<table>
<thead>
<tr>
<th>Core Safety Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active substance:</strong></td>
</tr>
<tr>
<td><strong>Pharmaceutical form(s)/strength:</strong></td>
</tr>
<tr>
<td><strong>P-RMS:</strong></td>
</tr>
<tr>
<td><strong>Date of FAR:</strong></td>
</tr>
</tbody>
</table>
4.3 Contraindications

Amikacin sulfate injection is contraindicated in patients with known allergy to amikacin or any component of the formulation.

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.

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 of treatment, even in healthy patients. 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.

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 such as tubocurarine, succinylcholine, decamethonium, or in patients receiving massive transfusions of citrate-anticoagulated blood (see section 4.5). 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 bisulfite, a sulfite that may cause
allergic-type reactions including anaphylactic symptoms and life-threatening or less severe
asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity
in the general population is uncommon and probably low. Sulfite sensitivity is seen more
frequently in asthmatic than in nonasthmatic 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 intravitreous administration (injection into the eye) of amikacin.

4.5 Interaction with other medicinal products and other forms of interaction

The concurrent or serial use of other neurotoxic, ototoxic or nephrotoxic agents, particularly bacitracin, cisplatin, amphotericin B, 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.

The concurrent use of amikacin sulfate injection with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

*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 bisulfite component of the amikacin sulfate formulation.

Indomethacin may increase the plasma concentration of amikacin in neonates.

*In patients receiving anesthetics, neuromuscular blocking agents, such as tubocurarine succinylcholine, decamethonium, atracurium, rocuronium, vecuronium or in patients receiving massive transfusions of citrate-anticoagulated blood there is risk of respiratory paralysis.*

4.6 Fertility, pregnancy and lactation

**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 newborn have not been reported in pregnant women treated with other aminoglycosides, the potential for harm exists. *In reproduction toxicity studies in mice and rats, no effects on fertility or foetal toxicity*
were reported. 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.

**Lactation**
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.

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

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

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).

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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>MedDRA Term</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>Uncommon</td>
<td>Superinfections or colonisation with resistant bacteria or yeast&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>Rare</td>
<td>Anaemia, eosinophilia</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Not known</td>
<td>Anaphylactic response (anaphylactic reaction, anaphylactic shock and anaphylactoid reaction), hypersensitivity</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Rare</td>
<td>Hypomagnesaemia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Not known</td>
<td>Paralysis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Tremor&lt;sup&gt;a&lt;/sup&gt;, paresthesia&lt;sup&gt;a&lt;/sup&gt;, headache, balance disorder&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Rare</td>
<td>Blindness&lt;sup&gt;b&lt;/sup&gt;, retinal infarction&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>Rare</td>
<td>Tinnitus&lt;sup&gt;a&lt;/sup&gt;, hypoacusis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Deafness&lt;sup&gt;a&lt;/sup&gt;, deafness neurosensory&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Rare</td>
<td>Hypotension</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Not known</td>
<td>Apnoea, bronchospasm</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Uncommon</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous</strong></td>
<td>Uncommon</td>
<td>Rash</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>MedDRA Term</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>tissue disorders</td>
<td>Rare</td>
<td>Pruritus, urticaria</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Rare</td>
<td>Arthralgia, muscle twitching&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Not known</td>
<td>Renal failure acute, nephropathy toxic, cells in urine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Oliguria&lt;sup&gt;a&lt;/sup&gt;, blood creatinine increased&lt;sup&gt;a&lt;/sup&gt;, albuminuria&lt;sup&gt;a&lt;/sup&gt;, azotemia&lt;sup&gt;a&lt;/sup&gt;, red blood cells urine&lt;sup&gt;a&lt;/sup&gt;, white blood cells urine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Rare</td>
<td>Pyrexia</td>
</tr>
</tbody>
</table>

<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 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.

4.9 Overdose

In case of overdosage there is a general risk for nephro-, oto- and neurotoxic (neuromuscular blockade) reactions. Neuromuscular blockade 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 hemodialysis 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.