

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0048/004/006**

Case No: 2050682

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Bristol-Myers Squibb (Holdings)**

**T/A Bristol-Myers Pharmaceuticals, Swords, Co. Dublin, Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Amikin Injection 500mg/2ml.**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/01/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Amikin Injection 500 mg/2 ml.

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml vial contains amikacin sulphate equivalent to amikacin activity 500 mg (500,000 international units) in 2 ml (250 mg/ml).

Excipients: Each vial contains 14.74 mg (0.64 mmol) sodium.

For a 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.

##### 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.

##### **Adults and children**

15mg/kg/day in two equally divided doses (equivalent to 500mg b.i.d. in adults): use of the 100mg/2ml strength is recommended for children for the accurate measurement of the appropriate dose.

##### **Neonates and premature infants**

An initial loading dose of 10mg/kg followed by 15mg/kg/day in two equally divided doses.

##### **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 neither 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 pseudomonal 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 alkalising agent may be administered concurrently.

**Impaired renal function**

In patients with impaired renal function, the daily dose should be reduced and/or the intervals between doses increased to avoid accumulation of the drug. The critical serum creatinine concentration is 1.5mg/100ml.

**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**

Hypersensitivity to any of the components of the product.

Use of amikacin intraperitoneally in young children or in patients under anaesthesia or muscle relaxing drugs.

Myasthenia gravis.

**4.4 Special warnings and precautions for use**

Patients should be well hydrated during amikacin therapy.

In patients with impaired renal function or diminished glomerular filtration, amikacin should be used cautiously. In such patients, 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.

Monitoring of drug levels should also be performed and trough concentrations > 4µg/ml should be avoided.

As with other aminoglycosides, ototoxicity and/or nephrotoxicity can result from the use of amikacin and are directly related to total dosage of drug, duration of therapy and degree of dehydration.

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

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.

**4.5 Interaction with other medicinal products and other forms of interaction**

The risk of ototoxicity is increased when amikacin is used in conjunction with rapidly acting diuretic drugs, particularly when the diuretic is administered intravenously. Such agents include frusemide and ethacrynic acid. Irreversible deafness may result.

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

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.

## 4.6 Pregnancy and lactation

The safety of Amikin in pregnancy has not yet been established. Amikacin should only be used in pregnancy or lactation if considered essential by the physician. The drug crosses the placenta but does not reach significant levels in breast milk.

## 4.7 Effects on ability to drive and use machines

None stated.

## 4.8 Undesirable effects

Side effects include allergic reactions, tinnitus, headache, anaemia, purpura and increased levels of bilirubin occasionally. Ototoxicity and nephrotoxicity are the most significant problems. Urinary signs of renal irritation (albumin, casts and red or white blood cells), azotaemia and oliguria have been reported. There have been reports of retinal toxicity following intravitreal injection of amikacin.

The sodium bisulphite content of the product may rarely cause severe hypersensitivity reactions and bronchospasm.

## 4.9 Overdose

In the event of overdosage or toxic reaction, peritoneal dialysis or haemodialysis will aid in the removal of amikacin from the blood.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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 11mg/l and 23mg/l are reached one hour after IM doses of 250mg and 500mg respectively. Levels 10 hours after injection are of the order of 0.3mg/l and 2.1mg/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 250mg 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 500mg IM dose average 832 mg/l in the first six hours.

Single doses of 500mg administered to normal adults as an intravenous infusion over a period of 30 minutes produce a mean peak serum concentration of 38mg/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.

### **5.3 Preclinical safety data**

No further relevant information.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium citrate  
Sodium bisulphite (E222)  
Sulphuric acid (for pH-adjustment)  
Water for injection

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products.

### **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**

2 ml flint glass Type 1 vial 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.

## **7 MARKETING AUTHORISATION HOLDER**

Bristol-Myers Squibb Holdings Ltd  
t/a Bristol-Myers Pharmaceuticals  
Swords  
Co. Dublin

## **8 MARKETING AUTHORISATION NUMBER**

PA 0048/004/006

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 15<sup>th</sup> July 1976

Date of last renewal: 15<sup>th</sup> July 2006

## **10 DATE OF REVISION OF THE TEXT**

August 2006