**Definition of Medication Error**

An error in prescribing, dispensing or administering of a drug, irrespective of whether such errors lead to adverse consequences or not [1–5].

Parenteral medication errors are a serious safety problem in Intensive Care Units (ICU) and are recognized as a high priority health care issue [6–8]. Errors have been shown to be associated with additional morbidity and mortality in an already critically ill population [9]. In their recently published multinational, observational and cross sectional study, Valentin et al. demonstrated that parenteral medication errors represent a common pattern across national borders, different ICU-settings and health care systems [10]. The Institute of Medicine estimated that in hospitals “a typical patient would be subject to one administration medication error per day” [11].
Medication errors are more common than adverse drug events, but result in harm less than 1% of the time. About 25% of adverse drug events are due to medication errors [13], shown in the green area at Fig. 1 in the right.

<table>
<thead>
<tr>
<th>Term</th>
<th>Description*</th>
<th>Example [13]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harm is incurred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event (AE)</td>
<td>Harm in a patient administered a drug but not necessarily caused by a drug [12]</td>
<td>Traumatic death while taking lovastatin</td>
</tr>
<tr>
<td>Adverse Drug Reaction (ADR)</td>
<td>Harm directly caused by a drug at normal doses [12]</td>
<td>Congestive heart failure from metoprolol</td>
</tr>
<tr>
<td>Adverse Drug Event (ADE)</td>
<td>Harm caused by the use of a drug [14,15]</td>
<td>Hematoma from tirofiban overdose</td>
</tr>
<tr>
<td>Harm may be incurred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication Error</td>
<td>Error in prescribing, dispensing or administering of a drug, irrespective of whether such errors lead to adverse consequences or not [1-5]</td>
<td>Failure to renew prednisolone order on transfer to medical ward</td>
</tr>
<tr>
<td>Harm is not incurred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential Adverse Drug Event</td>
<td>Circumstances that could potentially result in harm by the use of a drug but did not in fact harm the patient [13]</td>
<td>Receipt of another patient’s felodipine but no resulting hypotension</td>
</tr>
</tbody>
</table>

*Descriptions are abstracted from cited sources. See original text for definitions.

Tab. 1: Relevant definitions.

Fig. 1: Relationship of key terms.
Medication Error

Causes
The majority of medication errors do not occur in emergency situations but while performing routine clinical tasks [10]. The source of these errors can lie at any stage of the process from the initial prescription of an infusion to its administration [16]. This is a complex process [17] and can lead to a wide range of different errors [18-23] (Fig. 2).

Sources of Medication Error

One of the reasons adverse events are so common is that clinicians are human, and thus prone to error. The seminal study by Wilson et al. [24] found that human error was a significant factor. The majority (81%) of adverse events in their study were associated with one or more human factors, such as lack of knowledge, care or attention. Of the events that were considered highly preventable, less than 1% were not associated with human error. Other studies have also found human error to be a key factor contributing to adverse events [25–29].

Fig. 2: Sources of risks, that can lead to medication error.
Common examples which lead to Medication Error

Storage of different drugs, such as high alert drugs (KCl) and standard solution (NaCl) next to one other.

Same size – different scales.

Look alike / sound alike drug labels and names.

Two main causes increase the incidence of Medication Error [10]:

- nurse's workload (patient to nurse ratio, occupancy rate, ratio of beds per nurse)
- size of unit (complexity of organisation)
Consequences

Nearly all medication errors lead to a wrong dose of the drug (Tab. 2). Either the patient gets too much or too little of the prescribed dose. Wrong transcription and incorrect labeling can both lead to much more severe consequences than simply a wrong drug dose. These errors can lead to a mix-up of patients or a mix-up of the prescribed drug, to a wrong application route, a wrong time for application, omission of the drug or even to side effects or infections.

Tab. 2: Causes of medication error and resulting medication incident types.
Since the early 70s more and more studies of the quantity of parenteral medication errors have been published [30]. The National Patient Safety Agency in the United Kingdom has compiled figures showing the type of medication error incidents that actually occur (Fig. 3). More than 14,000 injectable medicine incident reports during 18 months were evaluated [31]. It was found that in more than 4,107 cases (28.9% of total) the most frequent medication error was wrong dose, strength or frequency of the prescribed drug.

Fig. 3: Percentage of medication incident type [31].
Consequences

Costs
The financial costs of adverse events, in terms of additional treatment and extra days in hospitals, are considerable. One of the most consistent findings from the record reviews is that, on average, a patient suffering an adverse event stays an extra six to eight days in the hospital. When the sums are done and the findings extrapolated nationally the costs are staggering [32].

In Britain, the cost of preventable adverse events is £1 billion per annum in lost bed days alone [33]. The wider costs of lost working time, disability benefits and further economic consequences are greater still.

The US Institute of Medicine report estimated that preventable medical errors result in total costs (including the expense of additional care caused by the errors, lost income, household productivity, and disability) of between $17 billion and $29 billion per year in US hospitals [34].

