64146AP

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 64146

Trade Name Amikacin Sulfate in 0.9% Sodium Chloride Injection, 5mg (base)/ml, 500mg(base)/100ml

Generic Name Amikacin Sulfate in 0.9% Sodium Chloride Injection, 5mg (base)/ml, 500mg (base)/100ml

Sponsor Abbott Laboratories

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 64146

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EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
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Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 64146

APPROVAL LETTER

APR • 2 1997

AADA 64-146

Abbott Laboratories
Hospital Products Division
Attention: Donald Mowles
200 Abbott Park Road, D-389 AP-30
Abbott Park, IL 60064-3537

Dear Sir:

This is in reference to your abbreviated antibiotic application dated December 30, 1994, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Amikacin Sulfate in 0.9% Sodium Chloride Injection, 5 mg (base)/mL, [500 mg (base)/100 mL)] packaged in Flexible Plastic Containers.

Reference is also made to your amendment dated November 27, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Amikacin Sulfate in 0.9% Sodium Chloride Injection, 5 mg (base)/mL, [500 mg (base)/100 mL], can be expected to have the same therapeutic effect as that of the reference listed product upon which the agency relied as the basis of safety and effectiveness.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64146

FINAL PRINTED LABELING

TO OPEN – TEAR AT NOTCH

100 mL

One Unit/NDC 0074-5795-23

AMIKACIN SULFATE

in 0.9% Sodium Chloride Injection

500 mg Amikacin (5 mg/mL)

++3007457952320

Each mL contains amikacin sulfate equivalent to 5 mg amikacin; sodium chloride 9 mg. Contains sulfuric acid and may contain sodium hydroxide for pH adjustment. 327 mOsmol/liter (calc.). pH 4.5 (3.5 to 5.5).

ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION.

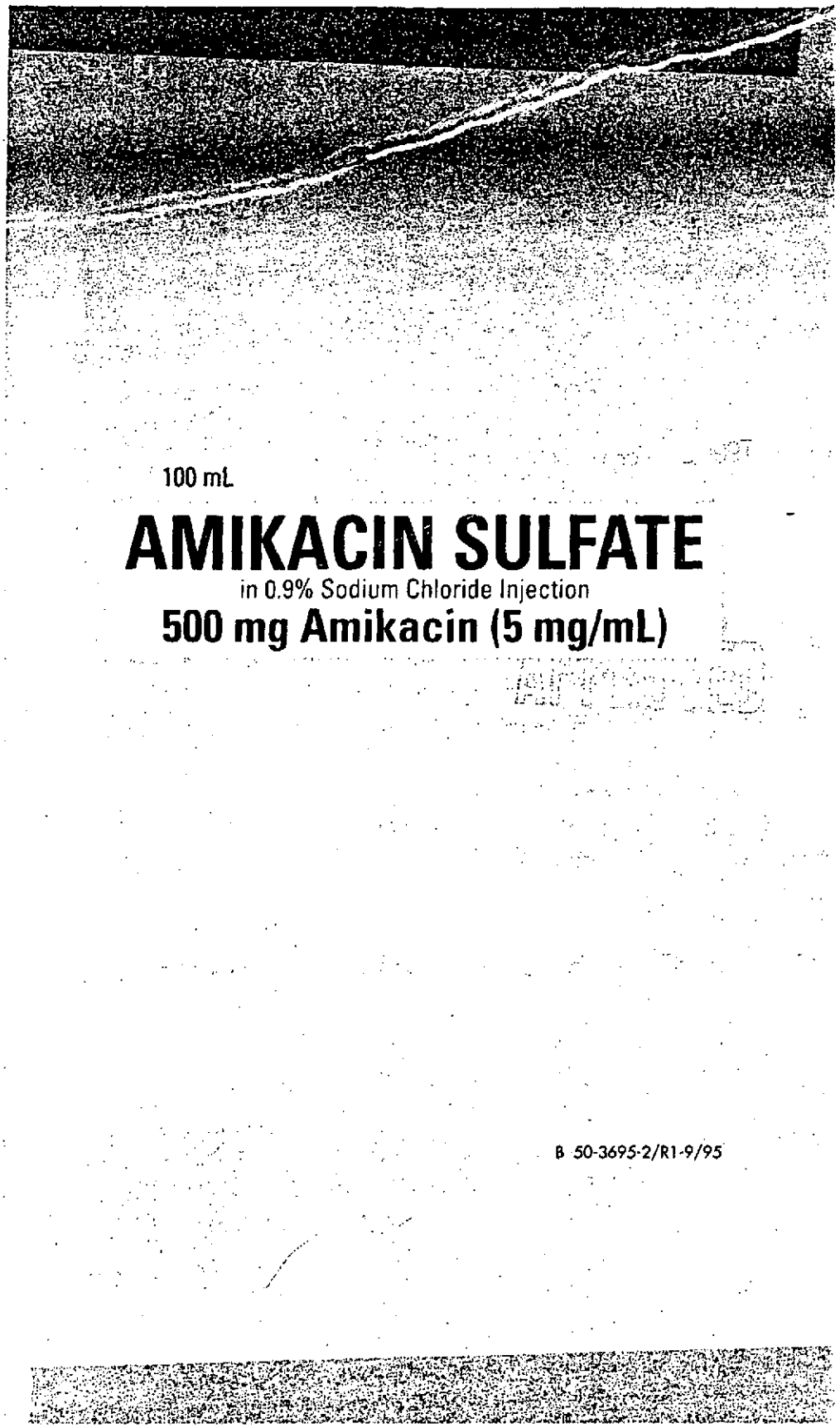
Single-dose container. For I.V. use. Usual dose: See insert. Sterile, nonpyrogenic. Use only if solution is clear. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired. Must not be used in series connections.

