Colistin may be administered in renal impairment only when in case of a vital indication. At about a serum creatinine of 1.3 mg/100 ml colistin accumulates, which may cause further deterioration of renal function up to acute renal failure and severe side effects. Furthermore, it can lead to neurotoxic reactions (e.g. tingling in the mouth, slurred speech, atactic gait) and neuromuscular blockade with respiratory paralysis. If the use of colistin can not be avoided, the initial dose should be the same as for patients with normal renal function. The maintenance dose should be reduced as a function of serum creatinine or the dosing interval extended: Only indicated in life threatening diseases: Serum creatinine <1,3mg/100ml: 50.000-75.000 IU/kg/day (daily dose 4,2-5,3 Mega/day) Serum creatinine 1,3-5mg/100ml: 15.000-30.000 IU/kg/24h (daily dose 1-2 Mega/day) Serum creatinine >5mg/100ml: 10.000-15.000 IU/kg/24h or the dosing interval extended:

- Serum creatinine >5mg/100ml in patients with creatinine clearance of <30 ml/min:
The maintenance dose should be reduced as a function of serum creatinine or the dosing interval extended. In severe infections caused by gram-negative bacteria, especially Proteus aeruginosa und Acinetobacter baumannii, if other antibiotics are not indicated or not active, e.g. pneumonia, sepsis, meningitis, urinary tract infections.

**Indications**

- For the treatment of the following infections caused by susceptible aerobic gram-negative bacteria: Hospital acquired pneumonia (HAP), Complicated urinary tract infections
- It is recommended to choose Colistimethate Atrium "Xellia" when antibacterial agents commonly used to treat these infections are not considered to be appropriate for the individual patient and / or the or the underlying pathogen

**PK, dosing information**

- COLISTIN iv

**Summary of Product Characteristics (SPC)**

**Austria**

Colistin Xellia 1 Million I.E. Pulver zur Herstellung einer Lösung. Solution for injection contains 1 million units of colistinmethanesulfonate per 10 mg of sodium. The free colistinbase is not excreted through the kidneys. With approximately 60% of a parenteral dose recovered in the urine. The penetration in tissues and body fluids is limited, the penetration into CSF is minimal even in case of inflammation. High concentrations in the urine, about 20-40 times higher than in the corresponding serum levels. Plasma protein binding is low (<10%). The serum half-life is 2-3 hours.

After intravenous infusion, the drug is eliminated primarily via glomerular filtration. Approx. 60% of the administered dose is excreted unchanged in the urine. The free colistinbase is not excreted through the kidneys.

**PK info**

- **Children**
  - School children (7–12 years): 1–2 Mega/day
  - Infants (3–6 months): 0.25–0.5 Mega/day
  - Infants (6 months–2 years): 0.5–1 Mega/day
  - School children (2 years–12 months): 0.5–1 Mega/day
  - Infants (1–6 years): 1–1.5 Mega/day
  - Infants (6 months–12 months): 1.5–2 Mega/day
  - Children: 2–5 Mega/day

- **PK info**

  - **Children**
    - School children (7–12 years): 1–2 Mega/day
    - Infants (3–6 months): 0.25–0.5 Mega/day
    - Infants (6 months–2 years): 0.5–1 Mega/day
    - School children (2 years–12 months): 0.5–1 Mega/day
    - Infants (1–6 years): 1–1.5 Mega/day
    - Infants (6 months–12 months): 1.5–2 Mega/day
    - Children: 2–5 Mega/day

**PK info**

- **Children**
  - School children (7–12 years): 1–2 Mega/day
  - Infants (3–6 months): 0.25–0.5 Mega/day
  - Infants (6 months–2 years): 0.5–1 Mega/day
  - School children (2 years–12 months): 0.5–1 Mega/day
  - Infants (1–6 years): 1–1.5 Mega/day
  - Infants (6 months–12 months): 1.5–2 Mega/day
  - Children: 2–5 Mega/day

**PK info**

- **Children**
  - School children (7–12 years): 1–2 Mega/day
  - Infants (3–6 months): 0.25–0.5 Mega/day
  - Infants (6 months–2 years): 0.5–1 Mega/day
  - School children (2 years–12 months): 0.5–1 Mega/day
  - Infants (1–6 years): 1–1.5 Mega/day
  - Infants (6 months–12 months): 1.5–2 Mega/day
  - Children: 2–5 Mega/day

**PK info**

- **Children**
  - School children (7–12 years): 1–2 Mega/day
  - Infants (3–6 months): 0.25–0.5 Mega/day
  - Infants (6 months–2 years): 0.5–1 Mega/day
  - School children (2 years–12 months): 0.5–1 Mega/day
  - Infants (1–6 years): 1–1.5 Mega/day
  - Infants (6 months–12 months): 1.5–2 Mega/day
  - Children: 2–5 Mega/day