Research in Australia showed that total costs of adverse events represent 15.7% of the total expenditure on direct hospital costs [35].

Other significant damages associated with adverse events are the human ones: the harm suffered by the patient. Patients experiencing an adverse event are 4-7 times more likely to die than those who do not [35]. Vincent et al. [32] found that 19% of adverse events result in moderate physical impairment, 6% in permanent impairment and 8% in death.
Fig. 4: Estimation of possible additional costs as a consequence of complications caused by medication error. In order to facilitate the attribution of each complication to the cost calculation, severity levels [Dean & Barber Scale 1] were introduced.

**Financial impact**

Adverse effects of medication error extend periods of patients' hospitalization and the total costs for hospitals.

Severe complications caused by medication error may lead to an additional cost for the healthcare provider of up to € 56,670 per single case.

**Risk related costs for the healthcare institution**

A cost evaluation of the risk can be done by assigning costs to their related clinical treatment and resulting extended length of stay. The cost can be calculated using the average daily cost [Gianino 2007, Bertolini 2005] of the expected clinical treatment. Fig. 4 shows the results of such a calculation for selected examples of complications.

**Conclusion**

The prevention of medication error can result in budget savings for the healthcare provider. In the case of severe complications which require full ICU treatment for diverse days of hospitalization, a hospital may save between € 7,556 and € 56,670 per single case.
Medication Error

Preventive strategies

To prevent medication error and effectively ensure safe patient treatment it is important to combine product and organizational measures.

The more successive safety checks that are added, the safer the whole system becomes. Some concrete preventive strategies to implement in clinical routine are described in Fig. 5.

It must be the aim of every employee in the healthcare sector, to ensure the 9 “Rights” shown in the green box at the far right.

Fig. 5: Examples to prevent medication error.
Medication Error
Preventive strategies

**Prevention**
- Right patient
- Right drug
- Right route
- Right time
- Right dose
- Right documentation
- Right action
- Right form
- Right response

Ward-based clinical pharmacists [46,47]

**Product Measures**

Barcode / Data Matrix to handle preparation data and close the loop to patient [10]

IV pumps with intuitive handling and integrated drug database [10,41-43]

**Organizational Measures**

Fig. 5: Examples to prevent medication error.
Medication Error

**Risk prevention**

### Pharmaceuticals

**Ready-to-use Drugs in Ecoflac® plus**
- B. Braun premixed drugs are ready for direct and convenient infusion.
- Reduced medication preparation steps and time.
- Reduced risk of medication error through higher accuracy of dosing.

**NuTRiflex® System**
- The NuTRiflex® System is the "ready-to-infuse" multi-chamber bag system for Total Parenteral Nutrition (TPN).
- It combines convenience with safety.
  - Reduced medication preparation steps and time vs. compounded products.
  - Latex, DEHP and PVC free.

**Mini-Plasco®**
- Mini-Plasco® is a family of small volume parenteral containers, which helps reducing medication errors through
  - Haptic differentiation based on a variety of container shapes.
  - Visual differentiation based on its safety labeling concept.

**Label Concept**
- B. Braun pharma products provide maximum protection against medication error based on an integrated labeling concept.
- Effective differentiation between solution and medication categories is achieved through colors and extra large text for relevant information.

**Ecoflac® plus**
- Drug adsorption to PVC can cause wrong dosaging and as consequence thereof medication error and additional costs.
- Ecoflac® plus is produced from a medical grade polyethylene. This polymer is chemically inert and toxicologically safe, free from plasticizers, additives and other compounds that may potentially migrate into the finished preparation.
Intrafix® SafeSet
The new roller clamp for IV administration sets: the infusion better under control – provides more accurate flow rate with less difficulty.
Eases the selection of drop rates – even the "KVO"-rate – with a finer, more flexible control of flow rates. The new design contributes to patient safety by means of more precision and flow stability.

B. Braun Space
Space Online Suite allows the networking of infusion pumps to:
- Review the dose overrides and corrections to improve clinical practice.
- Keep the drug lists in all pumps up-to-date by central drug library upload.
B. Braun Space infusion pumps have an integrated drug library to be edited by the hospital. It allows:
- Choosing drugs from a drug list to reduce typing errors.
- Programming dose limits to reduce dose errors.
B. Braun Space GlucoseControl realizes safe and reliable glucose levels in critically ill patients with a significantly reduced risk of hyper- and hypoglycemia.
- Intelligent dosage algorithm.
- Integrates enteral and parenteral nutrition and exactly determines insulin rate and next sampling time.

Certofix® Multilumen Catheters
Multilumen catheters prevent medication error by reducing drug incompatibilities through:
- Separate colour-coded lumens (distal, middle, proximal) prevents the mixing of solutions and drugs.
- Separate outlets ensure an immediate dilution of the individual solution / drug by the blood stream thereby preventing incompatibility reactions.

