is independent of plasma obtained at the peak (C_{max}). The risk of nephrotoxicity is greater in patients with impaired renal function, and in those who receive higher doses, or in those whose therapy is prolonged. Patients should be well hydrated during treatment and renal function should be assessed. A reduction of dosage is required if evidence of renal dysfunction occurs, such as presence of urinary casts, white or red cells, albuminuria, decreased creatinine clearance, decreased urine specific gravity, increased BUN, serum creatinine, or oliguria. If azotemia increases, or if a progressive decrease in urinary output occurs, treatment should be stopped. Elderly patients may have reduced renal function which may not be evident in routine screening tests such as BUN or serum creatinine. A creatinine clearance determination may be more useful. Monitoring of renal function in elderly patients during treatment with aminoglycosides is particularly important. Renal and eighth-cranial nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy, and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Blood urea nitrogen, serum creatinine, or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment. Concurrent and/or sequential, oral, or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides, should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration.

Neurotoxicity: Neurotoxicity, manifested as vestibular and/or bilateral ototoxicity, can occur in patients treated with aminoglycosides. The risk of aminoglycoside-induced ototoxicity is greater in patients with impaired renal function, and in those who receive high doses, or in those whose therapy is prolonged over 5-7 days of treatment, even in healthy patients. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions.

Ototoxicity: The risk of ototoxicity due to aminoglycosides increases with the degree of exposure to either persistently high peak or high trough serum concentrations. Patients developing cochlear or vestibular damage may not have symptoms during therapy to warn them of developing eighth nerve toxicity, and total or partial irreversible bilateral deafness or disabling vertigo may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible. Patients with mitochondrial DNA mutations, particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene may be at higher risk for ototoxicity, even if the patient's aminoglycoside serum levels were within the recommended range.

Neuromuscular Toxicity: The possibility of respiratory paralysis should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, atracurium, rocuronium, vecuronium or in patients receiving massive transfusions of citrate-anticoagulated blood. If neuromuscular blockade occurs, calcium salts may reverse respiratory paralysis, but mechanical respiratory assistance may be necessary. Amikacin must not be used in patients with myasthenia gravis. Aminoglycosides should be used with caution in patients with muscular disorders such as Parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

Allergic reactions: The use of amikacin in patients with a history of allergy to aminoglycosides or in patients who may have subclinical renal or eighth nerve damage induced by prior administration of nephrotoxic and/or ototoxic agents such as streptomycin, dihydrostreptomycin, gentamicin, tobramycin, kanamycin, neomycin, polymyxin B, colistin, cephaloridine or viomycin should be considered with caution, as toxicity may be additive. In these patients amikacin should be used only if, in the opinion of the physician, therapeutic advantages outweigh the potential risks. Large doses of amikacin administered during surgery have been responsible for a transient myasthenic syndrome. Amikacin sulfate injection in vials contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is uncommon and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic subjects.

Paediatric use: 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.

Other: Aminoglycosides are quickly and almost totally absorbed when they are applied topically, except to the urinary bladder, in association with surgical procedures. Irreversible deafness, renal failure and death due to neuromuscular blockade have been reported following irrigation of both small and large surgical fields with an aminoglycoside preparation. As with other antibiotics, the use of amikacin may result in overgrowth of non-susceptible organisms. If this occurs, appropriate therapy should be instituted. Macular infarction sometimes leading to permanent loss of vision has been reported following intra-vitreous administration (injection into the eye) of amikacin.

Sodium: Amikacin 25mg/ml, 50mg/ml, 100mg/2ml, 250mg/2ml and 500mg/2ml contains 0.37mg/ml, 0.74mg/ml, 2.97mg/2ml, 7.47mg/2ml and 14.96mg/2ml of sodium, equivalent to 0.037%, 0.074%, 0.1485%, 0.3735% and 0.748% respectively, of the WHO recommended maximum daily intake of 2g sodium for an adult.

Sodium metasulfite: May rarely cause severe hypersensitivity reaction and bronchospasm.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

- The concurrent or serial use of other neurotoxic, ototoxic or nephrotoxic agents, particularly bacitracin, cisplatin, amphotericin B, cyclosporin, tacrolimus, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided either systemically or topically because of the potential for additive effects. Where this is not possible, monitor carefully.
- Increased nephrotoxicity has been reported following concomitant parenteral administration of aminoglycoside antibiotics and cephalosporins. Concomitant cephalosporin use may spuriously elevate creatinine serum level determinations.
- The concurrent use of amikacin sulfate injection with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.
- There is an increased risk of hypocalcemia when aminoglycosides are administered with bisphosphonates.
- There is an increased risk of nephrotoxicity and possibly of ototoxicity when aminoglycosides are administered with platinum compounds.
- Concomitantly administered thiamine (vitamin B1) may be destroyed by the reactive sodium bisulfite component of the amikacin sulfate formulation.
- The intraperitoneal use of amikacin is not recommended in patients under the influence of anesthetics or muscle-relaxing drugs (including ether, halothane, d-tubocurarine, succinylcholine and decamethonium) as neuromuscular blockade and consequent respiratory depression may occur. Indomethacin may increase the plasma concentration of amikacin in neonates.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: In reproduction toxicity studies in mice and rats no effects on fertility or fetal toxicity were reported.