**PK info**

- **Children**
  - School children (7–12 years): 1–2 Mega/day
  - Infants (3–6 months): 0.25–0.5 Mega/day
  - Infants (6 months–2 years): 0.5–1 Mega/day
  - School children (2 years–12 months): 0.5–1 Mega/day
  - Infants (1–6 years): 1–1.5 Mega/day
  - Infants (6 months–12 months): 1.5–2 Mega/day
  - Children: 2–5 Mega/day
Austria
Tadim® 1 Million I.E.
Profile Pharma
Up to 60 kg: 50,000 IU / kg (4 mg / kg) of body weight of up to 75,000 IU / kg (6 mg / kg) over 24 hours. The total daily dose should be administered as three equal doses at 8-hour intervals. Over 60 kg: 1-2 million IU every 8 hour. The standard maximum dose is 6 million IU (480 mg) over 24 hours. Limited pharmacokinetic data from critically ill patients suggest that the use of a loading dose and doses that are higher than standarddose may be appropriate. In severe infections and in critically ill patients is reported in the literature doses up to 9 million IU per day in divided doses. The clinical data on efficacy and safety of these regimens are very limited and caution is advised.

see Xellia

see adults

see Xellia

Tadim is indicated for the treatment of the following infections caused by susceptible aerobic gram-negative bacteria: Hospital acquired pneumonia (HAP), Complicated urinary tract infections

It is recommended to choose Tadim when antibacterial agents commonly used to treat these infections are not considered to be appropriate for the individual patient and / or the or the underlying pathogen

Belgium
COLISTINEB 2 million IU. Powder for solution, injection, preparation for infusion
Forest UK
Up to 60kg: 50,000 units / kg / day to a maximum of 75,000 units / kg / day. The total daily dose is preferably divided into three doses with an interval of about 8 hours. Above 60 kg: 1-2 million units three times a day. The maximum dose is 6 million units per 24 hours.

Above 60 kg body weight:
20-50 (mild): 1 mill IU every 12-18h, c10 (severe): 1 mill IU every 18-24h

see adults

An estimate of the serum concentration is recommended, especially in renal failure, newborns and patients with cystic fibrosis. A concentration between 10 and 15 mg / l (about 125-200 units / ml) should normally be suitable for most infections. After administration to patients with cystic fibrosis of 7.5 mg / kg / day divided into doses administered as an IV infusion of 30 minutes until the steady state

Cmax was determined to be 23 ± 6 mg / l and Cmin after 8 hours was 4.5 ± 4 mg / l. In another study patients with cystic fibrosis who received 2 million units every 8 hours for 12 days, Cmax was 12.9 mg / l (5.7 to 29.6 mg / l) and Cmin was 2.76 mg / l (1.0 to 6.2 mg / l). In normal volunteers healthy that a bolus injection of 150 mg (approximately 2 million units) was was administered was observed maximum serum concentrations reached after 1 minute after injection.

Protein binding is low. Polymyxins remain in the liver, kidney, brain, heart and muscles. A study of patients with cystic fibrosis reports the volume of distribution at steady state as 0.09 l / kg.

Belgium
Colistin Alvogen
colistimethate sodium 1 MU or 2 MU
Alvogen IPCo S.a.
Czech Republic
COLOMYCIN INJEKCCE 1 000 000 maximálních jednotek
Forest UK
The dose is determined by the severity and type of infection and the age, weight and renal function of the patient. If clinical or bacteriological response was slow, dose may be increased according to the patient’s condition.

To 60 kg of body weight: 50,000 units / kg / day to a maximum of 75,000 units / kg / day. The total daily dose should be divided into three doses given approximately at 8-hour intervals.

Above 60 kg body weight: 1.2 million units three times a day. The maximum dose is 6 million units within 24 hours.

Above 60 kg body weight:
20-50 (mild): 3x1-2mill IU, 10-20 (moderate): 1 mill IU every 12-18h, c10 (severe): 1 mill IU every 18-24h

see adults

Evaluation of serum levels is recommended especially in renal impairment, neonates and patients with cystic fibrosis. Most infections should be sufficient levels of 10-15 mg / l (about 125-200 units / ml) of sodium colistimethate.

When administered to patients with cystic fibrosis, 7.5 mg / kg / day in divided doses administered as a 30 minute intravenous infusion Cmax (steady state) was determined to be 23 ± 6 mg / l and Cmin at 8 hours was 4.5 ± 4 mg / l. In another study patients with cystic fibrosis who received 2 million units every 8 hours for 12 days, the value of Cmax of 12.9 mg / l (5.7 to 29.6 mg / l) and Cmin was 2.76 mg / l (1.0 to 6.2 mg / l). In healthy volunteers who received a bolus injection of 150 mg (approximately 2 million units), peak serum levels of 18 mg / l observed 10 minutes after injection. Protein binding is low. Polymyxins persist in the liver, kidney, brain, heart and muscles. One study in patients with cystic fibrosis indicates the volume of distribution at steady state of 0.09 l / kg.