ConComp®
Free database on drugs compatible with Ecoflac® plus.
- Offers information on interactions between certain drugs, carrier solutions and container materials.
- Offers overview of scientific literature on drug incompatibility with the container.
Medication Error

Literature


Literature


**NuTRIflex® Lipid**

**Composition**

NutriFlex® Lipid (mixed and ready for use 1250 ml)

**Active ingredients**

<table>
<thead>
<tr>
<th>NuTRIflex® Lipid peri plus</th>
<th>plus without electrolytes</th>
<th>special</th>
<th>special without electrolytes</th>
</tr>
</thead>
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<tr>
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<td>2.82 g</td>
<td>4.10 g</td>
</tr>
<tr>
<td>Leucine 3.13 g</td>
<td>3.76 g</td>
<td>3.76 g</td>
<td>5.48 g</td>
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<tr>
<td>Lysine, hydrochloride 2.84 g</td>
<td>3.41 g</td>
<td>-</td>
<td>4.975 g</td>
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<td>Lysine 2.26 g</td>
<td>2.73 g</td>
<td>-</td>
<td>3.98 g</td>
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<td>2.35 g</td>
<td>2.35 g</td>
<td>3.42 g</td>
</tr>
<tr>
<td>Phenylalanine 3.51 g</td>
<td>4.21 g</td>
<td>4.21 g</td>
<td>6.145 g</td>
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<tr>
<td>Threonine 1.82 g</td>
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<td>2.18 g</td>
<td>3.175 g</td>
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<td>0.68 g</td>
<td>1.00 g</td>
</tr>
<tr>
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<td>3.24 g</td>
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<td>-</td>
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<td></td>
<td></td>
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<tr>
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<td>8.49 g</td>
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<td>1.98 g</td>
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</tr>
<tr>
<td>Glucose monoacetate acid</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Proline 3.40 g</td>
<td>4.08 g</td>
<td>4.08 g</td>
<td>5.95 g</td>
</tr>
<tr>
<td>Serine 3.00 g</td>
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<td>3.60 g</td>
<td>5.25 g</td>
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<tr>
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<td>165.0 g</td>
<td>165.0 g</td>
<td>198.0 g</td>
</tr>
<tr>
<td>Nonprotein 80.0 g</td>
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<td>150.0 g</td>
<td>180.0 g</td>
</tr>
<tr>
<td>Soya bean oil 25.0 g</td>
<td>25.0 g</td>
<td>25.0 g</td>
<td>25.0 g</td>
</tr>
<tr>
<td>Medium chain triglycerides</td>
<td>25.0 g</td>
<td>25.0 g</td>
<td>25.0 g</td>
</tr>
</tbody>
</table>

**Indications**

When oral or enteral feeding is not possible, insufficient or contraindicated.

**Contraindications**

Acute shock, acute phase of myocardial and cerebral infarction, severe disorders of blood coagulation, acute thrombo-embolism or fat embolism, irreversible liver damage, intrahepatic cholestasis, severe uraemia when dialysis facilities are not available, disorders of lipid metabolism such as pathological hyperlipaemia and conditions associated with triglyceride accumulation during parenteral nutrition, inborn errors of amino acid metabolism, untreated or complicated diabetes mellitus, especially in the presence of coma related to keto-acidosis or diabetic precama.

**Precautions**

Give with caution in conditions of impaired lipid metabolism as in renal insufficiency, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (if hypertriglyceridemic), sepsis and in conditions of altered amino acid metabolism.

As with other solutions containing glucose, administration of NuTRIflex® Lipid formulations may lead to hyperglycaemia. Blood glucose levels should be monitored and the rate of infusion adjusted or insulin should be administered if hyperglycaemia occurs.

The patient’s capacity to eliminate the infused fat from the circulation should be monitored. Especially where the product is administered for extended periods of time, the patient’s haemogram, blood coagulation, liver function, and platelet count should be regularly monitored.

In patients suspected to have disorders of fat metabolism, fasting lipaemia should be excluded. In the case of fasting hypertriglyceridaemia the administration of fat is contraindicated. Likewise, hypertriglyceridaemia 12 hours after fat infusion indicates disorders of fat metabolism.

Fluid, electrolyte, and acid-base balance should be monitored.

As with all parenteral solutions administered through a peripheral/central venous route.
Immediate (acute) reactions related to the lipid are dyspnoea, cyanosis, allergic reactions, hyperlipaemia, hypercoagulability of the blood, nausea, vomiting, headache, flushing, hyperthermia, sweating, chills, sleepiness, chest and back pain. The infusion should be stopped in these cases. The infusion can be resumed after the disappearance of the symptoms and/or the elevated serum triglyceride levels with reduced dose and/or reduced infusion rate. Close monitoring of the patient’s general condition and higher plasma triglyceride levels is recommended.

Subject to medical prescription.

