

**SUMMARY OF PRODUCT CHARACTERISTICS**  
**ORLOBIN®**  
(amikacin sulfate)

**1. Name of the medicinal product**

**ORLOBIN 500 mg/2ml SOLUTION FOR INJECTION/INFUSION**

**2. Qualitative and quantitative composition**

Orlobin 500 mg/2ml solution for injection/infusion: Each vial contains in 2 mL amikacin sulfate equivalent to amikacin activity 500 mg. Excipient with known effect: Each vial contains 13.2 mg sodium bisulphite (E223).

For the full list of excipients, see section 6.1.

**3. Pharmaceutical form**

Solution for injection/infusion.

Colorless to yellowish, practically free of particles, aqueous solution.

**4. Clinical particulars**

**4.1 Therapeutic indications**

Amikacin sulfate 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*.

Orlobin is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria. It may also be indicated for the treatment of known or suspected staphylococcal disease.

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, either slow bolus (2 to 3 minutes) or infusion (0.25% over 30 minutes) may be used.

#### Intramuscular and intravenous administration

Amikacin sulfate solution for injection/infusion may be given intramuscularly or intravenously.

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 solution for injection/infusion 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  $\geq 50$  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 100mL or 200mL of sterile diluent such as normal saline or 5% dextrose in water or any other compatible solution. 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 alkalinising 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.

<b>Serum Creatinine Concentration (mg/100mL)</b>		<b>Interval between AMIKACIN doses of 7.5 mg/kg/IM (hours)</b>
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 solution for injection/infusion 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 =

$$\frac{(\text{observed CrCl in mL/min} \times \text{calculated loading dose in mg})}{\text{normal CrCl in mL/min}}$$

(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.

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

#### Intraperitoneal use

Following exploration for established peritonitis, or after peritoneal contamination due to faecal spill during surgery, Orlobin may be used as an irrigant after recovery from anaesthesia in concentrations of 0.25% (2.5 mg/mL).

#### Other routes of administration

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

### **4.3 Contraindications**

Myasthenia gravis.

Amikacin sulfate solution for injection/infusion 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 aminoglycoside 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.

## **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.

Patients with mitochondrial DNA mutations, particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene may be at higher risk for ototoxicity, even if the patient's aminoglycoside serum levels were within the recommended range. In case of family history of aminoglycoside-induced deafness or known mitochondrial DNA mutations in the 12S rRNA gene, alternative treatments other than aminoglycosides should be considered.

## **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.

Amikacin must not be used in patients with Myasthenia Gravis. Aminoglycosides should be used with caution in patients with muscular disorders such as parkinsonism, since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

## **Renal toxicity**

Aminoglycosides are potentially nephrotoxic. Renal toxicity is independent of plasma obtained at the peak (C<sub>max</sub>). 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 solution for injection/infusion in vials contains sodium bisulphite (E223), a sulphite 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 sulphite sensitivity in the general population is uncommon and probably low. Sulphite sensitivity is seen more frequently in asthmatic than in non-asthmatic subjects.

### **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 nonsusceptible organisms. If this occurs, appropriate therapy should be instituted.

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.

Macular infarction sometimes leading to permanent loss of vision has been reported following intravitreal 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.

The intraperitoneal use of amikacin is not recommended in young children.

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

Concurrent or serial use with other neurotoxic, 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 potential for 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. Where this is not possible, monitor carefully. The risk of ototoxicity is increased when amikacin is used in conjunction with rapidly acting diuretic drugs, particularly when the diuretic is administered intravenously. Diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Such agents include furosemide and ethacrynic acid which is itself an ototoxic agent. 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.

Concomitantly administered thiamine (vitamin B1) may be destroyed by the reactive sodium bisulphite 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 ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1000$ ,  $< 1/100$ ), rare ( $\geq 1/10000$ ,  $< 1/1000$ ), very rare ( $< 1/10000$ ), and not known (cannot be estimated from the available data).

<b>System Organ Class</b>	<b>Frequency</b>	<b>MedDRA Term</b>
<i>Infections and infestations</i>	Uncommon	Superinfections or colonisation with resistant bacteria or yeast <sup>a</sup>
<i>Blood and lymphatic system disorders</i>	Rare	Anaemia, eosinophilia

<i>Immune system disorders</i>	Not known	Anaphylactic response (anaphylactic reaction, anaphylactic shock and anaphylactoid reaction), hypersensitivity
<i>Metabolism and nutrition disorders</i>	Rare	Hypomagnesaemia
<i>Nervous system disorders</i>	Not known	Paralysis <sup>a</sup>
	Rare	Tremor <sup>a</sup> , paresthesia <sup>a</sup> , headache, balance disorder <sup>a</sup>
<i>Eye disorders</i>	Rare	Blindness <sup>b</sup> , retinal infarction <sup>b</sup>
<i>Ear and labyrinth disorders</i>	Rare	Tinnitus <sup>a</sup> , hypoacusis <sup>a</sup>
	Not known	Deafness <sup>a</sup> , deafness neurosensory <sup>a</sup>
<i>Vascular disorders</i>	Rare	Hypotension
<i>Respiratory, thoracic and mediastinal disorders</i>	Not known	Apnoea, bronchospasm
<i>Gastrointestinal disorders</i>	Uncommon	Nausea, vomiting
<i>Skin and subcutaneous tissue disorders</i>	Uncommon	Rash
	Rare	Pruritus, urticaria
<i>Musculoskeletal, connective tissue and bone disorders</i>	Rare	Arthralgia, muscle twitching <sup>a</sup>
<i>Renal and urinary disorders</i>	Not known	Renal failure acute, nephropathy toxic, cells in urine <sup>a</sup>
	Rare	Oliguria <sup>a</sup> , blood creatinine increased <sup>a</sup> , albuminuria <sup>a</sup> , azotemia <sup>a</sup> , red blood cells urine <sup>a</sup> , white blood cells urine <sup>a</sup>
<i>General disorders and administration site conditions</i>	Rare	Pyrexia

<sup>a</sup> See section 4.4.

<sup>b</sup> Amikacin is not formulated for intravitreal use. Blindness and retinal infarction have been reported following intravitreal 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).

### **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.

## 4.9 Overdose

In case of overdosage there is a general risk for nephro-, oto- and neurotoxic (neuromuscular blockage) reactions. Neuromuscular blockage with respiratory arrest needs appropriate treatment including application of ionic calcium (e.g. as gluconate or 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 sulfate 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

Amikacin 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.

Amikacin 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. Amikacin 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 birth weights (<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 bisulphite (E223), sodium citrate, sulphuric acid, water for injection.

### **6.2 Incompatibilities**

None.

### **6.3 Shelf life**

ORLOBIN 500mg/2ml:

36 months

### **6.4 Special precautions for storage**

Do not store above 25°C.

### **6.5 Nature and contents of container**

Orlobin 500mg/2ml: Carton box which contains 1 vial with 2ml of solution for injection/infusion amikacin (as amikacin sulfate).

\*Some concentrations or/and pack sizes may not be marketed.

### **6.6 Special precautions for disposal and other handling**

For single use only, discard any unused solution.  
Parenteral 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.

**7. Marketing authorisation holder**

MEDICUS S.A., 10 Valaoritou St., GR 144 52 Metamorfosi, Attiki, Greece,  
T: +30 210 284 7818

**8. Marketing authorisation number(s)**

Orlobin 500 mg/2ml: 14427/22-11-2016

**9. Date of first authorisation/renewal of the authorisation**

Orlobin 500 mg/2ml: 19-1-1980/27-05-2011

**10. Date of revision of the text**

November 2022