The overwrap is a moisture barrier. Do not remove unit from overwrap until ready for use. Use unit promptly when pouch is opened. Recommended storage: *Room temperature (25°C). Avoid excessive heat. Protect from freezing.* See insert.

Caution: Federal (USA) law prohibits dispensing without prescription.

F 50-3695-2/R1-9/95

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA



100 mL

AMIKACIN SULFATE

in 0.9% Sodium Chloride Injection

500 mg Amikacin (5 mg/mL)

B 50-3695-2/R1-9/95

100 mL NDC 0074-5795-23

AMIKACIN SULFATE

in 0.9% Sodium Chloride Injection

500 mg Amikacin (5 mg/mL)

APR 2 1997

EACH mL CONTAINS AMIKACIN SULFATE EQUIVALENT TO 5 mg AMIKACIN; SODIUM CHLORIDE 9 mg. CONTAINS SULFURIC ACID AND MAY CONTAIN SODIUM HYDROXIDE FOR pH ADJUSTMENT.
327 mOsmol/LITER (CALC.). pH 4.5 (3.5 to 5.5).

ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION.

SINGLE-DOSE CONTAINER. FOR I.V. USE. USUAL DOSE: SEE INSERT. STERILE, NONPYROGENIC. CAUTION: FEDERAL (USA) LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. USE ONLY IF SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED. MUST NOT BE USED IN SERIES CONNECTIONS.

 RAO5204-2/R3-9/95 PRINTED IN USA
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

AMIKACIN SULFATE IN 0.9% SODIUM CHLORIDE INJECTION

500 mg Amikacin (5 mg/mL)

For Intravenous Infusion Only

Flexible Container

APR 2 1997

WARNINGS

Patients treated with Amikacin Sulfate in 0.9% Sodium Chloride Injection and 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.

Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with preexisting renal damage and in patients with normal renal function treated at higher doses and/or for periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions. The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations. Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible.

Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy.

Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary.

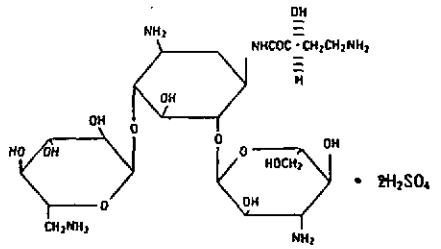
Renal and eighth-nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 micrograms per mL. Urine should be examined for decreased specific gravity, increased excretion of proteins, and the presence of cells or casts. 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 systemic, 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.

The concurrent use of amikacin 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.

DESCRIPTION

Amikacin sulfate is a semi-synthetic aminoglycoside antibiotic derived from kanamycin. Amikacin Sulfate in 0.9% Sodium Chloride Injection is an aqueous solution for parenteral administration. Amikacin Sulfate is $C_{22}H_{43}N_5O_{13} \cdot 2H_2SO_4$ **D-Streptamine, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1 → 6)-*O*-[6-amino-6-deoxy-α-D-glucopyranosyl-(1 → 4)]-*N*^{1}-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-,(*S*)-, sulfate (1:2)(salt).**



Molecular weight is 781.77.

Sodium Chloride, USP is chemically designated NaCl, a white crystalline compound freely soluble in water.

Water for Injection, USP is chemically designated H_2O.

Each milliliter (mL) of the 100 mL size container contains amikacin sulfate equivalent to 5 mg amikacin with sodium chloride 9 mg in water for injection. The pH is 4.5 (3.5 to 5.5). Contains sulfuric acid and may contain sodium hydroxide for pH adjustment.

