Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amikin Injection 100 mg/2 ml.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains amikacin sulfate equivalent to amikacin activity 100 mg (100,000 international units) in 2 mL (50 mg/mL).

Excipients with known effect:
Each vial contains 3 mg of sodium.
Each vial contains 2.64 mg sodium metabisulfite (E223).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of infections due to gram negative organisms sensitive to the anti-infective.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

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 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.

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 mcg/mL and trough concentrations (just prior to the next dose) above 10 mcg/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 35 mcg/mL.

The usual duration of treatment is 7 to 10 days. The total daily dose by all routes of administration should not exceed

15-20 mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin sulfate 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.

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 every 12 hours. 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 every 12 hours. 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 every 12 hours (see sections 4.4 and 5.2).

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

Specific recommendation for intravenous administration
The solution for intravenous use is prepared by adding the desired dose to 100 mL or 200 mL of sterile diluent such as normal saline or 5% dextrose in water .The solution is administered to adults over a 30 to 60 minute period.

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.

Amikacin should not be physically premixed with other drugs, but should be administered separately according to the recommended dose and route.

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 neither 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 pseudomonal infections):

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

Impaired renal function:

In patients with renal impairment reflected by creatinine clearance less than 50 mL/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. See below for dosage adjustments in patients with impaired renal function.

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 (i.e. that which would be given to patients with normal renal function on a twice daily schedule, 7.5 mg/kg) can be calculated by multiplying the patient's serum creatinine concentration (in mg/100mL) by nine; 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.

Serum Creatinine Concentration (mg/100mL)		**Interval between AMIKACIN doses of 7.5 mg/kg/IM (hours)**
1.5		13.5
2.0		18
2.5		22.5
3.0	X 9 =	27
3.5		31.5
4.0		36
4.5		40.5
5.0		45
5.5		49.5
6.0		54

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 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 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:

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 twelve-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.

Other routes of administration:

Amikin in concentrations of 0.25% may be used satisfactorily as an irrigating solution in abscess cavities, the pleural space and the peritoneum.

4.3 Contraindications

Amikacin sulfate injection is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

A history of hypersensitivity or serious toxic reactions to aminoglycosides may contraindicate the use of any aminoglycosides because of the known cross sensitivities of patients to drugs in this class.

4.4 Special warnings and precautions for use

Caution should be applied to patients with pre-existing renal insufficiency, or pre-existing hearing or vestibular damage. 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. Precautions on dosage and adequate hydration should be observed.

In patients with impaired renal function or diminished glomerular filtration, renal function should be assessed by the usual methods prior to therapy and periodically during therapy. Daily doses should be reduced and/or the interval between doses lengthened in accordance with serum creatinine concentrations to avoid accumulation of abnormally high blood levels and to minimise the risk of ototoxicity. Regular monitoring of serum drug concentration and of renal function is particularly important in elderly patients, who may have reduced renal function that may not be evident in the results of routine screening tests i.e. blood urea and serum creatinine.

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. Amikacin therapy should be stopped if tinnitus or subjective hearing loss develops, or if follow-up audiograms show significant loss of high frequency response.

Monitoring of drug levels should also be performed and trough concentrations> 10 mcg/mL should be avoided.

Monitoring of vestibular and auditory function should be carried out during and after treatment.

Neuro/Ototoxicity

Neurotoxicity, manifested as vestibular and/or bilateral auditory 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. 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 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.

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, bekanamycin, 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.

Neuromuscular toxicity

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 respiratory paralysis should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics, neuromuscular blocking agents (see section 4.5), 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. Neuromuscular blockade and muscular paralysis have been demonstrated in laboratory animals given high doses of amikacin.

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.

Renal toxicity

Aminoglycosides are potentially nephrotoxic. Renal toxicity is independent of plasma obtained at the peak (Cmax).The risk of nephrotoxicity is greater in patients with impaired renal function, and in those who receive high doses, or in those whose therapy is prolonged. Patients should be well hydrated during treatment and renal function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment. 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. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels. 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.

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).

Allergic reactions

Amikacin sulfate injection in vials contains sodium metabisulfite (E223), 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 nonasthmatic subjects. This medicinal product contains less than

1 mmol sodium (23 mg) per Amikin 100mg/ 2mL, i.e. essentially ‘sodium free’.

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 nonsus ceptible organisms. If this occurs, appropriate therapy should be instituted.

Macular infarction sometimes leading to permanent loss of vision has been reported following intravitreous administration (injection into the eye) of amikacin.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The concurrent or serial use of amikacin sulphate 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. Irreversible deafness may result.

The use of amikacin is not recommended in patients under the influence of anaesthetics or muscle-relaxing drugs (including ether, halothane, d-tubocurarine, succinylcholine,decamethonium; atracurium, rocuronium, vecuronium or in patients receiving massive transfusions of citrate-anticoagulated blood) as neuromuscular blockade and consequent respiratory depression may occur. If blockade occurs, calcium salts may reverse this phenomenon.

Indomethacin may increase the plasma concentration of amikacin in neonates.