Bulgaria
Croatia
not available
Cyprus
Colistin/Norma
1,000,000 IU / vial powder for solution for infusion

Czech Republic

Inhalation treatment of pulmonary infections caused by Pseudomonas aeruginosa in patients with cystic fibrosis.

Intravenous administration for the treatment of certain serious infections caused by Gram-negative bacteria, including infections of the lower respiratory tract and urinary tract.

Information based on current Summary of Product Characteristics (SPC) COLISTIN iv
PK, dosing information

Ursula Theuretzbacher, Center for Anti-Infective Agents
16.11.2013
Colistimethate sodium ("Xelia"), marketed by Atrium (DK), and by Xellia/Novo Nordisk (DK), is indicated for the treatment of the following infections caused by susceptible aerobic gram-negative bacteria: Hospital-acquired pneumonia (HAP), Complicated urinary tract infections

It is recommended to choose Colistimethate Atrium or "Xelia" when antibacterial agents commonly used to treat these infections are not considered to be appropriate for the individual patient and / or the underlying pathogen.

**Danmark**

Colistimethatnatrium ("Xelia")

Colistimethate is mainly excreted by glomerular filtration as polymyxin E1 and polymyxin E2 (colistin) in vivo. It is estimated that approximately 30% of colistimethate sodium is converted to colistin.

Elimination: The primary route of elimination of unchanged colistimethate sodium following parenteral administration is renal, with approximately 60% of a parenteral dose recovered in the urine within 8 hours. Since colistimethate primarily excreted in the urine, a dose reduction is necessary in renal impairment to prevent accumulation. See the table in section 4.3. The free colistin base is not excreted through the kidneys.

### Colistimethate Sodium

**Swedish Orphan Biovitrum GmbH**

### Colistin given parenterally, as colistimethate sodium, by intramuscular injection or slow intravenous injection or infusion. In the UK, usual doses are 1 to 2 million units 3 times daily (maximum dose 6 million units in 24 hours) for adults and children weighing more than 60 kg; those weighing up to 60 kg may be given 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily. In the USA, the usual dose is equivalent to colistin base 2.5 to 5 mg/kg daily in 2 to 4 divided doses. Monitoring of plasma concentrations is required in some patients.

**Colistin is given parenterally, as colistimethate sodium, by intramuscular injection or slow intravenous injection or infusion. In the UK, usual doses are 1 to 2 million units 3 times daily (maximum dose 6 million units in 24 hours) for adults and children weighing more than 60 kg; those weighing up to 60 kg may be given 50 000 units/kg daily in 3 divided doses up to a maximum of 75 000 units/kg daily. In the USA, the usual dose is equivalent to colistin base 2.5 to 5 mg/kg daily in 2 to 4 divided doses. Monitoring of plasma concentrations is required in some patients.**

### Plasma-concentration monitoring during systemic treatment is recommended in neonates, patients with renal impairment, and those with cystic fibrosis. Peak plasma-colistin concentrations of 10 to 15 mg/litre (about 125 to 200 units/ml) are recommended. Peak plasma concentrations usually occur 2 to 3 hours after an intramuscular injection of colistimethate sodium. Some colistimethate sodium may be hydrolysed to colistin in vivo. The serum half-life of colistimethate sodium is 2 to 3 hours but is prolonged in renal impairment. It may initially be prolonged in neonates but has been reported to fall to 2 to 3 hours after 3 or 4 days. Colistin is reversibly bound to body tissues, but binding does not occur with colistimethate.