The flexible plastic container is fabricated from a specially formulated polyvinyl chloride. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

Intramuscular Administration – Amikacin is rapidly absorbed after intramuscular administration. In normal adult volunteers, average peak serum concentrations of about 12, 16, and 21 mcg/mL are obtained 1 hour after intramuscular administration of 250-mg (3.7 mg/kg), 375-mg (5 mg/kg), 500-mg (7.5 mg/kg), single doses, respectively. At 10 hours, serum levels are about 0.3 mcg/mL, 1.2 mcg/mL, and 2.1 mcg/mL, respectively.

Tolerance studies in normal volunteers reveal that amikacin is well tolerated locally following repeated intramuscular dosing, and when given at maximally recommended doses, no ototoxicity or nephrotoxicity has been reported. There is no evidence of drug accumulation with repeated dosing for 10 days when administered according to recommended doses.

With normal renal function, about 91.9% of an intramuscular dose is excreted unchanged in the urine in the first 8 hours, and 98.2% within 24 hours. Mean urine concentrations for 6 hours are 563 mcg/mL following a 250-mg dose, 697 mcg/mL following a 375-mg dose, and 832 mcg/mL following a 500-mg dose.

Preliminary intramuscular studies in newborns of different weights (less than 1.5 kg, 1.5 to 2.0 kg, over 2.0 kg) at a dose of 7.5 mg/kg revealed that, like other aminoglycosides, serum half-life values were correlated inversely with post-natal age and renal clearances of amikacin. The volume of distribution indicates that amikacin, like other aminoglycosides, remains primarily in the extracellular fluid space of neonates. Repeated dosing every 12 hours in all the above groups did not demonstrate accumulation after 5 days.

Intravenous Administration – Single doses of 500 mg (7.5 mg/kg) administered to normal adults as an infusion over a period of 30 minutes produced a mean peak serum concentration of 38 mcg/mL at the end of the infusion, and levels of 24 mcg/mL, 18 mcg/mL, and 0.75 mcg/mL at 30 minutes, 1 hour, and 10 hours post-infusion, respectively. Eighty-four percent of the administered dose was excreted in the urine in 9 hours and about 94% within 24 hours.

Repeat infusions of 7.5 mg/kg every 12 hours in normal adults were well tolerated and caused no drug accumulation.

General – Pharmacokinetic studies in normal adult subjects reveal the mean serum half-life to be slightly over 2 hours with a mean total apparent volume of distribution of 24 liters (28% of the body weight). By the ultrafiltration technique, reports of serum protein binding range from 0 to 11%. The mean serum clearance rate is about 100 mL/min and the renal clearance rate is 94 mL/min in subjects with normal renal function.

Amikacin is excreted primarily by glomerular filtration. Patients with impaired renal function or diminished glomerular filtration pressure excrete the drug much more slowly (effectively prolonging the serum half-life). Therefore, renal function should be monitored carefully and dosage adjusted accordingly (see suggested dosage schedule under DOSAGE AND ADMINISTRATION).

Following administration at the recommended dose, therapeutic levels are found in bone, heart, gallbladder, and lung tissue in addition to significant concentrations in urine, bile, sputum, bronchial secretions, interstitial, pleural, and synovial fluids.

Spinal fluid levels in normal infants are approximately 10 to 20% of the serum concentrations and may reach 50% when the meninges are inflamed. Amikacin has been demonstrated to cross the placental barrier and yield significant concentrations in amniotic fluid. The peak fetal serum concentration is about 16% of the peak maternal serum concentration and maternal and fetal serum half-life values are about 2 and 3.7 hours, respectively.

Microbiology

Gram-negative – Amikacin is active *in vitro* against *Pseudomonas* species, *Escherichia coli*, *Proteus* species (indole-positive and indole-negative), *Providencia* species, *Klebsiella-Enterobacter-Serratia* species, *Acinetobacter* (formerly *Mima-Herellea*) species, and *Citrobacter freundii*.

When strains of the above organisms are found to be resistant to other aminoglycosides, including gentamicin, tobramycin and kanamycin, many are susceptible to amikacin *in vitro*.

Gram-positive – Amikacin is active *in vitro* against penicillinase and nonpenicillinase-producing *Staphylococcus* species including methicillin-resistant strains. However, aminoglycosides in general have a low order of activity against other Gram-positive organisms: viz, *Streptococcus pyogenes*, enterococci, and *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*).

Amikacin resists degradation by most aminoglycoside inactivating enzymes known to affect gentamicin, tobramycin, and kanamycin.

In vitro studies have shown that amikacin sulfate combined with a beta-lactam antibiotic acts synergistically against many clinically significant Gram-negative organisms.