B. Braun Melsungen AG
34209 Melsungen, Germany

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**Nutriflex®**

**Composition**

Nutriflex® (mixed and ready for use 1000 ml)

**Active ingredients**

<table>
<thead>
<tr>
<th>Nutriflex®</th>
<th>peri (40/80)</th>
<th>basal (32/125)</th>
<th>plus (48/150)</th>
<th>special (70/240)</th>
</tr>
</thead>
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<tr>
<td>L-isoleucine</td>
<td>2.34 g</td>
<td>1.88 g</td>
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<td>2.84 g</td>
<td>2.27 g</td>
<td>3.41 g</td>
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<tr>
<td>(equivalent to L-lysine)</td>
<td>2.27 g</td>
<td>1.82 g</td>
<td>2.73 g</td>
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<td>1.96 g</td>
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<td>(equivalent to Arginine)</td>
<td>2.70 g</td>
<td>2.16 g</td>
<td>3.24 g</td>
<td>4.73 g</td>
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<tr>
<td>and to Glutamic acid</td>
<td>2.28 g</td>
<td>1.82 g</td>
<td>2.74 g</td>
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<td>L-histidine · HCl · H2O</td>
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<td>1.35 g</td>
<td>2.03 g</td>
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<td>(equivalent to Histidine)</td>
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<td>1.00 g</td>
<td>1.50 g</td>
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<td>L-alanine</td>
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<td>3.88 g</td>
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<td>(equivalent to anhydrous glucose)</td>
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<tr>
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<td>–</td>
<td>–</td>
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<td>Potassium dihydrogen phosphate</td>
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<td>0.50 g</td>
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<tr>
<td>Water for injections to</td>
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<td>1000 ml</td>
<td>1000 ml</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>

**Nutriflex®**

<table>
<thead>
<tr>
<th>Nutriflex®</th>
<th>peri (40/80)</th>
<th>basal (32/125)</th>
<th>plus (48/150)</th>
<th>special (70/240)</th>
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</thead>
<tbody>
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<td>Total amino acids (g/l)</td>
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<td>70</td>
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<td>Total nitrogen (g/l)</td>
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<td>Total carbohydrates (g/l)</td>
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<td>150</td>
<td>240</td>
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<tr>
<td>Total energy kJ/l</td>
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<td>2640</td>
<td>3310</td>
<td>5190</td>
</tr>
<tr>
<td>(kcal/l)</td>
<td>480</td>
<td>630</td>
<td>790</td>
<td>1240</td>
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<td>Non-protein energy kJ/l</td>
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<td>2090</td>
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<td>(kcal/l)</td>
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<td>600</td>
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<td>Mg++</td>
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<tr>
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<tr>
<td>Acetate</td>
<td>19.5</td>
<td>35.0</td>
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<td>22.0</td>
</tr>
</tbody>
</table>

**Nutriflex®**

**Contraindications**

Nutriflex® is contraindicated in cases of hyperglycaemia, disorders of amino acid metabolism, manifest congestive cardiac failure, untreated shock, overhydration, enhanced plasma potassium levels, acidosis. In hepatic or renal insufficiency the dosage is to be individually adjusted. Because of the specific composition of the nutrients the use of Nutriflex® in newborns, infants and children up to the 2nd year of life is not recommended.

**Precautions**

Serum ionogram, water balance, blood glucose levels and acid-base balance are to be monitored. Possible intolerance reactions (nausea, vomiting, chills) and renal loss of glucose and amino acids with subsequent amino acid imbalances are due to a too rapid infusion rate.

**Adverse reactions**

Adverse reactions are not to be expected, and besides have not been reported so far, if contraindications, dosage recommendations, warnings and precautions are observed.

Subject to sale by pharmacists only.

B. Braun Melsungen AG
34209 Melsungen, Germany
Gentamicin

B. Braun 1mg/ml solution for infusion, B. Braun 3mg/ml solution for infusion

Prescribing information

Composition

Gentamicin 1 mg/ml: 1 ml of solution contains 1 mg of gentamicin, as gentamicin sulphate. 1 polyethylene bottle of 80 ml contains 80 mg of gentamicin.

Gentamicin 3 mg/ml: 1 ml of solution contains 3 mg of gentamicin, as gentamicin sulphate. 1 polyethylene bottle of 80 ml contains 240 mg of gentamicin. 1 polyethylene bottle of 120 ml contains 360 mg of gentamicin.

Indications: Treatment of severe infections due to bacteria susceptible to gentamicin.

Gentamicin 1 mg/ml and 3 mg/ml may be used for the treatment of:
- Complicated and recurrent urinary tract infections
- Meningoencephalitis respiratory tract infections including severe pneumonia
- Intra-abdominal infections including peritonitis
- Skin and soft tissue infections including severe burns
- Bone infections including joints
- Central nervous system infections including meningitis
- Septis including bacteraemia and neonatal sepsis
- Bacterial endocarditis
- Surgical infections

Contraindications: Hypersensitivity to gentamicin or other aminoglycosides or to any of the excipients.

