1. NAME OF THE VETERINARY MEDICINAL PRODUCT

GentaDug 85 mg/ml solution for injection for horses, cattle, pigs, dogs and cats.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1.0 ml solution for injection contains:

Active substance:
Gentamicin sulphate 85 mg
(equivalent to Gentamicin 50 mg)

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Methyl parahydroxybenzoate	0.9 mg
Propyl parahydroxybenzoate	0.1 mg
Sodium metabisulfite	
Water for injection	

A clear, colourless to slight yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Horses (non-food producing horses), cattle, pigs, dogs and cats.

3.2 Indications for use for each target species

Treatment of the following infections:

Horses: for the treatment of infections of the lower respiratory tract in horses caused by aerobic Gram-negative bacteria.
Cattle: infections of the genital tract.
Calves: infections of the respiratory tract, infections of the gastro-intestinal tract, septicaemia, infections of the joints, infections of the auditory meatus.
Pigs: infections of the respiratory tract, metritis, mastitis and agalactia (MMA) complex.
Piglets, weaners: infections of the respiratory tract, enzootic pneumonia, infections caused by *E. coli*.
Dogs, cats: infections of the respiratory tract, infections of the gastro-intestinal tract, infections of the kidneys, the urinary and the genital tract, septicaemia, infections of the auditory meatus.

3.3 Contraindications

Do not use in animals with impaired renal function.
Do not use in dehydrated animals due to the risk of acute renal failure.
Do not use in animals with disturbances of the vestibular or auditory systems.
Do not use in cases of known hypersensitivity to the active substance or to any of the excipients.
Do not inject intravenously if used concomitantly with muscle relaxants.
Do not use concomitantly with bacteriostatic antibiotics.
Do not administer concurrently with diuretics and potentially nephrotoxic medicinal products.
Do not exceed the proposed dosing regimen.

3.4 Special warnings

Within the group of aminoglycosides, complete cross-resistance is often observed.

3.5 Special precautions for use

Special precautions for safe use in the target species:
As gentamicin has a narrow therapeutic margin, to ensure a correct dosage, body weight should be determined as accurately as possible.

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.
Use of the product should be in accordance with official, national and regional antimicrobial policies.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for the first line treatment where susceptibility testing suggests the likely efficacy of this approach.

Because of the risk of occurrence of neuromuscular blockade, the veterinary medicinal product must be injected slowly when administered intravenously.

In dehydrated animals, fluid balance should be restored before treatment is initiated.

Horses:
Gentamicin is well known to induce nephrotoxicity even at therapeutic doses. There are also isolated reports of ototoxicity with gentamicin. No margin of safety has been established under the approved dosing regimen. As such, gentamicin has a narrow margin of safety.

The product should therefore only be used based on the benefit-risk assessment by the responsible veterinary surgeon for each individual horse, taking into account alternative available treatment.

In order to reduce the nephrotoxic risk, adequate hydration of animals under treatment should be ensured, and fluid therapy should be instituted, if required.

Close monitoring of horses being treated with gentamicin is strongly advised. This monitoring includes assessing relevant kidney parameters in blood (e.g. creatinine and urea) and urinalysis (e.g. gamma glutamyl transferase/creatinine ratio). Therapeutic blood monitoring of gentamicin concentration is also recommended because of known individual animal variations in peak and trough gentamicin plasma concentrations. Where blood monitoring is available, target peak plasma gentamicin concentrations should be approximately 16–20 μg/ml.

Particular caution should be taken when administering gentamicin with other potential nephrotoxic medicinal products (containing e.g. NSAIDs, furosemide, and other aminoglycosides).

Safety of gentamicin has not been established in foals and there is a lack of knowledge of the extra effects of gentamicin on foal kidneys, especially neonates. Current knowledge suggests that foals, especially neonates, are at a higher risk of gentamicin-induced nephrotoxicity compared to adults. Differences between neonatal foal kidneys and adults include a slower clearance of gentamicin in foals. As such, no margin of safety has been established in neonatal foals. It is therefore not recommended to use the product in foals.

Whenever possible, use of the product should be based on susceptibility testing of the bacteria isolated from the animal. Gentamicin is a narrow-spectrum Gram- negative bactericidal antimicrobial, without effects on anaerobe bacteria and mycoplasmas. Gentamicin does not penetrate intracellularly, or into abscesses.

Gentamicin is de-activated in the presence of inflammatory debris, low oxygen environments and low pH.

The dosing regimen must not be exceeded. Use of the product deviating from the instructions given in the SPC increases the risk of nephrotoxicity, and may increase the prevalence of bacteria resistant to gentamicin.

