WARNINGS

Patients treated with aminoglycosides should be under close clinical observation because of the potential toxicity associated with their use. As with other aminoglycosides, Gentamicin Injection is potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high dosage or prolonged therapy. Neurotoxicity manifested by ototoxicity, both vestibular and auditory, can occur in patients treated with gentamicin, primarily in those with pre-existing renal damage and in patients with normal renal function treated with higher doses and/or for longer periods than recommended. Aminoglycoside-induced ototoxicity is usually irreversible. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions. Renal and eighth cranial nerve function should be closely monitored, especially in patients with known or suspected pre-existing renal dysfunction at onset of therapy, and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Urine should be examined for decreased specific gravity, increased excretion of protein, and the presence of cells or casts. Blood urea nitrogen (BUN), serum creatinine, or creatinine clearance should be determined periodically. When feasible, it is recommended that serum aminoglycoside concentrations be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears or hearing loss) or nephrotoxicity requires dosage adjustment or discontinuation of the drug. As with other aminoglycosides, on rare occasions changes in renal and eighth cranial nerve function may not become manifest until soon after completion of therapy.

Serum concentrations of aminoglycosides should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels. When monitoring gentamicin peak concentrations, dosage should be adjusted so that prolonged levels above 12 mcg/mL are avoided.

When monitoring gentamicin trough concentrations, dosage should be adjusted so that levels above 2 mcg/mL are avoided. Excessive peak and/or trough serum concentrations of aminoglycosides may increase the risk of renal and eighth cranial nerve toxicity. In the event of overdose or toxic reactions, hemodialysis may aid in the removal of gentamicin from the blood, especially if renal function is, or becomes, compromised. The rate of removal of gentamicin is considerably less by peritoneal dialysis than by hemodialysis. In the newborn infant, exchange transfusion may also be considered.

Concurrent bacterial and/or fungal systemic or topical infection of other potentially neurotoxic and/or nephrotoxic drugs, such as cisplatin, cephaloridine, kanamycin, amikacin, neomycin, polymyxin B, colistin, paromomycin, streptomycin, polymyxin E, and vio- mycin, should be avoided. Other factors which may increase patient risk of toxicity are advanced age and dehydration.

The concurrent use of gentamicin with potent diuretics, such as thiazide diuretics or furosemide, should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering the antibiotic concentration in serum and tissue. Aminoglycosides may cause renal failure when administered to a pregnant woman (see WARNINGS section).

GENTAMICIN INJECTION, USP (Pediatric)

DESCRIPTION:

Gentamicin sulfate, a water-soluble antibiotic of the aminoglycoside group, is derived from Micromonospora purpurea, an actinomycete. It has the following structural formula:

\[
\text{Gentamicin} \quad \text{NH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{SO}\cdot \text{H}_2\text{O} \quad \text{C}_2 \quad \text{CH}_2 \cdot \text{NH}_2 \quad \text{NH}_2 \quad \text{CH}_2 \cdot \text{OH} \quad \text{CH}_2 \cdot \text{OH} \quad \text{CH}_2 \cdot \text{OH} \quad \text{CH}_2 \cdot \text{OH} \quad \text{CH}_2 \cdot \text{OH} 
\]

Gentamicin Injection is a sterile, nonpyrogenic, aqueous solution for parenteral administration and is available both with and without preservatives.

Each mL of the preservative free product contains: Gentamicin sulfate, equivalent to gentamicin 10 mg; Water for Injection q.s.; Sulfuric acid and/or sodium hydroxide may have been added for pH adjustment (3-5.5).

CLINICAL PHARMACOLOGY:

After intramuscular administration of gentamicin sulfate, peak serum concentrations usually occur between 30 and 60 minutes and serum levels are measurable for up to 8 hours. In infants, a single therapeutic dose of 2.5 mg/kg usually provides a peak serum level in the range of 3 to 5 mcg/mL. When gentamicin is administered by intravenous infusion over a two-hour period, the serum concentrations are similar to those obtained by intramuscular administration. Age markedly affects the peak concentrations: in one report, a 1 mg/kg dose produced mean peak concentrations of 6.4 mcg/mL and 2.81 mcg/mL in patients six months to five years old, 5 to 10 years old, and over 10 years old, respectively.

In infants one week to six months of age, the half-life is 3 to 3.5 hours. In full-term and large premature infants less than one week old, the approximate serum half-life of gentamicin is 5 hours. In small premature infants, the half-life is inversely related to birth weight. In premature infants weighing less than 1500 grams, the half-life is 11 hours. In those weighing 500 to 2000 grams, the half-life is eight hours; in those weighing over 2000 grams, the half-life is approximately five hours. The half-life is to be expected to be longer due to a number of variables such as age, body temperature and presence of pre-existing neurotoxic or nephrotoxic factors.