Disc Susceptibility Tests – Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs to test susceptibility to amikacin. Interpretation involves correlation of the diameters obtained in the disc test with MIC values for amikacin. When the causative organism is tested by the Kirby-Bauer method of disc susceptibility, a 30-mcg amikacin disc should give a zone of 17 mm or greater to indicate susceptibility. Zone sizes of 14 mm or less indicate resistance. Zone sizes of 15 to 16 mm indicate intermediate susceptibility. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

INDICATIONS AND USAGE

Amikacin Sulfate in 0.9% Sodium Chloride Injection is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including *Pseudomonas* species, *Escherichia coli*, species of indole-positive and indole-negative *Proteus*, *Providencia* species, *Klebsiella-Enterobacter-Serratia* species, and *Acinetobacter (Mima-Herellea)* species.

Clinical studies have shown Amikacin Sulfate Injection to be effective in bacterial septicemia (including neonatal sepsis); in serious infections of the respiratory tract, bones and joints, central nervous system (including meningitis) and skin and soft tissue; intra-abdominal infections (including peritonitis); and in burns and postoperative infections (including post-vascular surgery). Clinical studies have shown amikacin also to be effective in serious complicated and recurrent urinary tract infections due to these organisms. Aminoglycosides, including Amikacin Sulfate in 0.9% Sodium Chloride Injection, are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity.

Bacteriologic studies should be performed to identify causative organisms and their susceptibilities to amikacin. Amikacin may be considered as initial therapy in suspected Gram-negative infections and therapy may be instituted before obtaining the results of susceptibility testing. Clinical trials demonstrated that amikacin was effective in infections caused by gentamicin and/or tobramycin-resistant strains of Gram-negative organisms, particularly *Proteus rettgeri*, *Providencia stuartii*, *Serratia marcescens*, and *Pseudomonas aeruginosa*. The decision to continue therapy with the drug should be based on results of the susceptibility tests, the severity of the infection, the response of the patient and the important additional considerations contained in the "WARNINGS" box above.

Amikacin has also been shown to be effective in staphylococcal infections and may be considered as initial therapy under certain conditions in the treatment of known or suspected staphylococcal disease such as, severe infections where the causative organism may be either a Gram-negative bacterium or a staphylococcus, infections due to susceptible strains of staphylococci in patients allergic to other antibiotics, and in mixed staphylococcal/Gram-negative infections.

In certain severe infections such as neonatal sepsis, concomitant therapy with a penicillin-type drug may be indicated because of the possibility of infections due to Gram-positive organisms such as streptococci or pneumococci.

CONTRAINDICATIONS

A history of hypersensitivity to amikacin is a contraindication for its use. A history of hypersensitivity or serious toxic reactions to aminoglycosides may contraindicate the use of any other aminoglycoside because of the known cross-sensitivities of patients to drugs in this class.

WARNINGS

See "WARNINGS" box above.

Aminoglycosides can cause fetal harm when administered to a pregnant woman. 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 fetus or newborns have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists. Reproduction studies of amikacin have been performed in rats and mice and revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects to the fetus. If this drug 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 fetus.

PRECAUTIONS

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.

Amikacin sulfate injection is potentially nephrotoxic, ototoxic and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Increased nephrotoxicity has been reported following concomitant parenteral administration of aminoglycoside antibiotics and cephalosporins. Concomitant cephalosporins may spuriously elevate creatinine determinations.

Since amikacin is present in high concentrations in the renal excretory system, patients should be well-hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells, or albumin), hydration should be increased. A reduction in dosage (see DOSAGE AND ADMINISTRATION) may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance; decreased urine specific gravity; increased BUN, creatinine, or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal the risk of nephrotoxic reactions with amikacin sulfate is low if the dosage recommendations (see DOSAGE AND ADMINISTRATION) are not exceeded.

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 during treatment with aminoglycosides is particularly important.

Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

In vitro mixing of aminoglycosides with beta-lactam antibiotics (penicillin or cephalosporins) may result in a significant mutual inactivation. A reduction in serum half-life or serum level may occur when an aminoglycoside or penicillin-type drug is administered 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).

Cross-allergenicity among aminoglycosides has been demonstrated.

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

Aminoglycosides should not be given concurrently with potent diuretics (see WARNINGS box).

Carcinogenesis, Mutagenesis, Impairment of Fertility – Long term studies in animals to evaluate carcinogenic potential have not been performed; and mutagenicity has not been studied. Amikacin sulfate injection administered subcutaneously to rats at doses up to 4 times the human daily dose did not impair male or female fertility.

Pregnancy – Category D (see WARNINGS section).

Nursing Mothers – It is not known whether amikacin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from amikacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric 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.

ADVERSE REACTIONS

All aminoglycosides have the potential to induce auditory, vestibular, and renal toxicity and neuromuscular blockade (see WARNINGS box). They occur more frequently in patients with present or past history of renal impairment, of treatment with other ototoxic or nephrotoxic drugs, and in patients treated for longer periods and/or with higher doses than recommended.

Neurotoxicity-Ototoxicity – 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.