Extra caution is advised if using gentamicin in old horses, or with fever, endotoxemia, sepsis and dehydration.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to gentamicin, sodium metabisulfite or methyl- or propyl parahydroxybenzoate should avoid contact with the veterinary medicinal product.

3.6 Adverse events

Horses (non-food producing horses), cattle, pigs, dogs and cats:

Undetermined frequency (cannot be estimated from the available data):	Vestibular disorder[1] Internal ear disorder[1] Renal disorders[1] Proteinuria[2]

[1] May occur when administered for a treatment period exceeding the recommendations.

[2] Renal disorders may result in proteinuria associated with elevated blood urea nitrogen.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See also section “Contact details” of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety in pregnant horses has not been established. However, studies in laboratory animals have shown evidence of foetal nephrotoxicity. Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

When treating simultaneously with other pharmaceuticals, they should always be administered separately to avoid possible inactivation.
Do not use concomitantly with other oto- or nephrotoxic drugs.
Combined therapy with suitable antibiotics (e.g. ß-lactam antibiotics) may lead to a synergistic effect. Synergistic effects with acylaminopenicillins on *Pseudomonas aeruginosa* and with cephalosporins on *Klebsiella pneumoniae* have been described.
Please note that cross allergy to other aminoglycoside antibiotics may occur.

3.9 Administration routes and dosage

Horses:

For slow intravenous use.
Single dose of 11.2 mg gentamicin sulphate (= 6.6 mg gentamicin) per kg bodyweight, corresponding to 6.6 ml of the veterinary medicinal product per 50 kg bodyweight
given intravenously once daily for 3 - 5 consecutive days.

To ensure a correct dosage, bodyweight should be determined as accurately as possible. The dosing regimen should not be exceeded. The use of gentamicin in foals and neonates is not recommended.

Cattle, pigs:

For intramuscular or slow intravenous injection.
5.9 mg gentamicin sulphate (= 3.5 mg gentamicin) per kg bodyweight
corresponding to 3.5 ml of the veterinary medicinal product per 50 kg bodyweight
given twice daily at intervals of 12 hours for 3 to 5 days.

Calves, weaners, piglets in the first months of life:

Initial treatment:
5.9 mg gentamicin sulphate (= 3.5 mg gentamicin) per kg bodyweight
corresponding to 0.7 ml of the veterinary medicinal product per 10 kg bodyweight
Second and subsequent injections:
2.9 mg gentamicin sulphate (= 1.75 mg gentamicin) per kg bodyweight
corresponding to 0.3 ml of the veterinary medicinal product per 10 kg bodyweight
given twice daily at intervals of 12 hours for 3 to 5 days.

In pigs do not administer more than 1 ml per injection site.
Repeated injections should be made at different injection sites.

For intramuscular, subcutaneous or slow intravenous injection in dogs and cats.

Dogs older than 2 weeks:

6.5 mg gentamicin sulphate (= 3.85 mg gentamicin) per kg bodyweight
corresponding to 0.8 ml of the veterinary medicinal product per 10 kg bodyweight
given twice daily at intervals of 12 hours on the first day, thereafter once daily at intervals of 24 hours for 3 to 10 days.

Dogs younger than 2 weeks:

Initial treatment:
6.5 mg gentamicin sulphate (= 3.85 mg gentamicin) per kg bodyweight
corresponding to 0.23 ml of the veterinary medicinal product per 3 kg bodyweight
Second and subsequent injections:
3.25 mg gentamicin sulphate (= 1.925 mg gentamicin) per kg bodyweight
corresponding to 0.12 ml of the veterinary medicinal product per 3 kg bodyweight
given twice daily at intervals of 12 hours on the first day, thereafter once daily at intervals of 24 hours for 3 to 10 days.

Cats older than 2 weeks:

4.32 mg gentamicin sulphate (= 2.56 mg gentamicin) per kg bodyweight
corresponding to 0.25 ml of the veterinary medicinal product per 5 kg bodyweight
given twice daily at intervals of 12 hours for 3 to 10 days.

Cats younger than 2 weeks:

Initial treatment:
4.32 mg gentamicin sulphate (= 2.56 mg gentamicin) per kg bodyweight
corresponding to 0.13 ml of the veterinary medicinal product per 2.5 kg bodyweight
Second and further injections:
2.16 mg gentamicin sulphate (= 1.28 mg gentamicin) per kg bodyweight
corresponding to 0.06 ml of the veterinary medicinal product per 2.5 kg bodyweight
given twice daily at intervals of 12 hours for 3 to 10 days.

If no significant clinical improvement is noted within 3 days of treatment, the initial diagnosis should be reassessed and the therapy should be changed, if necessary.
In case an extended treatment is required, kidney function should be monitored.