### Colistin is a polymyxin antibiotic that has been used in the treatment of severe Gram-negative infections, especially those due to Pseudomonas aeruginosa, although other drugs are usually preferred.**
<table>
<thead>
<tr>
<th>Country</th>
<th>Manufacturer</th>
<th>Product</th>
<th>Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>COLIMYCINE</td>
<td>Promixin (colistimethate sodium)</td>
<td>Adults and older children: 75 000 - 150 000 IU / kg / day, administered in 1 - 3 doses, max. 12 IU / day; Infants: from 150 000 to 225 000 IU / kg / day administered in 1 to 3 injections, max. 12 MIU / day.</td>
</tr>
<tr>
<td>France</td>
<td>Sanofi-Aventis</td>
<td>Promixin 1 MIO I.E. Pulver zur Herstellung einer Inf. Lösung</td>
<td>Adults and children: 75 000 - 150 000 IU / kg / day, administered in 1 - 3 doses, max. 12 IU / day; CRI&lt;30 ml / min: normal dosing regimen. CRI 30 - 60 ml / min: 50 000 - 75 000 IU / kg / day; CRI &gt; 60 ml / min: 75 000 - 100 000 IU / kg / day every 12 - 18h.</td>
</tr>
<tr>
<td>Germany</td>
<td>Infectopharm</td>
<td>Up to 60 kg: 50 000 IU / kg (4 mg / kg) of body weight of up to 75 000 IU / kg (6 mg / kg) every 24 hours. The total daily dose should be administered as three equal doses at 8-hour intervals. Over 60 kg: 1 - 2 million IU every 8 hours. The standard maximum dose is 6 million IU (480 mg) over 24 hours. Limited pharmacokinetic data from critically ill patients suggest that the use of a loading dose and doses that are higher than standard dose may be appropriate. In severe infections and in critically ill patients is reported in the literature doses up to 9 million IU per day in divided doses. The clinical data on efficacy and safety of these regimens are very limited and caution is advised. The suggested dose recommendations for patients with renal impairment is based on the total daily standard dose of 3 - 6 million IU per day. In patients with renal impairment, for whom higher doses (eg. Up to 9 million IU per day) would be considered if their renal function was normal, corresponding proportional adjustments considered when the dose should be calculated. Caution is advised when Colistimethate Natrium Infectopharm administered to patients with impaired renal function because of the limited information that is available on the safety and appropriate dosage regimens. Cerebrospinal clearance (% of normal value): 76 - 100 % normal: 3x1.3 - 2 Mill IU, total daily dose 4 - 6 Mill IU, 40 - 75 (mild): 3x1 - 1.5, total daily dose 2 - 3 Mill IU, 25 - 40 (moderate): 1 - 1.2x 1 Mill IU, total daily dose 1 - 2 Mill IU, &lt;25 (severe): 1 - 1.5 Mill IU every 36 h, total daily dose 0.6 - 1 Mill IU see adults</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>Infectopharm</td>
<td>Up to 60 kg: 50 000 IU / kg (4 mg / kg) of body weight of up to 75 000 IU / kg (6 mg / kg) over 24 hours. The total daily dose should be administered as three equal doses at 8-hour intervals. Over 60 kg: 1 - 2 million IU every 8 hours. The standard maximum dose is 6 million IU (480 mg) over 24 hours. Limited pharmacokinetic data from critically ill patients suggest that the use of a loading dose and doses that are higher than standard dose may be appropriate. In severe infections and in critically ill patients is reported in the literature doses up to 9 million IU per day in divided doses. The clinical data on efficacy and safety of these regimens are very limited and caution is advised. The suggested dose recommendations for patients with renal impairment is based on the total daily standard dose of 3 - 6 million IU per day. In patients with renal impairment, for whom higher doses (eg. Up to 9 million IU per day) would be considered if their renal function was normal, corresponding proportional adjustments considered when the dose should be calculated. Caution is advised when Colistimethate Natrium Infectopharm administered to patients with impaired renal function because of the limited information that is available on the safety and appropriate dosage regimens. Cerebrospinal clearance (% of normal value): 76 - 100 % normal: 3x1.3 - 2 Mill IU, total daily dose 4 - 6 Mill IU, 40 - 75 (mild): 3x1 - 1.5, total daily dose 2 - 3 Mill IU, 25 - 40 (moderate): 1 - 1.2x 1 Mill IU, total daily dose 1 - 2 Mill IU, &lt;25 (severe): 1 - 1.5 Mill IU every 36 h, total daily dose 0.6 - 1 Mill IU see adults</td>
<td></td>
</tr>
</tbody>
</table>

**PK, dosing information**

Colistimethate sodium Infectopharm is indicated for the treatment of the following infections caused by susceptible aerobic gram-negative bacteria: - Nosocomial Pneumonia - Complicated urinary tract infections

2013/2
Colistimethate sodium (with an upper limit of 9,000,000 units) can be estimated by applying the following formula:

\[
\text{Total daily dose} = \text{desired concentration of colistin in plasma at steady state} \times (1.5 \times \text{creatinine clearance} + 30) \times 30,000
\]

Loading dose = desired concentration of colistin in plasma at steady state \(x\) (1.5 \times creatinine clearance + 30) \(\times 30,000\) can be calculated by applying the following formula:

Loading dose = desired concentration of colistin in plasma at steady state \(x\) (1.5 \times creatinine clearance + 30) \(\times 30,000\)

Colistin / Norma is indicated for the treatment of acute or chronic infections due to susceptible strains of the following gram-negative bacteria: Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae and, in particular, Pseudomonas aeruginosa. This antibiotic is not indicated for infections caused by Proteus and Neisseria.

Acute or chronic infections due to susceptible strains of the following gram-negative bacteria: Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae and, in particular, Pseudomonas aeruginosa. This antibiotic is not indicated for infections caused by Proteus and Neisseria.

Loading dose of 25,000 IU/kg, the maintenance dosage may be increased so, as required by the patient. Determination of serum levels of renal impairment is particularly recommended for infants and children. In patients with fibrosis, most infections of 10 - 15 mg / l sodium colistimethate level (about 125-200 IU / mL) is considered appropriate.

PK, dosing information
Serum level estimations are recommended especially in renal impairment, neonates and cystic fibrosis patients. Levels of 10–15 mg/l (approximately 125–200 units/ml) colistimethate sodium should be adequate for most infections. PK see Germany.

Severe systemic infections caused by susceptible strains of Gram-negative bacteria (for example, sepsis, infections of the urinary tract), when routinely used antibacterial agents may be contra-indicated or may be ineffective because of bacterial resistance.