Concentration of gentamicin is usually higher in patients old enough to be tested, particularly in those with impaired renal function. The more severe the impairment, the lower the clearance. (Dosage must be adjusted.)

Since gentamicin is distributed in extracellular fluid, peak serum concentrations may be lower than usual in patients who have a large volume of this fluid. Serum concentrations of gentamicin in fecal material may be lower than those in asymptomatic patients given the same dose. When body temperature returns to normal, serum concentrations of the drug may rise. Feces and anemic states may be associated with a shorter than usual serum half-life (dose adjustment is usually not necessary). In severely burned patients, the half-life may be significantly decreased and resulting serum concentrations may be lower than anticipated from the mg/kg dose.

Probenecid binds to gentamicin and has indicated that the degree of gentamicin binding is low, depending upon the methods used for testing, this may be between 0 and 30%.

In neonates less than three days old, approximately 10% of the administered dose is excreted in 12 hours, in infants 5 to 40 days old, approximately 40% is excreted over the same period. Excretion of gentamicin is affected by renal function and age and creatinine clearance. Thus, with increasing postnatal age and concomitant increase in renal maturity, gentamicin is excreted more rapidly. Little, if any, metabolic transformation occurs; the drug is excreted principally by glomerular filtration. After several days of treatment, the amount of gentamicin excreted in the urine approaches, but does not equal, the daily dose administered. As with other aminoglycosides, a small amount of the drug may be retained in the tissues, especially in the kidneys. Minute quantities of aminoglycosides have been detected in the urine of some patients weeks after drug administration was discontinued. Renal clearance of gentamicin is similar to that of endogenous creatinine.

In patients with marked impairment of renal function, there is a decrease in the concentration of aminoglycosides in urine and in their penetration into definitive renal parenchyma. This decreased drug excretion, together with the potential nephrotoxicity of aminoglycosides, should be considered when treating such patients who have urinary tract infections.

Gentamicin does not affect renal tubular transport of gentamicin.

The endogenous creatinine clearance rate and the serum creatinine level have a high correlation with the half-life of gentamicin in serum. Results of these tests may serve as guides for adjusting dosage in patients with abnormal renal function (see DOSAGE AND ADMINISTRATION).

Following parenteral administration, gentamicin can be detected in serum, lymph, tissues, spu- tum, and in pleural, synovial, and peritoneal fluids. Concentrations in renal cortex sometimes may be eight times higher than the usual serum levels. Concentrations in bile, in general, have been low and have suggested minimal biliary excretion. Gentamicin crosses the peritoneal as well as the placenta and umbilical cord. Since aminoglycosides may diffuse poorly into the subarachnoid space after parenteral administration, concentrations of gentamicin in cerebrospinal fluid are often low and dependent upon dose, rate of penetration, and degree of meningeal inflammation. There is minimal penetration of gentamicin into ocular...
tissues following intramuscular or intravenous administration.

Microbiology

In vitro studies have demonstrated that gentamicin is a bactericidal antibiotic which acts by inhibiting protein synthesis in susceptible microorganisms. It is active against a wide variety of pathogenic bacteria including Escherichia coli, Pseudomonas aeruginosa (both beta-lactamase-negative), Pseudomonas aeruginosa, species of the Citrobacter and Enterobacter group, Citrobacter species and Staphylococcus species (including penicillin- and methicillin-resistant strains) and also active in vitro against species of Salmonella and Shigella. The following bacteria have also shown that an aminglycoside combined with an antibiotic that interferes with cell wall synthesis may act synergistically against certain staphylococcal strains.

Gentamicin and penicillin G have a synergistic bactericidal effect against virtually all strains of Staphylococcus aureus and Streptococcus pneumoniae, most species of staphylococci, particularly group D and anaerobic organisms, and certain enterococci species.

Serum levels of gentamicin have shown that an aminglycoside combined with an antibiotic that interferes with cell wall synthesis may act synergistically against certain staphylococcal strains. The combination of gentamicin and penicillin G has a synergistic bactericidal effect against virtually all strains of Staphylococcus aureus and Streptococcus pneumoniae, most species of staphylococci, particularly group D, and anaerobic organisms, and certain enterococci species.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Gentamicin Injection, USP and other antibacterial drugs, Gentamicin Injection, USP should be used only to treat infections that are determined or strongly suspected to be caused by susceptible bacteria. In selecting or modifying antibacterial therapy, in vitro susceptibility test results should be closely correlated with knowledge of the pathogenic organism and its susceptibility.