Undesirable effects

Infections and infestations: Superinfection (with gentamicin-resistant germs)

Blood and lymphatic system: Thrombocytopenia, reticulocytopenia, leukopenia, eosinophilia, granulocytopenia, anemia, dyscrasias

Immune system: Hypersensitivity reactions of varying degrees of severity

Metabolism and nutrition disorders: Hypokalaemia, Hypocalcaemia, Hypomagnesaemia, loss of appetite

Psychiatric disorders: Confusion, hallucinations, mental depression

Nervous system: Polyneuropathies, peripheral paraesthesia, encephalopathy, convulsions, neuromuscular blockade, dizziness, vertigo, equilibrium disorder, headache

Ear and labyrinth disorders: Vestibular damage, hearing loss, Menière’s disease, tinnitus

Gastrointestinal disorders: Nausea, vomiting, hiccups, constipation, dry mouth

Skin and subcutaneous tissue disorders: Allergic skin exanthema, skin reddening

Musculoskeletal, connective tissue and bone disorders: Myalgia

Renal and urinary tract disorders: Renal function impairment, very rarely up to acute renal failure

General disorders, administration site conditions: Increased body temperature, weight loss, pain at injection site

Laboratory findings: Elevated values of SGOT, SGPT, alkaline phosphatase, blood urea nitrogen

Warnings/Precautions

In patients with advanced renal impairment or with pre-existing inner ear deafness, Gentamicin 1 mg/ml and 3 mg/ml should be used only if its use is considered essential by the physician. The frequency or dose of administration should be reduced in patients with impaired renal function. Since gentamicin has neuromuscular blocking properties, particular caution should be exercised in patients with pre-existing neuromuscular diseases (e.g. myasthenia gravis, Parkinson’s disease). This also applies to patients concurrently receiving muscle relaxants (e.g. in the perioperative administration of gentamicin). Cross resistance and hypersensitivity to aminoglycosides may occur. To reduce the risk of particularly nephrotoxic and ototoxic undesired effects, obey the following instructions:

- Monitor renal function before, during and after treatment.
- Adjust dosage strictly according to creatinine clearance (or serum creatinine concentration). In patients with impaired renal function, adjust the dosage according to renal performance.

- In patients with impaired renal function, take into account locally administered gentamicin (by inhalation, intratracheal instillation) when determining the dose for systemic administration.
- Monitor serum gentamicin concentrations during therapy in all problematic treatments.
- In patients with pre-existing inner ear damage (hearing impairment or balance function impairment), or where treatment is long-term, additional monitoring of the balance function and hearing is required.
- Therapy should be limited to 10 - 14 days (usually 7 - 10 days).
- Avoid therapy with aminoglycosides immediately subsequent to previous aminoglycoside treatment; if possible, there should be an interval of 7 - 14 days between treatments.
- If possible, avoid concurrent administration of other potentially ototoxic and/or nephrotoxic substances. If this is unavoidable, particular careful monitoring of renal function and hearing is mandatory.
- Ensure adequate hydration and urine production.

Interactions

Enhancement or even potentiation of the ototoxic or nephrotoxic effect must be considered when gentamicin is given concurrently with other substances having similar effects, such as amphotericin B, colistin, ciclosporin, cisplatin, vancomycin, and loop diuretics such as ethacrynic acid and furosemide. In particular, there is risk of severe kidney damage when performing anaesthesia with methoxyflurane in patients being treated with gentamicin. The neuromuscular blocking activity of aminoglycosides is enhanced by ether and muscle relaxants. In particular, if gentamicin is administered during or immediately after surgery, the neuromuscular blockade may be enhanced and prolonged if non-depolarising muscle relaxants are used.

Pregnancy

Administration should be restricted to cases where the indication is imperative.

Lactation:

Gentamicin is excreted in small quantities in breast milk. There is a risk that the infant’s intestinal flora is changed after ingestion of gentamicin with breast milk. Discontinuing breast-feeding during treatment or choosing a safer alternative treatment should be considered.

Effect on ability to drive/use machines:

Gentamicin may lead to dizziness or vertigo and may thus negatively influence the patient’s ability to drive or to use machines.

Keep out of the reach and sight of children.

For prescription only!

Date of first authorization/renewal of the authorization:
Marketing authorization holder:
B. Braun Melsungen AG
34200 Melsungen, Germany
**Tobramycin**

B. Braun 1 mg/ml solution for infusion, B. Braun 3 mg/ml solution for infusion.

**Prescribing information**

**Composition**

Tobramycin 1 mg/ml: 1 ml of solution contains 1 mg of tobramycin. 1 bottle of 80 ml contains 80 mg of tobramycin.

Tobramycin 3 mg/ml: 1 ml of solution contains 3 mg of tobramycin. 1 bottle of 80 ml contains 240 mg of tobramycin. 1 bottle of 120 ml contains 360 mg of tobramycin.

**Indications:** Treatment of severe infections due to bacteria susceptible to tobramycin. Tobramycin 1 mg/ml and 3 mg/ml solution for infusion may be used in: Septic disorders, Lower respiratory tract infections, Infections of the urinary organs, Intra-abdominal infections, Skin, soft tissue and bone infections, including burnwound infections, Bacterial endocarditis, Central nervous system infections including meningitis.