The closure should not be pierced more than 50 times.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Overdosage as well as a rapid intravenous injection may cause neuromuscular blockade possibly leading to convulsions, respiratory distress and circulatory depression. In case of neuromuscular blockade, associated with convulsions, respiratory distress and collapse, the drug must be withdrawn immediately. Calcium or neostigmine should be injected, if necessary.
In case of allergic or anaphylactic reactions, treatment should be discontinued immediately and therapy with epinephrine, antihistamines, and /or glucocorticoids should be initiated.
Due to the oto- and nephrotoxic potential of gentamicin, corresponding symptoms may occur following overdosage. Treatment should be discontinued immediately.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not authorised for use in horses producing meat or milk for human consumption.

Following intramuscular or intravenous injection:

Cattle:	Meat and offal:	214 days
	Milk:	7 days
Calves:	Meat and offal:	192 days
Pigs, piglets, weaners:	Meat and offal:	146 days

Due to accumulation of gentamicin in liver, kidneys and injection site, treatment should not be repeated during the withdrawal period.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01GB03

4.2 Pharmacodynamics

Gentamicin sulphate has concentration-dependent bactericidal properties.

The degree of antibacterial action increases when the gentamicin concentration exceeds the minimum inhibitory concentration (MIC) for a certain gram-negative pathogen, especially at a ratio of the maximum serum concentration (Cmax) to MIC of 8-10.

Gentamicin sulphate acts by binding irreversibly to the ribosomal 30S subunit and acts via two different mechanisms. In the case of one mechanism, gentamicin interferes with the polymerization and elongation of the correct amino acids.

This mechanism functions at high concentrations. Another mechanism predominates at low concentrations, at which codons of the amino acids are read incorrectly by tRNA and the proofreading is impaired. This leads to incorrect sequencing of amino acids and nonsense proteins.

The substance is highly polar and hydrophilic. Transport appears to be an active process closely associated with electron transport, oxidative phosphorylation and the respiratory quinones in the cell membrane. Gentamicin is primarily distributed within extracellular fluids. Gentamicin does not penetrate into the cerebrospinal fluid.

Gentamicin acts as a narrow-spectrum bactericidal antibiotic against gram-negative bacteria (e. g., *E. coli, Proteus spp., Pseudomonas spp.*). Gentamicin is not effective against anaerobic bacteria and mycoplasma.

Gentamicin does not penetrate intracellularly or into abscesses. Gentamicin is inactivated in the presence of inflammatory debris, a low-oxygen environment and low pH. 85-95 % of the gentamicin dose is excreted by via the kidneys by glomerular filtration.

There are several mechanisms by which various strains have developed resistance against aminoglycosides like gentamicin. Enzymatic modification is the most common mechanism of aminoglycoside resistance. More than 50 different enzymes have been identified. Enzymatic modification results in high resistance level. The genes encoding for the aminoglycoside-modifying enzymes are usually located on plasmids and transposons.

There are three types of aminoglycoside-modifying enzymes:
1. N-Acetyltransferases (AAC) – catalyse the AcetylCoA-dependent acetylation of an amino group
2. O-Adenyltransferases (ANT) – catalyse the ATP-dependent adenylation of a hydroxyl group
3. O-Phosphotransferases (APH) – catalyse the ATP-dependent phosphorylation of a hydroxyl group

Additional resistance mechanisms include ribosomal mutations at the binding site of aminoglycosides, the 30S subunit, and the decrease of permeability for aminoglycosides.

4.3 Pharmacokinetics

Following parenteral administration, gentamicin is absorbed rapidly and completely. More than 90% of the gentamicin absorbed is excreted unchanged via the kidneys within 1 to 2 days. However, residual quantities of gentamicin may accumulate in the renal cortex and the liver and may persist at the injection site(s).
Gentamicin is not permeable across the blood-brain barrier, but it penetrates the placental barrier, with serum concentrations of 15-50% of the maternal concentrations being reached in the foetus.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Incompatibilities exist with amphotericin, heparin, sulfadiazine, various penicillins and cephalosporins, chloramphenicol hydrogensuccinate sodium, oxacillin, vitamin B-complex.
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 36 months
Shelf life after first opening the immediate packaging: 14 days

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

100 ml clear glass vials with bromobutyl rubber stoppers and aluminium caps, packaged in a cardboard box.

Pack sizes:
1 x 100 ml
6 x 100 ml
12 x 100 ml

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Bela-Pharm GmbH & Co.KG
Lohner Str. 19
49377 Vechta
Germany

7. MARKETING AUTHORISATION NUMBER(S)

XXX

8. DATE OF FIRST AUTHORISATION

Date of first authorisation:{DD/MM/YYYY}

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (*https://medicines.health.europa.eu/veterinary*).