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

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

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

There is an increased risk of nephrotoxicity and possibly of ototoxicity when aminoglycosides are administered with platinum compounds. The concurrent or serial use of other ototoxic or nephrotoxic agents, particularly bacitracin, cisplatin, amphotericin B, cyclosporine, tacrolimus, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided either systemically or topically because of the potentialfor additive effects. Increased nephrotoxicity has been reported following concomitant parenteral administration of aminoglycoside antibiotics and cephalosporins. Concomitant cephalosporin use may spuriously elevate creatinine serum level determinations.

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy
Amikacin should be administered to pregnant women and neonatal infants only when clearly needed and under medical supervision (see section 4.4).

There are limited data on use of aminoglycosides in pregnancy. Aminoglycosides can cause foetal harm. Aminoglycosides cross the placenta and there have been reports of total, irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Although adverse effects on the foetus or newborns have not been reported in pregnant women treated with other aminoglycosides, the potential for harm exists. 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
It is not known whether 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 (see section 4.8) the ability to drive and use machinery may be impaired.

4.8 Undesirable effects

The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (< 1/10000), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	MedDRA Term
Infections and infestations	Uncommon	Superinfections or colonisation with resistant bacteria or yeast[a]
Blood and lymphatic system disorders	Rare	Anaemia, eosinophilia
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[a],
	Rare	Tremor[a], paresthesia[a], headache, balance disorder[a]
Eye disorders	Rare	Blindness[b], retinal infarction[b]
Ear and labyrinth disorders	Rare	Tinnitus[a], hypoacusis[a]
	Not known	Deafness[a], deafness neurosensory[a]

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[a]
Renal and urinary disorders	Not known	Renal failure acute, nephropathy toxic, cells in urine[a]
	Rare	Oliguria[a], blood creatinine increased[a], albuminuria[a], azotemia[a], red blood cells urine[a], white blood cells urine[a]
General disorders and administration site conditions	Rare	Pyrexia

[a] See section 4.4.
[b] Amikacin is not formulated for intavitreal 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 (see section 4.4).

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 (see section 4.4).

Macular infarction sometimes leading to permanent loss of vision has been reported following intravitreous administration (injection into the eye) of amikacin (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL-Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

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 gluconat or lactobionat in 10-20% solution) (see section 4.4). 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 hemofiltration. In the newborn infant, exchange transfusion may also be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectives for systemic use, ATC code: J01GB06

Amikacin sulphate is an aminoglycoside antibiotic which is active against a broad spectrum of gram-negative organisms, including *Pseudomonas* spp, *Escherichia coli*, indole-positive and indole-negative *Proteus* spp, *Klebsiella-Enterobacter-Serratia* spp, *Salmonella, Shigella, Minea-Herellae, Citrobacter freundii* and *Providencia* spp..

Many strains of these gram-negative organisms resistant to gentamicin and tobramycin may show sensitivity to amikacin *in vitro*. The principal gram-positive organism sensitive to amikacin is *Staphylococcus aureus*, including methicillin-resistant strains. Amikacin has some activity against other gram-positive organisms including certain strains of *Streptococcus pyogenes*, Enterococci and *Diplococcus pneumoniae*.

5.2 Pharmacokinetic properties

Amikin is rapidly absorbed after intramuscular injection. Peak serum levels of approximately 11 mg/L and 23 mg/L are reached one hour after intramuscular doses of 250 mg and 500 mg respectively. Levels 10 hours after injection are of the order of 0.3 mg/L and 2.1 mg/L respectively.

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.

Amikin diffuses readily through extracellular fluids and is excreted in the urine unchanged, primarily by glomerular filtration. Half-life in individuals with normal renal functions is two to three hours.

Following intramuscular administration of a 250 mg dose, about 65% is excreted in six hours and 91% within 24 hours. The urinary concentrations average 563 mg/L in the first 6 hours and 163 mg/L over 6 to 12 hours. Mean urine concentrations after a 500 mg intramuscular dose average 832 mg/L in the first six hours.

Single doses of 500 mg administered to normal adults as an intravenous infusion over a period of 30 minutes produce a mean peak serum concentration of 38 mg/L at the end of the infusion. Repeated infusions do not produce drug accumulation.

Amikin has been found in cerebrospinal fluid, pleural fluid, amniotic fluid and in the peritoneal cavity following parenteral administration.

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.

Intramuscular and intravenous administration
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 was 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

No further relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Sodium metabisulfite (E223)
Sulphuric acid (for pH-adjustment)
Water for injection

6.2 Incompatibilities

The incompatibilities for Amikin are listed as the following:

- Intravenous fluids: Surbex T with 5% Dextrose
- Drug products: Amphotericin B. sodium cephalothin, sodium novobiocin, and sodium ampicillin.

6.3 Shelf life

Unopened: 3 years.

To be used immediately after opening. Any remaining contents must be discarded.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Five 2 mL flint glass Type 1 vials with butyl rubber stopper and aluminium seal.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only, discard any unused solution.
Parental drug products should be inspected visually for particulate matter and discolouration prior to administration whenever the solution and container permit.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
For instructions on dilution of the product before administration, see section 4.2.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharmaceuticals uc
Plaza 254
Blanchardstown Corporate Park 2
Ballycoolin,
Dublin 15
D15 T867
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2255/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th July 1976

Date of last renewal: 15th July 2006

10 DATE OF REVISION OF THE TEXT

April 2018