**Contraindications:** Hypersensitivity to tobramycin or other aminoglycosides or to any of the excipients.

**Undesirable effects**

Under certain conditions tobramycin shows ototoxic and/or nephrotoxic effects. Renal impairment is uncommonly observed in patients treated with tobramycin and is usually reversible upon withdrawal of the drug. Toxicity occurs more frequently in persons with renal failure, in patients that have other ototoxic or nephrotoxic substances administered, in long-term and recurrent treatment and/or in persons that exceed the recommended dose. Ototoxic risk may increase with older age and dehydration.

**Warnings/Precautions**

Due to the nephrotoxic and ototoxic potential of aminoglycosides, patients should be kept under close clinical observation during treatment. When possible, it is recommended to obtain serial audiograms in patients old enough to be tested, particularly high-risk patients. Monitoring of renal function and eighth cranial nerve function is essential in the case of proven or suspected renal impairment and also in those whose renal function is initially normal but who present with signs of renal dysfunction during treatment. Serum concentrations of the drug should be monitored during treatment whenever possible. It is particularly important to monitor serum levels closely in patients with known renal impairment. Trough serum concentrations of more than 2 micrograms/ml may indicate accumulation in tissue and must be avoided by either dose reduction or by increasing the interval between the doses. Maximum serum concentrations of more than 12 micrograms/ml over a longer period of time can be associated with toxic effects and should be avoided. Urine should be examined for increased excretion of protein, cells and casts. Serum creatinine or creatinine clearance should be measured periodically. When possible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Serum calcium, magnesium and sodium should be monitored. The risk of toxic reactions is greater for patients with impaired renal function, the elderly, dehydrated patients and those patients on high-dose- and long-term treatment and repeated courses of treatment. Caution is advised in patients with vestibular or cochlear abnormalities. Association of tobramycin with very potent diuretics or in general with any ototoxic or nephrotoxic substance should be avoided. Signs of nephrotoxicity or ototoxicity require dose adjustment or discontinuation of the drug. Neurovascular blockade and respiratory paralysis have been reported in animals after dosages several times higher than the recommended dose. The possibility of such reactions occurring in humans cannot be excluded, and particularly where the drug is administered to patients receiving neuromuscular blockers, anesthetic or massive transfusions of citrate-anticoagulated blood. If neuromuscular blockade occurs, it can be reversed by the administration of calcium salts. Due to the neuromuscular blocking effects, aminoglycosides should be used with caution in patients with neuromuscular disorders, e.g. myasthenia gravis or parkinsonism. In patients with extensive burn injuries, the phamacokinetics of aminoglycosides may be altered and may result in reduced serum concentrations. It is important to monitor serum concentrations. It is important that patients being treated with aminoglycosides be well-hydrated during treatment. Aminoglycosides may be absorbed in significant quantities from body surfaces for local irrigation or application and may cause neuotoxicity and nephrotoxicity. This must also be taken into account in the total dosage in concurrent systemic administration. Tobramycin must be administered with caution to premature babies and in neonates because of their renal immaturity; this results in a lengthening of the serum half-life of the product.

**For prescription only!**

**Date of first authorization/renewal of the authorization:**

**Marketing authorization holder:**

B. Braun Melsungen AG
34209 Melsungen, Germany

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0.9% w/v Sodium Chloride Intravenous Infusion

**Pharmaceutical form**

Solution for infusion

**Composition**

1000 ml of solution contains

- Sodium Chloride: 9.0 g
- Excipients:

**Water for Injections**

**Electrolyte concentrations:**

- Sodium: 154 mmol/l
- Chloride: 154 mmol/l
- Theoretical osmolarity: 308 mOsm/l
- Titration acidity (to pH 7.4): < 0.3 mmol/l
- pH: 4.5 - 7.0

**Indications**

- Fluid and electrolyte substitution in hypochloremic alkalosis;
- Chloride losses;
- Short-term intravascular volume substitution;
- Hypotonic dehydration;
- Isotonic dehydration;
- Vehicle solution for compatible electrolyte concentrates and medicaments;
- Externally for wound irrigation and moistening of wound dressings.

**Contraindications**

0.9% w/v Sodium Chloride Intravenous Infusion must not be used in states of hyperhydration.

**Special warnings and precautions for use**

0.9% w/v Sodium Chloride Intravenous Infusion should only be administered with caution in cases of

- hypokalaemia
- hyponatraemia
- hyperchloraemia
- disorders where restriction of sodium intake is indicated, such as cardiac insufficiency, generalised oedema, pulmonary oedema, hypertension, eclampsia, severe renal insufficiency.

Patient monitoring should include regular checks of the serum ionogram and the water balance. High infusion rates should be avoided in cases of hypertonic dehydration because of possible increases of plasma osmolarity and plasma sodium concentration. In case of pressure infusion, which may be necessary in vital emergencies, all air must be removed from the container and the infusion set before the solution is administered.

**Undesirable effects**

Administration may lead to hyponatraemia and hyperchloraemia.