Information based on current Summary of Product Characteristics (SPC)
### Romania

**COLISTINĂ ANTIBIOTICE 1.000.**

**COLISTINĂ ANTIBIOTICE 1.000.**

**COLISTINĂ ANTIBIOTICE 1.000.**

The usual dose is 50,000 IU of colistin / kg body weight. The dose depends on the severity and type of infection, age, weight and degree of impairment of kidney function. If the clinical or bacteriological response is not adequate, the dosage may be increased depending on the condition of the patient.

Up to 60 kg body weight: 50,000 IU / kg body weight up to a maximum of 75,000 IU / kg body weight per day. The total daily dose should be divided into 3 equal doses administered every 8 hours. More than 60 kg: 1-2 million IU three times a day at intervals of 8 hours. The maximum dose is 6 million IU per day.

In moderate and severe renal impairment, the excretion of colistimethate sodium is delayed. Accordingly, doses and dose ranges will be adjusted to prevent the accumulation of the drug. Patients with >60 kg body weight:

Creatinine Clearance (Ml / min) 20-50: 1-2 MU every 8 hours
Creatinine Clearance (Ml / min) 10-20: 1 MU every 12-18 hours
Creatinine Clearance (Ml / min) <10: 1 MU every 18-24 hours

It is recommended to measure serum concentrations of colistin, especially in renal impairment, in neonates. Serum concentrations of 125-200 IU / ml are adequate to treat most infections.

### Slovakia

**Colimycine plv ino 1 MIU (v 1 liekovke) 1x50 lag**

Sanofi-aventis Slovakia

An average of 50-100,000 IU / kg / day, i.e. usually 3 million IU / day in 2-3 divided doses intramuscularly or 1 hour intravenous infusion.

Serum creatinine level <15 mg / l, creatinine clearance >80 ml / min: 50000 IU / kg / day and the maximum dose of 150000 IU / kg / day.

Serum creatinine level 15-35 mg / l, creatinine clearance 30-80 ml / min: 30000 IU / kg / day and the maximum dose of 60000 IU / kg / day.

Serum creatinine level 35-100 mg / l, creatinine clearance 5-30 ml / min: 15000 IU / kg / day and the maximum dose of 30 000 IU / kg / day.

Serum creatinine level >100 mg / l, creatinine clearance <5 ml / min: 1000 IU / kg every 2-3 days and a maximum dose of 30 000 IU / kg / day, further to 1 million IU twice a week.

Aruria at a dose of 1 million IU after each hemodialysis, a maximum dose of 30 thousand. IU / kg and continuing with up to 1 million IU after each hemodialysis.

*It is recommended to measure serum concentrations of colistin, especially in renal impairment, in neonates. Serum concentrations of 125-200 IU / ml are adequate to treat most infections.*

### Slovenia

**KOLOMYCÍN INJEKCIA 1 milión IU**

Forest UK

An average of 50-100,000 IU / kg / day, i.e. usually 3 million IU / day in 2-3 divided doses intramuscularly or 1 hour intravenous infusion.

Serum creatinine level <15 mg / l, creatinine clearance >80 ml / min: 50000 IU / kg / day and the maximum dose of 150000 IU / kg / day.

Serum creatinine level 15-35 mg / l, creatinine clearance 30-80 ml / min: 30000 IU / kg / day and the maximum dose of 60000 IU / kg / day.

Serum creatinine level 35-100 mg / l, creatinine clearance 5-30 ml / min: 15000 IU / kg / day and the maximum dose of 30 000 IU / kg / day.

Serum creatinine level >100 mg / l, creatinine clearance <5 ml / min: 1000 IU / kg every 2-3 days and a maximum dose of 30 000 IU / kg / day, further to 1 million IU twice a week.

Aruria at a dose of 1 million IU after each hemodialysis, a maximum dose of 30 thousand. IU / kg and continuing with up to 1 million IU after each hemodialysis.

In children, neonates and premature infants at a dose of 50 to 100 thousand / kg / day according to the severity of the infection. Total daily dose is divided into 2-3 single doses to be administered intramuscularly or by slow intravenous infusion (1 h).

**Severe infections caused by Gram-negative, including lower respiratory tract and urinary tract, if other antibiotics for systemic use are contraindicated or resistant**

