Summary of Product Characteristics

1. Name of the medicinal product

Epigent Ampoules

2. Qualitative and quantitative composition

Composition:
Each ampoule contains:
Gentamicin (as sulphate) ……..…….. 20, 40 or 80 mg
For excipients, see 6.1

3. Pharmaceutical form

Clear colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

EPIGENT is indicated in adults and children (see sections 4.4 and 5.1):
Curative Treatment for severe infections due to identified or suspected bacterial species, microbiologically sensitive to gentamicin. Under these conditions, EPIGENT can be used:
in the following infections:
- urinary tract infections,
- endocarditis,
- meningitis,
- osteo-articular infections,
- listeriosis,

Patients who may present with bacteremia associated or suspected to be associated with one of the infections mentioned above,
In particular in risky situations (septic shock not microbiologically documented, late nosocomial injections, foreign body infections),
In particular in subjects at risk (immunocompromised patients, newborns).
Preventive treatment , prophylaxis of post-operative infections and prophylaxis during radiological procedures and interventional medicine, according to the recommendations for the proper use of antibiotics.
Gentamicin is generally used as a curative treatment in combination with other antibiotics, in particular with beta-lactams. However, it can be prescribed as monotherapy in certain clinical situations, in particular in the treatment of urinary tract infections.
Consideration should be given to official recommendations regarding the appropriate use of antibacterial.

4.2 Posology and method of administration.

CAUTION: In the absence of data, administration of Gentamicin solution for injection by inhalation is not recommended (see section 4.4).

Dosage

The dose depends on the severity of the clinical picture, the site, the renal function of the patient and the bacteria identified.

The dose is expressed according to the patient's body weight.

There are several presentations of gentamicin, some of which are more suitable for high doses to be administered intravenously (160 mg strength).

INTRAVENOUS AND INTRAMUSCULAR ROUTE

The administration schedules are identical for the intravenous route and for the intramuscular route.

Adult

In subjects with normal renal function

Cure

Administration rates

The preferred dosage regimen is the single daily dose (DUJ), i.e. the entire daily dose administered in a single daily injection (see section 4.4).

A daily dose divided into 2 to 3 daily injections is possible, in particular in certain situations (in particular endocarditis).

Doses

The dose varies from 3 to 8 mg / kg / day according to official recommendations, the maximum dose of 8 mg / kg / day being especially recommended at the start of treatment, in serious infections and / or in cases of risk of infection due to to a bacterial strain of decreased sensitivity with an increased minimum inhibitory concentration (MIC) to gentamicin.

Duration of the treatment

Gentamicin is generally used at the start of treatment with a combination of antibiotics, and for a maximum of 5 days, generally stopping after 24 to 72 hours of treatment (corresponding to obtaining the results of the antibiogram).

Plasma assays

As with any aminoglycoside, monitoring of treatment with gentamicin may require monitoring of the plasma concentrations of the antibiotic. The plasma peak (Cmax) assesses efficacy (achievement of pharmacokinetic-pharmacodynamic objectives, see section 5.1) and the residual concentration (Cmin) is predictive of toxicity. Plasma determinations should not be systematic and should be reserved for certain situations according to the recommendations in force.

Among other things, there is no need to perform plasma assays for a treatment lasting a maximum of 3 days in patients for whom no modification of the pharmacokinetic parameters is expected. On the other hand, the plasma assays are to be carried out as follows:

- Peak plasma dosage to be performed: 30 minutes after the end of the aminoglycoside infusion (the duration of which should also be 30 minutes); after the first injection of aminoglycoside in severe patients.
- Dosage of the residual concentration to be carried out: if the duration of treatment is greater than 5 days (dosage to be carried out after 48 hours of treatment) or in the event of renal insufficiency; if the residual levels (Cmin) are greater than the maximum concentration objectives for gentamicin [Peak (Cmax) = 30 to 40 mg / l; Residual (Cmin) <0.5 mg / l] requiring injection spacing.