**Subject to sale by pharmacists only.**

B. Braun Melsungen AG
34209 Melsungen, Germany
Amikacin
2.5 mg/ml, 5 mg/ml, 10 mg/ml solution for infusion

**Prescribing information**

**Qualitative and quantitative composition**

2.5 mg/ml solution for i.v. infusion: 1 ml of solution for infusion contains 2.5 mg of amikacin, as amikacin sulphate. 1 bottle of 100 ml contains 250 mg of amikacin (as amikacin sulphate).

5 mg/ml solution for i.v. infusion: 1 ml of solution for infusion contains 5 mg of amikacin, as amikacin sulphate. 1 bottle of 100 ml contains 500 mg of amikacin (as amikacin sulphate).

10 mg/ml solution for i.v. infusion: 1 ml of solution for infusion contains 10 mg of amikacin, as amikacin sulphate. 1 bottle of 100 ml contains 1,000 mg of amikacin (as amikacin sulphate).

**Excipient**: Each 100 ml contains 15 mmol (354 mg) sodium.

**List of excipients**: Sodium chloride, Sodium hydroxide (for pH adjustment), Water for injections

**Therapeutic indications**: For the treatment of the following severe infections due to bacteria susceptible to amikacin when less toxic antimicrobial agents are not effective: Nosocomial lower respiratory tract infections including severe pneumonia, Intraabdominal infections, including peritonitis. Complicated and recurrent urinary tract infections, Skin and soft tissue infections including burn-wound infections, Bacterial endocarditis, Post-operative intra-abdominal infections. Amikacin 2.5 mg/ml, 5 mg/ml, and 10 mg/ml solution for infusion can also be used in the treatment of patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Amikacin 2.5 mg/ml, 5 mg/ml, and 10 mg/ml solution for infusion is commonly used in combination with other appropriate antibiotics to cover the bacterial spectrum encountered in the respective infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents

**Contraindications**: Hypersensitivity to amikacin or other aminoglycosides or to any of the excipients.Myasthenia gravis.

**Special warnings and precautions for use**

Caution is necessary on administration to patients with renal impairment, to patients with auditory or vestibular damage, to patients with neuromuscular disorders, and if patients were treated with another aminoglycoside drug immediately prior to amikacin. The toxic effects of aminoglycosides, including amikacin, are more frequent in patients with renal impairment, if doses in excess of those recommended are administered, and the toxic effects of aminoglycosides act on the neuro-muscular junction similarly to curare and they may thus worsen muscle weakness. Aminoglycosides applied locally as part of a surgical procedure are quickly and nearly completely absorbed (with the exception of the urinary bladder). In association with irrigation of the surgical field using aminoglycoside preparations (regardless of the extent) development of irreversible deafness, renal failure and death due to neuromuscular blockade have been reported.

**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. The medicinal products contain 15 mmol (or 354 mg) sodium per 100 ml. This is to be taken into consideration for patients on a controlled sodium diet.

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

A synergistic antibacterial effect results from the combination with beta-lactam antibiotic drugs. Concomitant or subsequent administration and systemic or topical administration of other ototoxic or nephrotoxic substances should be avoided in view of the possibility of additive effects. Amikacin toxicity may be increased by the following ototoxic and/or nephrotoxic substances: Other aminoglycosides, Other anti-infective chemotherapy e.g. bacitracin, amphotericin B, cephalosporins, vancomycin, kanamycin, polymyxin B, colistin, Cystoticysts: carboplatin (at high doses), cisplatin, oxaliplatin (particularly in cases of pre-existing renal insufficiency), Immunosuppressants: cyclosporine, tacrolimus, Rapid acting diuretics e.g. furosemide or ethacrynic acid (functional renal insufficiency due to dehydration, potential ototoxic action by themselves). Irreversible deafness may result. When amikacin is combined with a potentially nephro- or ototoxic agent, hearing capacity and renal function must be monitored very closely. In the case of concurrent use with a rapid acting diuretic the patient’s hydration status should be monitored.

Amikacin/methoxyflurane anaesthesia: Aminoglycosides may increase the kidney damaging effect of methoxyflurane. When used concurrently, extremely severe neuropathies are possible. Amikacin/muscle relaxants and other substances: On concurrent treatment with amikacin and a muscle-relaxant drug (e.g. d-tubocurarine), curareing agents, butyltinum toxi, polymyxin antibiotics, procaainamide, large quantities of citrated blood or inhalation anaesthesia (e.g. halothane) it must be expected that the neuromuscular blockade exerted by those drugs will be increased. In the event of surgery the anaesthetist should be informed that this medicinal product is being administered. Injection of calcium salts may reverse the neuromuscular blockade due to aminoglycosides. Indomethacin may increase the plasma concentration of amikacin in neonates.