### 2012/12

**Urinary infections, ENT and respiratory infections, intraabdominal infections, biliary tract infections, septicemia, meningitis**
Spain COLISTIMATO DE SODIO G.E.S Polvo 1 MIU/vial The active substance is sodium colistimethate. Each vial contains 1 million international units (MIU) equivalent to approximately 80 mg of colistimethate sodium. Up to 60 kg: 50,000 IU / kg body weight per day. Total daily dose should be given as three equal doses at 8 hour intervals. More than 60 kg body weight: 1 to 2 MIU every 8 hours (three times a day) without exceeding a maximum daily dose of 6 MIU. Dosing instructions for inhalation available. Additional adjustments may be required according to the individual needs of each patient. Creatinine 1,2-1,46 mg/100 ml: creatinine clearance (40-75% of normal): 1,5 MIU/12 h, up to a maximal daily dose of 2-3 MIU. Creatinine 1,47-2,42 mg/100 ml: creatinine clearance (35-40% of normal): 0,8-2 MIU/12-24 h, up to a maximal daily dose of 1,5-2 MIU. Creatinine 2,43-3,85 mg/100 ml: creatinine clearance (<25% of normal): 0,8-1,5 MIU/36 h, up to a maximal daily dose of 0,6-1 MIU. Additional dosing recommendations only for inhalation. Sodium colistimethate has a low plasma protein binding. Polymyxins are known to persist in muscle tissue, liver, kidney, heart and brain. In a study in which patients with cystic fibrosis received 5-7 mg/kg / day divided into 3 doses that were administered by intravenous infusion over 30 minutes Cmax was 21,4 ± 5 mg / l and Cmin was 2,8 ± 1,8 mg / l. The Cmax at steady state was 23 ± 6 mg/l and Cmin was 4,5 ± 4 mg / l. In another study in patients with cystic fibrosis who received 2 MIU every 8 hours for 12 days, Cmax was 12,9 mg / l (5,7 to 29,6 mg / l) and Cmin was 2,76 mg / l (1,0 to 6,2 mg / l). Intravenous administration of 150 mg (about 2 MIU) to healthy volunteers produced serum levels of 18 mg / l at 10 minutes. The volume of distribution obtained in a study in patients with cystic fibrosis was 0,09 l / kg. In vivo sodium colistimethate is converted to its base. Approximately 80% of the dose is recovered in urine unchanged. There is no biliary excretion. After intravenous administration, excretion is primarily renal with recovery of 40% of the parenteral dose in the urine within 8 hours and about 80% at 24 hours. Following intravenous administration to healthy adults, the half-life is approximately 1,5 hours, in contrast to a half-life of 3,4 ± 1,4 hours in patients with cystic fibrosis who were administered a single intravenous infusion over 3 minutes. Sodium colistimethate G.E.S. is an antibiotic used to treat serious infections in the respiratory and urinary tract if they are caused by microorganisms susceptible to colistimethate sodium. It also can be used to treat certain infections in patients with cystic fibrosis.
Up to 60 kg: 50,000 IU / kg (4 mg / kg) of body weight of up to 75,000 IU / kg (6 mg / kg) over 24 hours. The total daily dose should be administered as three equal doses at 8-hour intervals. Over 60 kg: 1-2 million IU every 8 hour. The standard maximum dose is 6 million IU (480 mg) over 24 hours.

Limited pharmacokinetic data from critically ill patients suggest that the use of a loading dose and doses that are higher than standard dose may be appropriate. In severe infections and in critically ill patients is reported in the literature doses up to 9 million IU per day in divided doses. The clinical data on efficacy and safety of these regimens are very limited and caution is advised.

The suggested dose recommendations for patients with renal impairment is based on the total daily standard dose of 3-6 million IU per day. In patients with renal impairment, for whom higher doses (eg. Up to 9 million IU per day) would be considered if their renal function was normal, corresponding proportional adjustments considered when the dose should be calculated. Caution is advised when Tadim is administered to patients with impaired renal function because of the limited information that is available on the safety and appropriate dosage regimens. Limited pharmacokinetic data from critically ill patients suggest that the use of a loading dose and doses that are higher than standard dose may be appropriate. In severe infections and in critically ill patients is reported in the literature doses up to 9 million IU per day in divided doses. The clinical data on efficacy and safety of these regimens are very limited and caution is advised.

The volume of distribution of colistin following administration of colistimethate sodium in healthy volunteers and in patients with cystic fibrosis has been reported to be 12.4 l and 20.4 l. In comparison, the volume of distribution for colistin following administration of colistimethate sodium is found to be between 90.6 and 139 l, 9 l in critically ill patients. The increased volume of distribution in critically ill patients may lead to a delay in achieving effective plasma concentrations. Therefore, using an initial loading dose of up to 9 million IU proposed, particularly in critically ill patients.

Of critically ill patients receiving colistimethate 2 million IU and 3 million IU intravenously three times per day was observed peak plasma concentrations of 2.21 and 2.93 mg / L. The elimination of colistin is primarily excreted unchanged in the urine where hydrolysis to the active portion continues. Following intravenous administration is 62% of the dose in the urine within 8 hours. Colistin is not excreted by the kidneys. Half-life of colistin following administration of colistimethate sodium in healthy volunteers and in patients with cystic fibrosis has been reported to be 3 hours and 4.2 hours. Half-life of colistin following administration of colistimethate sodium has been reported to increase when administered to critically ill patients compared with healthy volunteers, and the mean half-life is estimated to vary from about 5.9 hours to 7.4 hours after intravenous administration in critically ill patients. In patients with impaired renal function decreases elimination of colistimethate sodium and a higher percentage can be converted to colistin, leading to increased colistin concentration in plasma.