General

Gentamicin Injection is indicated in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (including Providencia stuartii, Enterobacter cloacae, Klebsiella-Enterobacter-Serratia species, Citrobacter species, and Staphylococcus species (coagulase-negative and coagulase-positive)).

Clinical studies have shown Gentamicin Injection is effective in the treatment of infections due to susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (including Providencia stuartii, Enterobacter cloacae, Klebsiella-Enterobacter-Serratia species, Citrobacter species, and Staphylococcus species (coagulase-negative and coagulase-positive)).

Serum levels of gentamicin have shown that an aminglycoside combined with an antibiotic that interferes with cell wall synthesis may act synergistically against certain staphylococcal strains. The combination of gentamicin and penicillin G has a synergistic bactericidal effect against virtually all strains of Staphylococcus aureus and Streptococcus pneumoniae, most species of staphylococci, particularly group D, and anaerobic organisms, and certain enterococci species.

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removal of gentamicin is considerably less by peri-
toneal dialysis than it is by hemodialysis. In the
newborn infant, exchange transfusions may also be
considered.

**DOSEAGE AND ADMINISTRATION:**

Gentamicin Injection may be given intramuscu-
larly or intravenously. The patient’s pretreatment
body weight should be obtained for calculation of
correct dosage. The dosage of aminoglycosides in
obese patients should be based on an esti-
mate of the lean body mass. It is desirable to
limit the duration of treatment with aminogly-
co sides to short term.

**DOSEAGE FOR PATIENTS WITH NORMAL RENAL FUNCTION**

**Children:** 6 to 7.5 mg/kg/day. (2 to 2.5 mg/kg
administered every 8 hours.)

**Infants and Neonates:** 7.5 mg/kg/day. (2.5 mg/kg
administered every 8 hours.)

**Premature or Full-term Neonates One Week or Less of Age or Less:** 5 mg/kg/day. (2.5 mg/kg administered
every 12 hours.)

It is desirable to measure periodically both peak
and trough serum concentrations of gentamicin
when feasible during therapy to assure adequate but not excessive drug levels. For example, the
peak concentration (at 30 to 60 minutes after intra-
muscular injection) is expected to be in the range
of 3 to 5 mcg/mL. When monitoring peak con-
centrations after intramuscular or intravenous admininstration, dosage should be adjusted so that
prolonged levels above 12 mcg/mL are avoided.
When monitoring trough concentrations (just prior
to the next dose), dosage should be adjusted so
that levels above 2 mcg/mL are avoided. Deter-
mination of the adequacy of a serum level for a
particular patient must take into consideration the
susceptibility of the causative organism, the sever-
ity of the infection, and the status of the patient’s
host-defense mechanisms.

In patients with extended burns, altered pharma-
cokinetics may result in reduced serum
concentrations of aminoglycosides. In such
patients treated with gentamicin, measurement
of serum concentrations is recommended as a basis for dosage adjustment.

The usual duration of treatment is 7 to 10 days.
In difficult and complicated infections, a longer
duration of therapy may be necessary. In such cases
monitoring of renal, auditory, and vestibular func-
tions is recommended, since toxicity is more apt
to occur with treatment extended for more than
10 days. Dosage should be reduced if clinically indi-
cated.

**For Intravenous Administration**
The intravenous administration of gentamicin may
be particularly useful for treating patients with
bacterial septicemia or those in shock. It may also
be the preferred route of administration for some
patients with congestive heart failure, hematopo-
etic disorders, severe burns, or those with
reduced muscle mass.

For intermittent intravenous administration, a
single dose of Gentamicin Injection may be
administered in 0.9% Sodium Chloride Injection or
in 5% Dextrose Injection. The solution may be
infused over a period of one-half to two hours.
The recommended dosage for intravenous and intramuscular administration is identical.

Gentamicin Injection should not be physically
premixed with other drugs, but should be admin-
istered separately in accordance with the recom-
manded route of administration and dosage schedule.