**Undesirable effects**

Under certain conditions amikacin shows ototoxic and/or nephrotoxic effects. Renal impairment is uncommonly observed in patients treated with amikacin and is usually reversible upon withdrawal of the drug. Important note on therapy: Renal impairment and hearing impairment due to neurological effects can be for the most part avoided with the observance of precautionary measures. Control renal status as well as the senses of hearing and equilibrium before, during and after therapy. Maintain adequate hydration and urine production. Monitor the drug concentration in serum for patients at particular risk and adjust dosage accordingly. The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. The following terminologies have been used in order to classify the occurrence of undesirable effects: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

**Infections and infestations**: Rare: Supra-infection or colonisation (with resistant microbes or yeast-like fungi)

**Blood and lymphatic system disorders**: Rare: anaemia, leukaopenia, granulocytopenia, thrombocytopenia, eosinophilia

**Immune system disorders**: Rare: Hypersensitivity reactions, Very rare: Anaphylactic shock (isolated cases), Not known: Cross-allergy between aminoglycosides
Medication Error

Metabolism and nutrition disorders: Rare: Hypomagnesaemia

Nervous system disorders: Uncommon: Dizziness¹, vertigo¹, Rare: Headache, migraine, paraesthesia, tremor

Eye disorders: Uncommon: Nystagmus¹

Ear and labyrinth disorders: Uncommon: Tinnitus¹, pressure in the ears¹, hearing impairment¹, Very rare: Deafness¹ (isolated cases)

Vascular disorders: Rare: Hypotension

Respiratory, thoracic and mediastinal disorders: Rare: Respiratory function depression⁴, Very rare: Respiratory paralysis⁴ (isolated cases)

Gastrointestinal disorders: Uncommon: Nausea¹, Rare: Vomiting

Eye disorders: Uncommon: Nystagmus¹

Ear and labyrinth disorders: Uncommon: Tinnitus¹, pressure in the ears¹, hearing impairment¹, Very rare: Deafness¹ (isolated cases)

Vascular disorders: Rare: Hypotension

Respiratory, thoracic and mediastinal disorders: Rare: Respiratory function depression⁴, Very rare: Respiratory paralysis⁴ (isolated cases)

Gastrointestinal disorders: Uncommon: Nausea¹, Rare: Vomiting

Skin and subcutaneous tissue disorders: Rare: Skin rash, exanthema, pruritus, urticaria (hypersensitivity reactions)³

Musculo-skeletal and connective tissue disorders: Rare: Arthralgia, Very rare: Neuromuscular blockage

Renal or urinary disorders: Uncommon: Damage to renal tubuli², renal impairment², Very rare: Toxic nephropathy, acute renal failure

General disorders and administration site conditions: Rare: Drug-related fever³

Investigations: Rare: Aspartate aminotransferase increased, Alanine aminotransferase increased, alkaline phosphatase increased (slight and transient)

Further information on particular undesirable effects: (1) These effects were seen in particular when the recommended dosage level was exceeded, in treatment lasting longer than 10 days, or when the dose was not adequately reduced for patients with renal dysfunction. Initial symptoms of vestibular disturbances are dizziness, nausea and vomiting. The clinical examination often reveals a nystagmus. Vestibular disturbances are reversible in almost any case. The first symptoms of cochlear dysfunction often include a loss of high-tone perception (≥4,000 Hertz) that precedes hearing loss and is detected only by audiometry. (2) Another uncommon adverse effect is damage to the renal tubules with renal impairment. The mechanism of renal damage involves accumulation in the lysosomes, phospholipase inhibition and necrosis of tubular cells after repeated administration of amikacin. Once daily dosing may reduce the risk of nephrotoxicity. Renal damage is reversible to varying degrees but exacerbates the risk of a cumulative process which may cause or intensify ototoxic effects. An increase in the serum creatinine concentration, the presence of albumin, red and white blood cells or cylinders in urine, ureaemia and oliguria are possible. (3) Rare adverse effects are hypersensitivity reactions such as exanthema, itching, hives, and drug fever. (4) In rare cases, if intravenous infusion of the drug is too fast, respiratory functions may be seriously depressed. In isolated cases this can lead to respiratory paralysis; the risk also exists when amikacin is administered in combination with anaesthesia and muscle relaxants.

Shelf life

Unopened: 3 years. In-use shelf-life (after opening): From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

Nature and contents of container

Amikacin 2.5 mg/ml, 5 mg/ml, 10 mg/ml: Bottles of low-density polyethylene, containing 100 ml, available in pack sizes of 10 x 100 ml, 20 x 100 ml; Not all pack sizes may be marketed.

Marketing authorization holder:

B. Braun Melsungen AG
34209 Melsungen, Germany

Date of information: 12/2010

See local prescribing information for full details, as prescribing information may vary from country to country.
The summarized scientific information in this document has been prepared for healthcare professionals. It is based on an analysis of public literature and guidelines. The intention is to give an introduction to the risks commonly associated with infusion therapy and to increase the awareness of healthcare workers to these kinds of problems. Due to its summary nature, this text is limited to an overview and does not take into account all types of local conditions. B. Braun does not assume responsibility for any consequences that may result from therapeutical interventions based on this overview.