Tadim is indicated for the treatment of the following infections caused by susceptible aerobic gram-negative bacteria - Nosocomial Pneumonia - Complicated urinary tract infections
The Netherlands Tadim, 1 miljoen internationale eenheden (IE) poeder voor oplossing voor injectie. Elke injectiefles bevat 1 miljoen internationale eenheden (IE) wat overeenkomt met ongeveer 80 mg colistimethaatsodium.

Profile Pharma

Up to 60 kg: 50,000 IU / kg (4 mg / kg) of body weight of up to 75,000 IU / kg (6 mg / kg) over 24 hours. The total daily dose should be administered as three equal doses at 8-hour intervals. Over 60 kg: 1-2 million IU every 8 hour. The standard maximum dose is 6 million IU (480 mg) over 24 hours. Limited pharmacokinetic data from critically ill patients suggest that the use of a loading dose and doses that are higher than standard dose may be appropriate. In severe infections and in critically ill patients is reported in the literature doses up to 9 million IU per day in divided doses. Clinical data on efficacy and safety of these regimens are very limited and caution is advised.

The Netherlands COLISTINEB 2 miljoen I.E. poeder voor oplossing voor injectie, infusie of inhalatie. Elke injectiefles bevat 2 miljoen internationale Eenheden natriumcolistimethaat. De bevat 2 miljoen internationale eenheden (IE) wat overeenkomt met ongeveer 80 mg colistimethaatsodium.

Forest UK

Up to 60 Kg: 50,000 IU-75,000 IU/Kg dailys. The total daily dose should be administered as three equal doses at 8-hour intervals. Over 60 kg: 1-2 million IU every 8 hour. The standard maximum dose is 6 million IU (480 mg) over 24 hours. Limited pharmacokinetic data from critically ill patients suggest that the use of a loading dose and doses that are higher than standard dose may be appropriate. In severe infections and in critically ill patients is reported in the literature doses up to 9 million IU per day in divided doses. Clinical data on efficacy and safety of these regimens are very limited and caution is advised.

UK Promain, 1 million International Units (IU), Powder for Solution for Infusion

IU, mg/kg (dosing)

Up to 60 Kg: 50,000 IU/Kg (4 mg/Kg), in 24 hours. The total daily dose should be administered as three equal doses at 8-hour intervals. Over 60 Kg: 1-2 million IU every 8 hour. The maximum standard dose is 6 million IU (480 mg) in 24 hours.

Creatinine clearance (mL/min), Over 60kg bodyweight:

- 20-50 (moderate): 1-1.5 ml/IU
- 10-20 (moderate): 1 ml/IU every 12-18h,
- <10 (severe): 1 ml/IU every 18-24h

Distribution

The volume of distribution of colistin following administration of colistimethate sodium in healthy volunteers and in patients with cystic fibrosis has been reported to be 12.4 l and 20.4 l. In comparison, the volume of distribution for colistin following administration of colistimethate sodium is found to be between 90.6 and 139 l, 9 l in critically ill patients. The increased volume of distribution in critically ill patients may lead to a delay in achieving effective plasma concentrations. Therefore, using an initial loading dose of up to 9 million IU proposed, particularly in critically ill patients. Of critically ill patients receiving colistimethate sodium 2 million IU and 3 million IU intravenously three times per day was observed peak plasma concentrations of 2.21 and 2.93 mg/L.

Biotransformation

Colistimethate converted in vivo to polymyxin E1 and polymyxin E2 (colistin). It has been estimated that about 30% of colistimethate sodium is converted to colistin. Elimination

Colistimethate is primarily excreted unchanged in the urine where hydrolysis to the active portion continues. Following intravenous administration is 62% of the dose in the urine within 8 hours. Colistin is not excreted by the kidneys. Half-life of colistin following administration of colistimethate sodium in healthy volunteers and in patients with cystic fibrosis has been reported to be 3 hours and 4.2 hours. Half-life of colistin following administration of colistimethate sodium has been reported to increase when administered to critically ill patients compared with healthy volunteers, and the mean half-life is estimated to vary from about 5.9 hours to 7.4 hours after intravenous administration in critically ill patients.

In patients with impaired renal function eliminates colistimethate sodium and a higher percentage can be converted to colistin, leading to increased colistin concentration in plasma.