Pregnancy: 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 use of aminoglycosides in pregnancy. Aminoglycosides cross the placenta and there have been reports of total, irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Adverse effects on the fetus or newborns have been reported in pregnant women treated with other aminoglycosides. If amikacin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus.

Breast-feeding: Amikacin is excreted in human milk. A decision should be made whether to discontinue breast-feeding or to discontinue therapy.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

No studies on the effects on the ability to drive and use machines have been performed. Due to the occurrence of some adverse reactions the ability to drive and use machines may be impaired.

4.8. UNDESIRABLE EFFECTS:

Infections and Infestations: ***Uncommon:*** Superinfections or colonization with resistant bacteria or yeast.
Blood and lymphatic system disorders: ***Rare:*** Anemia, oeosinophilia.
Immune system disorders: ***Not known:*** Anaphylactic response (anaphylactic reaction, anaphylactic shock and anaphylactoid reaction), hypersensitivity.
Metabolism and nutrition disorders: ***Rare:*** Hypomagnesaemia.
Nervous system disorders: ***Not known:*** Paralysis. ***Rare:*** Tremor, paraethesia, headache, balance disorder.
Eye disorders: ***Rare:*** Blindness, retinal infarction.
Ear and labyrinth Disorders: ***Rare:*** Tinnitus, hypoacusis. ***Not known:*** Deafness, deafness neurosensory
Vascular disorders: ***Rare:*** Hypotension.
Respiratory, thoracic and mediastinal disorders: ***Not known:*** Apnoea, bronchospasm.
Gastrointestinal disorders: ***Uncommon:*** Nausea, vomiting.
Skin and subcutaneous tissue disorders: ***Uncommon:*** Rash, ***Rare:*** Pruritus, urticaria.
Musculoskeletal, connective tissue and bone disorders: ***Rare:*** Arthralgia, muscle twitching.

SUMMARY OF PRODUCT CHARACTERISTICS

Renal and urinary disorders: ***Not known:*** Acute renal failure acute, toxic nephropathy, cells in urine. ***Rare:*** Oliguria, blood creatinine increased, albuminuria, azotemia, red blood cells urine, white blood cells urine.
General disorders and administration site condition: ***Rare:*** Pyrexia

- Amikacin is not formulated for intravitreal use. Blindness and retinal infarction have been reported following intravitreous administrations (injection into the eye) of amikacin.
- All aminoglycosides have the potential to induce ototoxicity, renal toxicity, and neuromuscular blockade. These toxicities occur more frequently in patients with renal impairment, in patients treated with other ototoxic or nephrotoxic drugs, and in patients treated for longer periods and/or with higher doses than recommended. Renal function changes are usually reversible when the drug is discontinued.
- Toxic effects on the eighth cranial nerve can result in hearing loss, loss of balance, or both.
- Amikacin primarily affects auditory function. Cochlear damage includes high frequency deafness and usually occurs before clinical hearing loss can be detected by audiometric testing.
- Macular infarction sometimes leading to permanent loss of vision has been reported following intravitreous administration (injection into the eye) of amikacin.
- When the recommended precautions and dosages are followed the incidence of toxic reactions, such as tinnitus, vertigo, and partial reversible deafness, skin rash, drug fever, headache, paraethesia, nausea and vomiting is low.
- Urinary signs of renal irritation (albumin, casts, and red or white cells), azotemia and oliguria have been reported although they are rare.

4.9. OVERDOSE:
In case of overdosage there is a general risk for nephro-, oto- and neurotoxic (neuromuscular blockage) reactions. Neuromuscular blockage with respiratory arrest needs appropriate treatment including application of ionic calcium (e.g. as gluconate or lactobionate in 10-20% solution). In the event of overdosage or toxic reaction, peritoneal dialysis or haemodialysis will aid in the removal of amikacin from the blood. Amikacin levels are also reduced during continuous arteriovenous haemofiltration. In the newborn infant, exchange transfusion may also be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:
Therapeutic Group: Aminoglycosides.
ATC code: J01G B06
Amikacin is a semi-synthetic aminoglycoside antibiotic derived from Kanamycin A. It is active against a broad spectrum of Gram-negative organisms, including *Pseudomonas, Escherichia coli* and some Gram-positive organisms, e.g. *Staphylococcus aureus.* 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.