Prophylactic treatment

Antibiotic prophylaxis in surgery and interventional medicine should be of short duration, most often limited to the preoperative period, sometimes 24 hours, but never more than 48 hours. The administration of the antibiotic should precede the start of the procedure by approximately 30

minutes.
Intravenous administration is required.

In subjects with renal insufficiency

Cure

It is essential to favor the DUJ scheme, to practice plasma dosages (peak and residual) to adjust the dosages and the intervals between each injection, to favor short durations of treatment (as a general rule: 1 or 2 injections), to take into account other risk factors favoring the nephrotoxicity of aminoglycosides, monitor renal and hearing functions (see sections 4.4 and 4.8).

First injection

The dosage of the first injection is identical to that of the subject with normal renal function, regardless of the degree of renal insufficiency (including all situations of extra-renal purification).
In case of dialysis, injections should be given 2 to 4 hours before the dialysis session to reduce the potential for toxicity.

If several injections

Reinjections should be given at the same dose as that of the first injection, unless it is necessary to adjust the unit dose according to the peak dosage.
Renal insufficiency without extra-renal purification : no reinjection should be carried out as long as the residual level is above the toxicity threshold (see sections 4.2 and 4.4).
If the dosage of the residual (usually performed at the 24 th hour) is higher than the toxicity threshold, repeat the dose 24 hours later.
If it is not possible to perform dosages, the time of reinjection is determined by the value of the creatinine clearance (*Hartford Hospital* diagram) according to the table below:

Creatinine clearance (ml / min)	Time between 2 injections
90-60	24 hours
60-40	36 hours
40-20	48 hours
<20	Determination of the residual rate

Continuous extra-renal purification : adjustment of the treatment should be considered by carrying out repeated dosages of the residual; Gentamicin should only be reinjected when the level is below the toxicity threshold (see sections 4.2 and 4.4).

Elderly subject

The treatment modalities must be adapted to the renal function.

Obese subject

The dose in mg / kg should be calculated based on the corrected weight:

Corrected weight = ideal weight [1] + 0.43 x overweight

(Overweight = total weight - ideal weight)

[1] Lorentz formula (ideal weight expressed in kg):
Woman = Height (cm) - 100 - [Height (cm) - 150] / 2
Man = Height (cm) - 100 - [Height (cm) - 150] / 4
Conditions for using this formula:
- Age over 18;
- Size between 140 and 220 cm.

Hepatic impairment

Gentamicin is contraindicated in severe cirrhosis of grades B and C according to the Child-Pugh classification (see section 4.3). In other cases of hepatic impairment, the prescription of gentamicin is possible and no dosage adjustment is necessary.

Pediatric population

Cure

Particular attention should be paid to the preparation (dilution) and the amount administered. Any error, however small, can have a major impact on the serum concentrations obtained.

The doses expressed in mg / kg in infants and children are the same as in adults, and the single daily dose remains the rule.

For newborns, the dosages should be adapted according to the post-conceptual age, taking into account the recommendations in force.

Administration mode

Administration intravenously (as a 30-minute infusion) or intramuscularly.

For the intravenous route, the amount of gentamicin to be administered should be diluted in a solution for infusion (Glucose 5% or NaCl 0.9%) at a rate of approximately 50 to 200 ml, respecting a maximum concentration of 10 mg / ml.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Grades of cirrhosis B and C according to Child-Pugh classification,
- Myasthenia gravis,
- Administration by the subcutaneous route to lack of efficacy and onset of necrosis at the injection site,
- Simultaneous administration of another aminoglycoside (see section 4.5).

4.4 Special warnings and precautions for use

In the absence of data, the use of Gentamicin solution for injection by inhalation is not recommended.

The use of aminoglycosides must fall within a strict framework of prescription (indications limited to severe infections or due to resistant bacteria, administration schedules to be observed) and be accompanied by appropriate monitoring. Prescribing gentamicin should meet this objective.