Neurotoxicity-Neuromuscular Blockage – Acute muscular paralysis and apnea can occur following treatment with aminoglycoside drugs.

Nephrotoxicity – Elevation of serum creatinine, albuminuria, presence of red and white cells, casts, azotemia, and oliguria have been reported. Renal function changes are usually reversible when the drug is discontinued.

Other – In addition to those described above, other adverse reactions which have been reported on rare occasions are skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, and hypotension.

OVERDOSAGE

In the event of overdosage or toxic reaction, peritoneal dialysis or hemodialysis will aid in the removal of amikacin from the blood. In the newborn infant, exchange transfusion may also be considered.

DOSAGE AND ADMINISTRATION

Amikacin Sulfate in 0.9% Sodium Chloride Injection is administered by intravenous infusion only. The patient's pretreatment body weight 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 35 micrograms per mL and trough concentrations (just prior to the next dose) above 10 micrograms per mL should be avoided. Dosage should be adjusted as indicated.

Patients with Normal Renal Function – The recommended dosage for adults, children and older infants (see "WARNINGS" box) with normal renal function is 15 mg/kg/day divided into 2 or 3 equal doses administered at equally-divided intervals, i.e., 7.5 mg/kg every 12 hours or 5 mg/kg every 8 hours. Treatment of patients in the heavier weight classes should not exceed 1.5 gram/day. When amikacin is indicated in newborns (see "WARNINGS" box), it is recommended that a loading dose of 10 mg/kg be administered initially to be followed with 7.5 mg/kg every 12 hours.

The usual duration of treatment is 7 to 10 days. It is desirable to limit the duration of treatment to short term whenever feasible. The total daily dose by all routes of administration should not exceed 15 mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin should be re-evaluated. If continued, amikacin serum levels and renal, auditory, and vestibular functions should be monitored. At the recommended dosage level, uncomplicated infections due to amikacin-sensitive organisms should respond in 24 to 48 hours. 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.

When amikacin is indicated in uncomplicated urinary tract infections, a dose of 250 mg twice daily may be used.

DOSAGE GUIDELINES			
ADULTS AND CHILDREN WITH NORMAL RENAL FUNCTION			
Patient Weight		Dosage	
lbs.	kg	7.5 mg/kg q.12h	OR 5 mg/kg q. 8h
99	45	337.5 mg	225 mg
110	50	375 mg	250 mg
121	55	412.5 mg	275 mg
132	60	450 mg	300 mg
143	65	487.5 mg	325 mg
154	70	525 mg	350 mg
165	75	562.5 mg	375 mg
176	80	600 mg	400 mg
187	85	637.5 mg	425 mg
198	90	675 mg	450 mg
209	95	712.5 mg	475 mg
220	100	750 mg	500 mg

Amikacin should be administered to adults and children over a 30 to 60 minute period. The total daily dose should not exceed 15 mg/kg/day and may be divided into either 2 or 3 equally divided doses at equally divided intervals. Infants should receive doses of amikacin over a 1 to 2 hour period.

Patients with Impaired Renal Function – Whenever possible, serum amikacin sulfate concentrations should be monitored by appropriate assay procedures. Doses may be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval.

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. Neither method should be used when dialysis is being performed.

Normal Dosage at Prolonged Intervals – If the creatinine clearance rate is not available and the patient's condition is stable, a dosage interval in hours for the normal dose can be calculated by multiplying the patient's serum creatinine by 9, e.g., if the serum creatinine concentration is 2 mg/100 mL, the recommended single dose (7.5 mg/kg) should be administered every 18 hours.

Reduced Dosage at Fixed Time Intervals – When renal function is impaired and it is desirable to administer amikacin at a fixed time interval, dosage must be reduced. In these patients serum amikacin concentrations should be measured to assure accurate administration of amikacin and to avoid concentrations above 35 mcg/mL. If serum assay determinations are not available and the 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 loading dose is the same as the normally recommended dose which would be calculated for a patient with a normal renal function as described above.

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:

$$\text{Maintenance Dose Every 12 Hours} = \frac{\text{observed CC in mL/min}}{\text{normal CC in mL/min}} \times \text{calculated loading dose in mg}$$

(CC = 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.

Additives should not be made to Amikacin in 0.9% Sodium Chloride Injection.

Amikacin Sulfate in 0.9% Sodium Chloride Injection is a ready-to-use isotonic solution. NO DILUTION OR BUFFERING IS REQUIRED.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit.

Aminoglycosides should not be physically premixed with other drugs but should be administered separately.

Because of the potential toxicity of aminoglycosides, "fixed dosage" recommendations which are not based upon body weight are not advised. Rather, it is essential to calculate the dosage to fit the needs of each patient.