**DOSEAGE FOR PATIENTS WITH IMPAIRED RENAL FUNCTION**

Dosage must be adjusted in patients with impaired
renal function to assure therapeutically adequate
but not excessive, blood levels. Whenever possi-le, serum concentrations of gentamicin should be
monitored. One method of dosage adjustment is
to increase the interval between administration
of the usual doses. Since the serum creatinine
concentration has a high correlation with the
serum half-life of gentamicin, this laboratory test
may provide guidance for adjustment of the inter-
val between doses. In adults, the interval between
doses (in hours) may be approximated by multi-
plying the serum creatinine level (mg/100 mL) by
8. For example, a patient weighing 60 kg with a
serum creatinine level of 2 mg/100 mL could be
given 60 mg (1 mg/kg) every 16 hours (2 x 8). These
guidelines may be considered when treating
infants and children with serious renal impairment.

In patients with serious systemic infections and
renal impairment, it may be desirable to adminis-
ter the antibiotic more frequently but in reduced
dosage. In such patients, serum concentrations of
gentamicin should be measured so that adequate
but not excessive levels result.

A peak and trough concentration measured intermittently during therapy will provide optimal
guidance for adjusting dosage. After the usual
initial dose, a rough guide for determining reduced
dosage at eight-hour intervals is to divide the nor-
mally recommended dose by the serum creati-
nine level (Table I). For example, after an initial
dose of 20 mg (2 mg/kg), a child weighing 10 kg
with a serum creatinine level of 2 mg/100 mL
could be given 10 mg every eight hours (20 x 2). It
should be noted that the status of renal function
may be changing over the course of the infec-
tious process. It is important to recognize that
deteriorating renal function may require a greater
reduction in dosage than that specified in the
above guidelines for patients with stable renal impairment.

**TABLE I**

**DOSEAGE ADJUSTMENT GUIDE FOR PATIENTS WITH RENAL IMPAIRMENT**

(Dosage at Eight-Hour Intervals After the Usual Initial Dose)

<table>
<thead>
<tr>
<th>Serum Creatinine (mg%)</th>
<th>Approximate Creatinine Clearance Rate (mL/min/1.73m²)</th>
<th>Percent of Usual Doses Shown Above</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.1-1.3</td>
<td>100-100</td>
<td>100</td>
</tr>
<tr>
<td>1.1-1.3</td>
<td>100-100</td>
<td>100</td>
</tr>
<tr>
<td>1.4-1.6</td>
<td>55-70</td>
<td>65</td>
</tr>
<tr>
<td>1.7-1.9</td>
<td>45-55</td>
<td>55</td>
</tr>
<tr>
<td>2.0-2.2</td>
<td>40-45</td>
<td>50</td>
</tr>
<tr>
<td>2.3-2.5</td>
<td>35-40</td>
<td>40</td>
</tr>
<tr>
<td>2.6-3</td>
<td>30-35</td>
<td>35</td>
</tr>
<tr>
<td>3.1-3.5</td>
<td>25-35</td>
<td>25</td>
</tr>
<tr>
<td>3.6-4</td>
<td>22-25</td>
<td>22</td>
</tr>
<tr>
<td>4.1-5.1</td>
<td>20-20</td>
<td>20</td>
</tr>
<tr>
<td>5.2-6.6</td>
<td>10-15</td>
<td>15</td>
</tr>
<tr>
<td>6.7-8</td>
<td>&lt;10</td>
<td>10</td>
</tr>
</tbody>
</table>

In patients with renal failure undergoing hemo-
dialysis, the amount of gentamicin removed from
the blood may vary depending upon several fac-
tors including the dialysis method used. An eight-
hour hemodialysis may reduce serum concen-
trations of gentamicin by approximately 50%.
Children, the recommended dose at the end of
each dialysis period is 2 to 2.5 mg/kg depending
upon the severity of the infection.

The above dosage schedules are not intended as
rigid recommendations but are provided as
guides to dosage when the measurement of
gentamicin serum levels is not possible.

A variety of methods are available to measure
gentamicin concentrations in body fluids; these
include microbiologic, enzymatic and radio-
immunoassay techniques.

Parenteral drug products should be inspected
visually for particulate matter and discoloration
prior to administration, whenever solution and con-
tainer permit.

**HOW SUPPLIED:**

Gentamicin Injection, USP (Preservative Free) is
supplied as:

<table>
<thead>
<tr>
<th>Strength</th>
<th>No.</th>
<th>No.</th>
</tr>
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<tbody>
<tr>
<td>10 mg/mL</td>
<td>17302</td>
<td>63323-173-02</td>
</tr>
</tbody>
</table>

Dosage at Eight-Hour Intervals

After the Usual Initial Dose

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<tr>
<th>Serum Creatinine (mg%)</th>
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visually for particulate matter and discoloration
prior to administration, whenever solution and con-
tainer permit.

**Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].**

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