Treatment with gentamicin may cause the overgrowth of resistant microorganisms. In this case, appropriate treatment should be put in place.

Single daily dose

Data on the single daily dose (DUJ) show that this prescription:

- Optimize the pharmacokinetic-pharmacodynamic parameters (see section 5.1)
- Promotes tissue distribution,

- Has clinical efficacy at least identical to that obtained after administration divided into multiple daily injections
- Is responsible for renal toxicities and comparable hearing even lower than those observed with other methods of administration,
- Decreases the risk of emergence of resistant mutants.

Renal failure

In the presence of pre-existing acute or chronic renal failure, aminoglycoside is only used if absolutely necessary. All possible non-nephrotoxic alternatives should be investigated.
In patients with renal impairment, dose adjustments are required (see section 4.2).

Renal and cochleo-vestibular damage

Impaired kidney function

The clinical signs of renal damage are: proteinuria, cylindruria, hematuria, aloguria, increased blood concentrations of creatinine and urea. In isolated cases, acute renal failure may occur (see section 4.8).

Effects on the cochleo-vestibular nerves

Damage to the cochleo-vestibular nerves (eighth cranial nerve) where balance and hearing are affected, is possible. Vestibular involvement is the most common of the ototoxic reactions. Hearing loss manifests itself first as a decrease in the acuity of loud sounds and is usually irreversible.
Symptoms of ototoxicity are: dizziness, auditory buzzing / wheezing (tinnitus), vertigo and less commonly, hearing loss (see section 4.8).
In patients with end-stage renal disease, on intermittent hemodialysis or on chronic peritoneal dialysis, the toxicity is mainly auditory, the kidney no longer being functional.

Pediatric population

Based on available data, renal and auditory toxicities remain rare in newborns and children.

Risk factors

The risks of occurrence of renal and auditory toxicities increase for durations of treatment greater than 5-7 days, even in healthy subjects; they are increased in renal failure. However, early toxicity may appear from the first doses.
Renal toxicity is independent of the peak plasma concentration (Cmax).
Regarding auditory and vestibular toxicities, no data shows the existence of a correlation with the level of plasma concentration obtained at the peak, even if the treatment is administered as a single daily dose.
The main risk factors for nephrotoxicity (and ototoxicity for some) are:
- The most common clinical situations favoring renal hypoperfusion and accompanied by a lesser elimination of aminoglycosides

- age> 75 years (physiological deterioration of renal function from 60 years),
- dehydration, often related to age,
- combination with certain drugs, especially loop diuretics (see section 4.5),
- left ventricular failure, hypovolaemia, state of shock,
- hypoalbuminemia,

Grade B and C cirrhosis according to the Child-Pugh classification (see section 4.3),

 Clinical situations increasing the risk of kidney damage

- pre-existing or concomitant nephropathy,
- combination with certain medicines (see section 4.5).

Neuromuscular disorders

Since gentamicin has neuromuscular blocking properties, special care should be taken in patients with pre-existing neuromuscular disease (eg Parkinson's disease). Close monitoring of such patients is imperative (see section 4.8).

Neuromuscular blockages and respiratory paralysis have been reported following administration of aminoglycosides in patients who have received curares during anesthesia. These patients should also be monitored very closely (see section 4.8).

Diarrhea associated with antibiotics and pseudomembranous colitis

Antibiotic-related diarrhea and pseudomembranous colitis have been observed with concomitant use of gentamicin with other antibiotics. These diagnoses should be considered in any patient who develops diarrhea during or after treatment. Gentamicin should be discontinued if severe and / or bloody diarrhea occurs during treatment and appropriate therapy should be initiated. Medicines which inhibit peristalsis should not be administered (see section 4.8).

Drug combinations

The intake of this medicinal product should be avoided during treatment with polymyxin B or botulinum toxin (see section 4.5).