Preparation for Intravenous Administration

Tear outer wrap at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

(Use aseptic technique)

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. **Note:** See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Open flow control clamp and clear air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Regulate rate of administration with flow control clamp.

Warning: Do not use flexible container in series connections.

HOW SUPPLIED

Amikacin Sulfate in 0.9% Sodium Chloride Injection is supplied in a single-dose flexible container as follows:

List No.	Volume	Total Amikacin Content	Osmolarity mOsmol/L (calc.)
5795	100 mL	500 mg	327

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

Caution: Federal (USA) law prohibits dispensing without prescription.

*Bauer, A.W., Kirby, W.M.M., Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method. Am.J.Clin.Pathol., 45:493, 1966; Standardized Disc Susceptibility Test, FEDERAL REGISTER, 37:20527-29, 1972.

RAO5205-R4-9/95

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ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64146

CHEMISTRY REVIEW(S)

DW

1. CHEMIST'S REVIEW NO. 3

2. AADA # 64-146

3. NAME AND ADDRESS OF APPLICANT

Abbott Laboratories
Attention: Donald Mowles
200 Abbott Park Road, D-389 AP-30
Abbott Park, IL 60064-3537

(847) 937-7597

4. LEGAL BASIS FOR SUBMISSION

21 CFR § 444.206

5. SUPPLEMENT(S)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Amikacin Sulfate in 0.9% Sodium Chloride Injection in Flexible Containers.

8. SUPPLEMENT(S) PROVIDE(S) FOR

N/A

9. AMENDMENTS AND OTHER DATES

Original Submission: 12/30/94
Receipt: 01/10/95
Confirmation of receipt: 03/10/95
Amendment to N/A letter 6/12/95: 08/30/96
Amendment 9/18/96 (Labeling)
Amendment 11/27/96 to N/A letter 10/25/96

10. PHARMACOLOGICAL CATEGORY

Antibacterial

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

Previously approved Abbott amikacin applications:
AADA 63-283
63-266
63-263
63-264
63-265

13. DOSAGE FORM

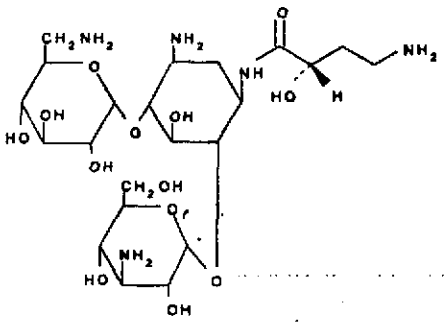
SVT

14. POTENCY

500 mg Amikacin base (5 mg/mL)

15. CHEMICAL NAME AND STRUCTURE

Amikacin USP
$C_{22}H_{43}N_5O_{13}$; M.W. = 585.61



O-3-Amino-3-deoxy-α-D-glucopyranosyl(1→4)-
O-[6-amino-6-deoxy-α-D-glucopyranosyl(1→6)]-
N^3-(4-amino-L-2-hydroxy-butyryl)-2-deoxy-L-streptamine.
CAS [37517-28-5]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

In Amendment 11/27/96 Firm responds in order:

Q1.

AADA 64-146 will be for 500 mg Amikacin, 5 mg/mL, List 5795 only. In the enclosed Form 356h for communications dated 8/30/96 and 9/18/96, Please clarify.

A1. Firm confirms that AADA 64-146 is for 5 mg/mL only and provides the revised Form 356h.

Regarding the Certificate of Analysis for Amikacin, USP:

Q2. The enclosed COA from (page 1-6) is not legible (some numbers are very difficult to comprehend). Please resubmit a readable copy.

A2. Firm submits a readable copy of COA from as requested.

Q3. We note that your specifications for and impurities are different from the new supplier's. It appears that has more strict limits. Please comment.

A3. Firm lowers their limits according to ıe revised specifications are acceptable (listed under #23).

Comments:
Abbott states that their method does not test for the specifically, but if this compound is present in the bulk drug, it will be reported as a Post-amikacin impurity. Abbott's limit for ıs less than

Regarding the submitted executed batch records for exhibit lot 12-325-JE:

Q4. We note under IV. Quality Assurance, the specification for sodium chloride content is listed as (page 2-170). The Release Target for sodium chloride listed everywhere else is Please clarify.

A4. Firm states that this change from for the lower limit was based on having sufficient room within

the release target for sodium chloride when compared to the final product specification limit of They believe that the release limit of for sodium chloride provides sufficient release control for the product to remain within the final product limits throughout the shelf life.

Q5. Regarding your response to item 6c in our deficiency letter dated June 12, 1995, it is noted in the submitted COA (page 2-5) for product Exhibit batch Lot 12-325-JE, the potency is listed as Shouldn't it be expressed as Please comment.