5.2. PHARMACOKINETIC PROPERTIES:
Amikacin is rapidly absorbed after intramuscular injection. Peak plasma concentrations equivalent to about 20mg/ml are achieved one hour after IM doses of 500mg, reducing to about 2µg/ml 10 hours after injections. 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. Single doses of 500mg administered as an intravenous infusion over a period of 30 minutes produce a mean peak serum concentration of 38µg/ml. Repeated infusions do not produce drug accumulation in adults with normal renal function. However, decreased renal function will lead to accumulation. 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 563µg/ml in the first 6 hours following a single 250mg IM dose and 163µg/ml over 6-12 hours. Following a single 500mg IM dose urine concentrations average 832µg/ml in adults with normal renal function. Amikacin diffuses readily through extracellular fluids and is excreted in the urine unchanged, primarily by glomerular filtration. It has been found in pleural fluid, amniotic fluid and in the peritoneal cavity following parenteral administration. Available data from multiple daily dose trials show that spinal fluid levels in normal infants are approximately 10 to 20% of the serum concentrations and may reach 50% in meningitis. In neonates and particularly in premature babies, the renal elimination of amikacin is reduced.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Grasil® 25mg/ml Injection: ● Sodium Metabisulphite ● Sodium Citrate ● Citric Acid Anhydrous ● Sulphuric Acid ● Water for Injection
Grasil® 50mg/ml Injection: ● Sodium Metabisulphite ● Sodium Citrate ● Citric Acid Anhydrous ● Sulphuric Acid ● Water for Injection
Grasil® 100mg/2ml Injection: ● Sodium Metabisulphite ● Sodium Citrate ● Citric Acid Anhydrous ● Sulphuric Acid ● Water for Injection
Grasil® 250mg/2ml Injection: ● Sodium Metabisulphite ● Sodium Citrate ● Citric Acid Anhydrous ● Sulphuric Acid ● Water for Injection
Grasil® 500mg/2ml Injection: ● Sodium Metabisulphite ● Sodium Citrate ● Citric Acid Anhydrous ● Sulphuric Acid ● Water for Injection

6.2. INCOMPATIBILITIES:
Amikacin is incompatible with some penicillin's and cephalosporins, amphotericin chlorothiazide sodium, erythromycin gluceptate, heparin, nitrofurantoin sodium, phenytoin sodium, thiopentone sodium and warfarin sodium, and depending on the composition and strength of the vehicle, tetracyclines, vitamins of the B group with vitamin C, and potassium chloride. At times, amikacin may be indicated as concurrent therapy with other antibacterial agents in mixed or superinfections. In such instances, amikacin should not be physically mixed with other antibacterial agents in syringes, infusion bottles or any other equipment. Each agent should be administered separately.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and freezing. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Following dilution in sodium chloride 0.9 % (9mg/ml) solution for injection or glucose 5 % (50mg/ml) solution for injection, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and at 25°C, in non-PVC bags. 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 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.
Keep out of reach of children. Injection should not be used if container is leaking, solution is cloudy or it contains undissolved particles(s).

6.5. NATURE AND CONTENTS OF CONTAINER:
Grasil® 25mg/ml Injection: 1ml colourless clear glass ampoule (USP Type-I), pack size 5 x 1ml ampoules.
Grasil® 50mg/ml Injection: 1ml colourless clear glass ampoule (USP Type-I), pack size 5 x 1ml ampoules.
Grasil® 100mg/2ml Injection: 2ml clear glass vial (USP Type-I) with bromobutyl rubber stopper, sealed with flip off seal, pack size 1 x 2ml vial.
Grasil® 250mg/2ml Injection: 2ml clear glass vial (USP Type-I) with bromobutyl rubber stopper, sealed with flip off seal, pack size 1 x 2ml vial.
Grasil® 500mg/2ml Injection: 2ml clear glass vial (USP Type-I) with bromobutyl rubber stopper, sealed with flip off seal, pack size 1 x 2ml vial.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:
Single use only. The solution may darken from colourless to a pale yellow but this does not indicate a loss of potency. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
BP Specs.

7. MARKETING AUTHORISATION HOLDER

Manufacturing & Release Site:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

Packing Site:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-140/A, S.I.T.E., Karachi-Pakistan
Mfg. Lic. No. 000938

8. MARKETING AUTHORISATION NUMBER(S)

Grasil® 25mg/ml Injection: 047143
Grasil® 50mg/ml Injection: 047144
Grasil® 100mg/2ml Injection: 019704
Grasil® 250mg/2ml Injection: 013530
Grasil® 500mg/2ml Injection: 014251

9. DATE OF FIRST AUTHORISATION

Grasil® 25mg/ml Injection: 21st September, 2007
Grasil® 50mg/ml Injection: 21st September, 2007
Grasil® 100mg/2ml Injection: 6th January, 1997
Grasil® 250mg/2ml Injection: 18th October, 1994
Grasil® 500mg/2ml Injection: 22nd June, 1994

10. DATE OF REVISION OF THE TEXT

گریسل انجکشن
(امیکاسن سلفیٹ)

ہدایات:
خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو دھوپ، گرمی اور منجمد ہونے سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔
انجکشن کے ایک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پزیر
شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