Excipients

This medicine contains less than 1 mmol (23 mg) sodium per milliliter, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction.

Nephrotoxic drugs

The joint use of drugs with their own renal toxicity increases the risk of nephrotoxicity. If such a combination is necessary, renal biological monitoring should be reinforced. The drugs concerned are represented in particular by iodinated contrast products, aminoglycosides, organoplatins, high-dose methotrexate, certain antivirals (such as “ciclovirs”, foscarnet), pentamidine, ciclosporin or tacrolimus.

Ototoxic drugs

The joint use of drugs with their own ototoxicity increases the risk of cochleo-vestibular damage. If such a combination is necessary, monitoring of hearing function should be strengthened. The drugs concerned are represented in particular by antibiotics of the glycopeptide family, such as vancomycin and teicoplanin, aminoglycosides, cytotoxics such as organoplatins, and loop diuretics.

Contraindicated associations

- Other aminoglycosides in simultaneous administration

Increased risk of nephrotoxicity and ototoxicity.

Not recommended associations

- Polymyxin B

Addition of nephrotoxic effects. If the association cannot be avoided, strict monitoring with indisputable bacteriological justification.

- Botulinum toxin

Risk of increased effects of botulinum toxin with aminoglycosides (by extrapolation from the effects observed during botulism). Use another antibiotic.

Combinations subject to precautions for use

- Cefalotin

The increase in the nephrotoxicity of aminoglycosides by cefalotin is discussed.

Monitoring of renal function.

- Curares

Potentiation of curares when the antibiotic is administered parenterally and / or peritoneally before, during or after the curarizing agent.

Monitor the degree of curarization at the end of anesthesia.

- Loop diuretics

Increased nephrotoxic and ototoxic risks of aminoglycoside (functional renal failure linked to dehydration caused by the diuretic).

Possible association under the control of the state of hydration, renal and cochleo-vestibular functions, plasma concentrations of aminoglycoside.

Associations to take into account

- Other aminoglycosides in successive administration

Take into account the risk of cumulative ototoxicity.

- Amphotericin B administered by IV route

Increased risk of nephrotoxicity.

- Ciclosporin

Greater increase in serum creatinine than with cyclosporine alone, with increased nephrotoxic risk.

- Organoplatins

Addition of nephrotoxic and / or ototoxic effects, in particular in the event of previous renal failure.

- Tacrolimus

Greater increase in serum creatinine than with tacrolimus alone (synergy of the nephrotoxic effects of the two substances).

Specific problems of INR imbalance

Many cases of increased activity of vitamin K antagonists have been reported in patients receiving antibiotics. The marked infectious or inflammatory context, the age and general condition of the patient appear to be risk factors. Under these circumstances, it appears difficult to distinguish between the infectious pathology and its treatment in the occurrence of the INR imbalance. However, certain classes of antibiotics are more involved: these include fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins.

4.6 Fertility, pregnancy and lactation:

Pregnancy

The indications should be limited to severe clinical pictures in the absence of an alternative. In the case of exposure during pregnancy, it is desirable to assess the hearing function of the newborn (oto-emissions).

Feeding with milk

Breast-feeding is possible during treatment with gentamicin.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed.

As this treatment is likely to cause balance disturbances, drivers and users of machines should be warned of this potential risk.

4.8 Undesirable effects

The side effects considered to be most likely related to the treatment are listed below by organ and frequency. The frequencies are defined by:

Very common (≥ 1/10);

Common (≥ 1/100, <1/10);

Uncommon (≥ 1/1000, <1/100);

Rare (≥ 1 / 10,000, <1 / 1,000);

Very rare (<1 / 10,000);

Not known (frequency cannot be estimated from the available data).