A5. Firm states that the value, s a rounded value. The Target Assay Limit is cherefore, the final result is reported as a whole number.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval recommended (pending on issues regarding sample validation and EER).

19. REVIEWER: DATE COMPLETED:

Maria C. Shih 1/9/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64146

BIOEQUIVALENCE REVIEW(S)

SEP 14 1995

Amikacin Sulfate
in 0.9% Sodium Chloride
Injection in Flexible
Plastic Containers
5 mg (base)/mL

Abbott Laboratories
Abbott Park, IL
Submission Date:

December 30, 1994

AADA # 64-146
Reviewer: L. Chuang

Review of a Waiver Request

Amikacin sulfate is a semi-synthetic aminoglycoside antibiotic derived from kanamycin. Amikacin base is freely soluble in water, insoluble in alcohol. Amikacin is converted to the sulfate salt in preparing injection dosage forms. Amikacin sulfate is commercially available as injections, 50 mg/mL (in 2 mL vials) and 250 mg/mL (in 2 mL and 4 mL vials, and 2 mL disposable syringes).

The firm is requesting a waiver of bioavailability requirements per 21 CFR320.22(b)(1). The test drugs are intended for intravenous administration. The cited listed drugs are Amikin^R in Sodium Chloride 0.9% in plastic container, 5 mg/mL and 10 mg/mL, approved 11/30/87 under NDA 50-618, manufactured by Bristol Laboratories. These products were discontinued on March 4, 1993 because they were not found to be marketable and were never placed on the market. No safety or efficacy concerns have surfaced. The products remain approved products (not withdrawn) but they are not being marketed through applicant's choice (see attached comments by Mark Anderson, CSO HFD-643, of form 3291, dated 3/17/95).

The comparative formulations of the test product and Amikin^R, manufactured by Bristol Laboratories, are presented below:

Ingredient	Amikin^R (Bristol)	Amikacin Sulfate (Abbott)
Amikacin	5 mg/mL	5 mg/mL
Sulfuric Acid	pH adjustment	pH adjustment
Sodium Hydroxide	pH adjustment	pH adjustment
Sodium Chloride	9.0 mg/mL	9.0 mg/mL
Water for Injection	Q.S.	Q.S.

Comments:

1. The test drugs meet both of the following criteria of 21 CFR Section 320.22(b)(1):

   * The drug product is a parenteral solution intended solely for administration by injection; and

   * The drug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA.

Therefore a waiver for the requirement to submit evidence obtained *in vivo* demonstrating the bioavailability or bioequivalence of the test products is granted.

2. The firm has, in this AADA, included the labeling of the higher strengths of Amikin[R], 50 mg/mL and 100 mg/mL, which have different formulations from the listed drugs with lower strengths, 5 mg/mL **The labeling reviewer should take this into consideration.**

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories Inc. demonstrates that its Amikacin Sulfate in 0.9% Sodium Chloride Injections, 5 mg (base)/mL falls under 21 CFR Section 320.22 (b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of in-vivo bioequivalence study for the test products is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulations to be bioequivalent to Amikin[R] at identical strength, manufactured by Bristol Laboratories.

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

9/20/95

Concurrence — 9/19/95

cc: ANDA 64-146 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Chuang), Drug File, Division File.

LWC/dbm/082995/WP 64146W.d94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64146

ADMINISTRATIVE DOCUMENTS

This Approval Summary superseded that of September 13, 1996

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

AADA Number: 64-146 **Date of Submission:** 11-27-96

Applicant's Name: Abbott Laboratories

Established Name: Amikacin Sulfate in 0.9% Sodium Chloride Injection, 5 mg (base)/mL 100 mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 100 mL - Submitted 8/30/96 and 11/27/96

Carton Labeling: (OVERWRAP) - Submitted 8/30/96 and 11/27/96

Professional Package Insert Labeling: Submitted 8/18/96 and 11/27/96

Revisions needed post-approval: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Amikin

NDA Number: 50-618 and 62-311 - See FTR

NDA Drug Name: Amikacin Sulfate Injection in 0.9% NaCl

NDA Firm: Apothecon

Date of Approval of NDA Insert and supplement #: **AADA 62-311/S-025 approved 7/31/96**

Has this been verified by the MIS system for the AADA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Listed drug

Basis of Approval for the Carton Labeling: Listed drug

Other Comments:

FOR THE RECORD:

1. **Most of the following FTR text is taken from the review done 9/13/96. For the checklist see the review dated 9/13/96.**

2. **Bristol-Myers Squibb (Apothecon) is the holder of the only other amikacin product manufactured in flexible plastic containers (NDA 50-618). This product was never put into the market because the firm felt that it was not marketable (see response to consult to HFD-520 dated 3-10-95).**

3. **Insert labeling modeled after AMIKIN® (Apothecon, approved 7/31/96, revised 1/94) and the labeling for Abbott's approved gentamicin and tobramycin products in flexible plastic containers. The Apothecon products (NDA's 50-618 and 50-495), are currently not being marketed and are no longer listed in the Orange Book. AADA 62-311, Apothecon's "generic" amikacin sulfate, is currently the holder of the "reference listed drug" in the Orange Book (16th ed.).**

4. **Storage recommendations; Abbott insert:**

   > **Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.**

   Abbott overwrap:

   > Room temperature (25°C). Avoid excessive heat. Protect from freezing. See insert.