Creatinine clearance (mL/min), Over 60kg bodyweight:

- 20-50 (moderate): 1-1.5 ml/IU
- 10-20 (moderate): 1 ml/IU every 12-18h,
- <10 (severe): 1 ml/IU every 18-24h

The suggested dose recommendations for patients with renal impairment is based on the total daily standard dose of 3-6 million IU per day. In patients with renal impairment, for whom higher doses (eg. Up to 9 million IU per day) would be considered if their renal function was normal, corresponding proportional adjustments considered when the dose should be calculated. Caution is advised when Tadim is administered to patients with impaired renal function because of the limited information that is available on the safety and appropriate dosage regimens. Creatinine clearance (% of normal value) 76-100 (normal): 3x3.3-2.1

Mill IU, total daily dose 4-6 ml IU.
- 40-75 (mild): 2x1-1.5, total daily dose 2-3 ML/IU
- 25-40 (moderate): 1.2x1-1.5 ML/IU, total daily dose 1-2 ML IU
- <25 (severe): 1.5 ML IU every 36 h, total daily dose 0.6-1 ML IU

PK, dosing information

The Netherlands Tadim is indicated for the treatment of the following infections caused by susceptible aerobic gram-negative bacteria

- Nosocomial Pneumonia
- Complicated urinary tract infections

Information based on current Summary of Product Characteristics (SPC) COLISTIN iv
<table>
<thead>
<tr>
<th>Country</th>
<th>Drug Name</th>
<th>Description</th>
<th>Dosage Guidelines</th>
<th>PK Information</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Colistimethate Sodium 1 Million I.U. Powder for Solution for Injection</td>
<td>Beacon Pharmace</td>
<td>Up to 60 Kg: 50,000 IU-75,000 IU/Kg daily. The total daily dose should be administered as three equal doses at 8 hourly intervals. Over 60 Kg: 1-2 million IU every 8 hours. The maximum standard dose is 6 million IU (480 mg) in 24 hours. Estimation of serum levels is particularly recommended for patients with renal impairment, neonates and patients with cystic fibrosis. Serum levels of 10-15 mg/l (approximately 125-200 units/ml) should be adequate for most infections.</td>
<td>Creatinine clearance (ml/min). Over 60kg bodyweight: 20-50 (mild): 3x1-2ml IU, 10-20 (moderate): 1 ml IU every 12-18h, &lt;10 (severe): 1 ml IU every 18-24h</td>
<td>see adults</td>
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<td>PK info only in CF</td>
<td>Intravenous administration for the treatment of some serious infections caused by Gram-negative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents may be contra-indicated or may be ineffective because of bacterial resistance</td>
</tr>
<tr>
<td>UK</td>
<td>Colomycin Injection 1 million or 2 million International Units. Powder for solution for injection, infusion or inhalation.</td>
<td>Forest Laboratories UK</td>
<td>Up to 60 Kg: 50,000 IU-75,000 IU/Kg daily. The total daily dose should be administered as three equal doses at 8 hourly intervals. Over 60 Kg: 1-2 million IU every 8 hours. The maximum standard dose is 6 million IU (480 mg) in 24 hours. Anomalous distribution in patients with cystic fibrosis may require higher doses in order to maintain therapeutic serum levels.</td>
<td>Creatinine clearance (ml/min). Over 60kg bodyweight: 20-50 (mild): 3x1-2ml IU, 10-20 (moderate): 1 ml IU every 12-18h, &lt;10 (severe): 1 ml IU every 18-24h</td>
<td>see adults</td>
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<td></td>
<td></td>
<td></td>
<td>Serum level estimations are recommended especially in renal impairment, neonates and cystic fibrosis patients. Levels of 10–15 mg/l (approximately 125-200 units/ml) colistimethate sodium should be adequate for most infections.</td>
<td>Intravenous administration for the treatment of some serious infections caused by Gram-negative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents may be contra-indicated or may be ineffective because of bacterial resistance</td>
</tr>
<tr>
<td>UK</td>
<td>Promixin, 1 million International Units (IU), Powder for Solution for Infusion</td>
<td>Profile Pharma</td>
<td>Up to 60 Kg: 50,000 IU/Kg (4 mg/Kg) to a maximum of 75,000 IU/Kg (6 mg/Kg), in 24 hours. The total daily dose should be administered as three equal doses at 8 hourly intervals. Over 60 Kg: 1-2 million IU every 8 hours. The maximum standard dose is 6 million IU (480 mg) in 24 hours. Limited pharmacokinetic data from critically ill patients suggest that use of a loading dose and higher than standard doses may be appropriate. For severe infections and in critically ill patients, doses up to 9 million IU per day in divided doses, have been reported in the literature. Clinical efficacy and safety data with these regimens are very limited and caution is advised.</td>
<td>Creatinine Clearance (% of normal): 76-100 (normal): 3x 1.3 to 2 mill IU (4-6 total daily dose), 40 - 75 (mild): 2x 1.1-1.5 (2-6 total daily dose), 25-40 (moderate): 1-2x 1 mill IU (3-2 total daily dose), &lt;25 (severe): 1-1.5 every 36 hours (0.6-1 total daily dose)</td>
<td>see adults</td>
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<td>In critically ill patients given colistimethate sodium 2 million IU and 3 million IU three times a day intravenously, peak colistin plasma concentrations of 2.21 and 2.93 mg/L, respectively, were observed.</td>
<td>Hospital acquired pneumonia (HAP, Complicated urinary tract infections)</td>
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</tbody>
</table>

16.11.2013