System organ class	Common (≥ 1/100, <1/10)	Uncommon (≥ 1/1000, <1/100)	Rare (≥ 1 / 10,000, <1/1000)	Very rare (<1 / 10,000)	Not known (frequency cannot be estimated from the available data)
Injections and infestations					Super infection (with organisms resistant to gentamicin), pseudomembranous colitis (see section 4.4) [1]
Blood and lymphatic system disorders		Dyscrasia		Thrombocytopenia, reticulocytopenia, leukopenia, eosinophilia, granulocytopenia, anemia	
Immune system disorders					Hypersensitivity reactions of varying degrees of severity ranging from rash and pruritus, drug-induced fever to severe acute hypersensitivity reactions (anaphylaxis), up to anaphylactic shock
Metabolism and nutrition disorders			Hypokalaemia, hypocalcaemia, hypomagnesemia, Bartter-like syndrome in patients treated with high doses for a long time (more than 4 weeks), loss of appetite, weight loss	Hypophosphatemia	

System organ class	Common (≥ 1/100, <1/10)	Uncommon (≥ 1/1000, <1/100)	Rare (≥ 1 / 10,000, <1/1000)	Very rare (<1 / 10,000)	Not known (frequency cannot be estimated from the available data)
Psychiatric disorders				Confusion, hallucinations, depression	
Nervous system disorders			Polyneuropathies, peripheral paresthesias	Encephalopathy, convulsions, neuromuscular blockade, dizziness, vertigo, balance disturbance, headache (see section 4.4)	
Eye disorders				Visual disturbances	
Ear and labyrinth disorders				Vestibular involvement, hearing loss, Ménière's disease, tinnitus (see section 4.4)	Irreversible hearing loss, deafness
Vascular disorders				Hypotension, hypertension	
Gastrointestinal disorders			Vomiting, nausea, increased salivation, stomatitis		
Hepatobiliary disorders			Increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALAT), increased alkaline phosphatase (ALP) (all are reversible)		
Skin and subcutaneous tissue disorders		Allergic skin rash	Red discoloration of the skin	erythema multiforme, alopecia	Stevens-Johnson syndrome, toxic epidermal necrolysis [2]

System organ class	Common (≥ 1/100, <1/10)	Uncommon (≥ 1/1000, <1/100)	Rare (≥ 1 / 10,000, <1/1000)	Very rare (<1 / 10,000)	Not known (frequency cannot be estimated from the available data)
Muscular-skeletal and connective tissue disorders			Muscle pain (myalgia)	Amyostasis	
Kidney and urinary tract disorders	Impaired kidney function		Increased azotemia (reversible)	Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi syndrome in patients receiving long-term high dose therapy (see section 4.4)	
General disorders and administration site conditions			Increased body temperature	Pain at the injection site	

[1] Usually in these cases other antibiotics are also involved.

[2] May occur as hypersensitivity reactions.

4.9 Overdose

Gentamicin has a narrow therapeutic window. If accumulated, kidney damage and damage to the vestibulo-cochlear nerves may appear.

Treatment for overdose

Stop the treatment. There is no specific antidote. Gentamicin can be removed from the blood by dialysis.

Treatment of neuromuscular blockages

In the event of neuromuscular blockade, the administration of calcium chloride is recommended as well as the use of artificial ventilation if necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other aminoglycosides, ATC code: J01GB03

Action mechanism

Gentamicin is an antibiotic from the aminoglycoside family.

Gentamicin has a bactericidal effect on both the proliferation and the latency state of bacteria. It forms a bond with the 30S subunits of bacterial ribosomes, resulting in a "spurious reading" of the mRNA.

Pharmacodynamic effects

The bactericide of aminoglycosides is *in vitro* "concentration-dependent". This bactericide is accompanied by a prolonged post-antibiotic effect (EPA) and adaptive resistance to the first dose (decrease in the rate of bactericide, increase in MICs and decrease in the duration of EPA).

In terms of pharmacokinetics-pharmacodynamics (PK / PD), the efficacy is linked to the relationship that exists between the maximum concentration obtained after an injection (Cmax) and the MIC for the germ involved.