   Abbott container label: No storage conditions.

   These storage recommendations are consistent with those of Abbott's approved applications for gentamicin and tobramycin in flexible plastic containers. The container is to be retained in the moisture resistant overwrap until time of use.

   USP: preserve in single-dose or in multiple-dose containers, preferably of type 1 or type II glass

5. The drug is not light sensitive.

6. **The inactive ingredients listed in the DESCRIPTION section, are consistent with the listing in the composition statement appearing on page 1-42 of the 8/30/96 submission. The firm describes inactive ingredients used for pH adjustment as follows, "contains sulfuric acid and may contain sodium hydroxide". This statement is consistent with Step 6 on**

page 2-10 of the same submission. Since the manufacture of this product begins with amikacin base, sulfuric acid must be used in the manufacture process and therefore should always be listed, whereas the sodium hydroxide is only used if there is need to adjust pH upward.

7. A warning cautioning use of products containing sodium chloride in patients with congestive heart failure, severe renal insufficiency and edema, is standard labeling for some firms' products in parenteral electrolyte solution. This warning does not appear in labeling for Abbott's approved gentamicin or tobramycin products, there is a "For The Record" for gentamicin that this warning is optional, and the warning does not appear in labeling submitted to this application. We will not ask that this warning be added.

8. We will not request that the firm list osmolar concentration in the HOW SUPPLIED section since this has not been done for Abbott's other approved aminoglycoside in flexible plastic container applications and since a "For The Record", dated 5/16/91, for gentamicin in 0.9% sodium chloride injection states that this is not required.

9. The DOSAGE AND ADMINISTRATION sections of Abbott's other aminoglycoside in normal saline applications include a paragraph regarding the adjustment of dosage for these products. The insert submitted to this application does not include this language. We will not request that this language be included based on a "For The Record" for the gentamicin product. This "For The Record", dated 5/16/91, states that piggyback bags should not be manipulated to adjust the dose. One concern, for example, is the possible compromise of sterility resulting from adding to or removing material from the bag.

10. The firm has been asked to comment on the last paragraph of the DESCRIPTION section. This text does not appear in the approved insert labeling of either gentamicin or tobramycin in flexible containers.

11. This product contains an overfill which is targeted at 52-56 mL for the 50 mL product and 102-112 mL for the 100 mL product (see page H-260 of the 8/30/96 submission). This overage helps offset loss of the drug by permeation through the container. The overage is troublesome for this product because of the narrow therapeutic index of the drug.

12. CLINICAL PHARMACOLOGY:

The applicant deleted the entire Intramuscular Administration subsection. The firm was requested to add the text back into the section since the information was deemed to be informational (not entirely specific to the intramuscular route of administration) and might be useful

for comparison's sake to the IV route. The information also does not constitute a claim that this product can be used by the IM route.

13. DOSAGE AND ADMINISTRATION:

a. The firm was requested to delete the last sentence of the first paragraph, "The volume of Amikacin Sulfate in 0.9% Sodium Chloride Injection to be administered will depend on the dose of amikacin prescribed.". This sentence is not in the approved labeling of the listed drug and implies that the product may be manipulated to adjust the dosage. We do not want to encourage addition or removal from the piggyback bag.

b. Although this product (500 mg) should not be used in patients with normal renal function weighing less than approximately 150 lbs. (b.i.d. dosage), it was decided (Phillips, White, Grace, Hoppes) to retain the text regarding dosing in infants, such as the following statement, in this section.

Infants should receive doses of amikacin over a 1 to 2 hour period.

This statement provides the health care practitioner with useful information. Also, the statement does not specifically recommend the use of this product in infants.

14. Only 8 labels and labeling are included for approval (4 in blue jacket and 4 in red jacket). Although, the firm states that the labels and labeling are draft, we consider them to be FPL. Therefore an approval summary was prepared because there are no Labeling deficiency comments. We asked the firm to submit 4 additional labels and labeling and they have done so in this submission.

Date of Review: 12-16-96 **Date of Submission:** 11-27-96

Primary Reviewer: **Date:**

Team Leader: **Date:**

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cc:

ANDA: 64-146
DUP/DIVISION FILE
HFD-613/AVezza/JGrace (no cc)
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Review