The therapeutic effect is maximal if the Cmax / MIC ration is ≥ 8 to 10; the dosage used must make it possible to obtain peak plasma concentrations of a value at least equal to 8-10 times the MIC of the germ.

Since gentamicin is most often prescribed probabilistically (germ and / or sensitivity not known), to achieve the PK / PD objectives, taking into account the critical concentrations of gentamicin (critical concentration greater than 4 mg / l), the maximum plasma peak target is 30 to 40 mg / l /

The objectives of PK / PD remain the same whatever the site (renal insufficiency, elderly subject> 75 years old, obese, pregnant and lactating women).

The effectiveness of aminoglycosides is not influenced by bacterial density (absence of inoculum effect).

Mechanisms of resistance

The mechanisms of acquired resistance to aminoglycosides are very varied. The most frequent are of plasmid origin, through genes encoding enzymes which modify, in a variable manner, the various aminoglycosides.

The other mechanisms of acquired resistance are efflux, impermeability or mutation of ribosomal proteins. They also affect the different aminoglycosides in a variable way. The enzyme AAC (6 ') - Ib-cr is the first capable of inactivating both aminoglycosides and quinolones by acetylation.

The frequency of resistance in the intestinal flora during systemic treatments is negligible because these molecules are not eliminated by the digestive route.

Critical concentrations

Critical concentrations separate susceptible strains from intermediate susceptibility strains, and the latter from resistant ones:

EUCAST Recommendations (version 2.0, 2.012-01-01)

Micro-organisms	Sensitive	Resistant
Enterobacteriaceae	S ≤ 2 mg / l	R> 4 mg / l
Pseudomonas spp.	S ≤ 4 mg / l	R> 4 mg / l
Acinetobacter spp.	S ≤ 4 mg / l	R> 4 mg / l
Staphylococcus (*S. aureus* , coagulase negative staphylococci)	S ≤ 1 mg / l	R> 1 mg / l
Critical concentrations unrelated to species	S ≤ 2 mg / l	R> 4 mg / l

Spectrum of anti-bacterial activity

The prevalence of acquired resistance may vary depending on geography and time for some species. It is therefore useful to have information on the prevalence of local resistance, especially for the treatment of severe infections. If necessary, it is desirable to obtain a specialist opinion mainly when the benefit of the drug in certain infections may be called into question due to the level of prevalence of local resistance.

USUALLY SENSITIVE SPECIES
Gram-positive aerobes
Listeria monocytogenes
Methicillin- sensitive *Staphylococcus aureus*
Gram-negative aerobes
Campylobacter coli
Campylobacter jejuni
Citrobacter koseri

Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Francisella tularensis
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus vulgaris
Salmonella enterica subsp. *enterica*
Serratia marcescens
Yersinia enterolotica
Yersinia pseudotuberculosis
INCONSTALLY SENSITIVE SPECIES **ACQUIRED RESISTANCE ≥ 10%**
Gram-positive aerobes
Methicillin- resistant *Staphylococcus aureus*
Staphylococcus epidermidis
Staphylococcus haemolyticus
Gram-negative aerobes
Acinetobacter spp.
Citrobacter freundii
Morganella morganii
Proteus mirabilis
Pseudomonas aeruginosa
NATURALLY RESISTANT SPECIES
Gram-positive aerobes
Enterococcus faecalis

Enterococcus faecium
Streptococcus spp.
Gram-negative aerobes
Burkholderia cepacia
Legionella pneumophila
Stenotrophomonas maltophilia
Anaerobic
Others
Atypical pathogens
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum

Combinations with other antibiotics

The association of aminoglycosides with beta-lactams is synergistic *in vitro* and shows an interest in animal models in terms of efficacy and limitation of the emergence of resistance.

Aminoglycosides are used as part of a combination in order to seek a bactericidal synergy (essentially demonstrated *in vitro*), to prevent the emergence of resistance and to broaden the spectrum of activity of the treatment.

5.2 Pharmacokinetic properties

Distribution

Serum Concentrations

-In subjects with normal renal function

After IM administration at a unit dose of 1 mg / kg, the serum peak, reached after 30 to 60 minutes, is of the order of 4 µg / ml. Active plasma concentrations persist for approximately 6 hours.

After IM administration at a unit dose of 160 mg, the serum peak, reached after 30 to 60 minutes, is of the order of 9 µg / ml. Active plasma concentrations persist for approximately 8 hours.

After intravenous administration by infusion over 30 minutes at 4 mg / kg of body weight per day, divided into 3 doses, the maximum and minimum gentamicin concentrations measured in adults were 4.7 µg / ml and 1, 0 µg / ml respectively. With the same daily dose administered once, maximum and minimum concentrations of 9.5 µg / ml and 0.4 µg / ml were measured.

o In subjects with renal insufficiency

The serum peak is slightly higher and plasma concentrations are more prolonged.

Half-lives

The half-life of gentamicin is just over 2 hours in normal renal adults.

It is 3.0 - 3.30 h in infants and 5.25 - 5.50 h in newborns.

In the presence of a renal function deficit, this half-life is all the more prolonged as the deficit is greater.

Tissue and humoral Distribution

After parenteral administration, gentamicin is found in most tissues and body fluids.

Therapeutic levels are present in the serum.

The concentrations in the renal parenchyma are much higher than the plasma levels.

Concentrations of the order of 40 percent and above are found in bronchial secretions, infected bone, synovial fluid and tissue, skin, pleura, pericardium, peritoneal cavity, and ascitic fluid.

Gentamicin does not enter the prostate.

It crosses the fetal-placental barrier.

On the other hand, it hardly crosses the hemo-meningeal barrier.

Passage into breast milk is negligible.

Gentamicin diffuses through the membranes used in hemodialysis.

Plasma protein binding

At therapeutic levels and under normal physiological conditions, the binding of gentamicin to plasma proteins is weak, ranging from 0 to 3 percent.

Biotransformation

Gentamicin does not undergo metabolic transformation.

Elimination

Excretion of the antibiotic is primarily through the kidneys by glomerular filtration in an unmetabolized and therefore active form. There is a small tubular reabsorption. On average, 60 percent of the injected dose is excreted in the urine within the first 6 hours and 85 percent after 24 hours.

After an injection of 160 mg of gentamicin, urinary levels are, on average, 188 µg / ml during the 8 hours following the injection, 60 µg / ml from the 8 th to 16 th hour and 34 µg / ml of the 16 th to the 24 th hour.

Urinary elimination decreases as the degree of renal failure increases.

However, in non-anuric renal failure, urinary concentrations obtained in samples collected 12 to 24 hours after injection (8 to 10 µg / ml) remain above the MIC of susceptible organisms.

Renal clearance of gentamicin decreases in proportion to renal failure, but without a significant change in the renal clearance / creatinine clearance ratio, which remains in the region of 60 to 70 percent.

Bile concentrations are generally low reflecting poor bile elimination.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium metabisulphite, methylparaben, propylparaben, edetate disodium, water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years .

6.4 Special precautions for storage

Store at a temperature 15° - 25°C.

6.5 Nature and contents of container

Epigent 20 mg Ampoules: Pack of 3 ampoules of 2 ml each.
Epigent 40 mg Ampoules: Pack of 3 ampoules of 2 ml each.
Epigent 80 mg Ampoules: Pack of 3 ampoules of 2 ml each.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. Marketing authorisation holder

Egyptian international pharmaceutical industries company (EIPICO)

8. MARKETING AUTHORISATION NUMBER(S)

06871/07721/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06871/07721/REN/2020

10. Date of revision of the text

May 2021