# Annex I

# List of the names, pharmaceutical forms, strengths of the veterinary medicinal products, animal species, applicants / marketing authorisation holders in the Member States

| Member State EU/EEA | Applicant/Marketing Authorisation Holder | Product name | INN | Strength | Pharmaceutical form | Animal species |
|---|---|---|---|---|---|---|
| Austria | Vana GmbH<br>Wolfgang Schmälzl Gasse 6<br>1020 Wien<br>Austria | Gentavan 5%-Durchstichflasche für Tiere | Gentamicin (as gentamicin sulphate) | 50 mg/ml | Solution for injection | Horse, foal, cattle, calf, pig, dog, cat |
| Belgium | EMDOKA bvba<br>John Lijsenstraat 16<br>B-2321 Hoogstraten<br>Belgium | Emdogent 100 | Gentamicin | 100 mg/ml | Solution for injection | Horses, cattle, pigs, dogs and cats |
| Belgium | Franklin Pharmaceuticals Ltd.<br>Athboy Road<br>Trim<br>Co. Meath<br>Ireland | Genta Equine | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Horses (non food producing horses) |
| Croatia | Krka - Farma d.o.o.<br>Radnička cesta 48<br>10000 Zagreb<br>Croatia | GENTAMICIN 8% | Gentamicin (as gentamicin sulphate) | 80 mg/ml | Solution for injection | Cattle, horses (non-food producing), pigs, dogs and cats |
| Croatia | PROPHARMA VET d.o.o.<br>Vijenac A. Cesarca 16<br>31000 Osijek<br>Croatia | NEOGENT | Gentamicin (as gentamicin sulphate) | 80 mg/ml | Solution for injection | Cattle, pigs, horses, dogs, cats |
| Czech Republic | FATRO S.p.A.<br>Via Emilia 285<br>Ozzano Emilia (Bologna)<br>Italy | AAGENT 50 mg/ml injekční roztok | Gentamicin | 50 mg/ml | Solution for injection | Calves, foals and piglets at the age of one month |
| Denmark | Franklin Pharmaceuticals Ltd.<br>Athboy Road<br>Trim<br>Co. Meath<br>Ireland | Genta Equine | Gentamicin | 100 mg/ml | Solution for injection | Horses |

| Member State EU/EEA | Applicant/Marketing Authorisation Holder | Product name | INN | Strength | Pharmaceutical form | Animal species |
|---|---|---|---|---|---|---|
| Estonia | Interchemie werken "De Adelaar" Eesti AS<br>Vanapere tee 14, Pringi<br>74001 Viimsi<br>Harjumaa<br>Estonia | Genta-100 EE | Gentamicin | 100 mg/ml | Solution for injection | Cattle, horse, swine |
| Germany | CP-Pharma Handelsgesellschaft mbH<br>Ostlandring 13<br>31303 Burgdorf<br>Germany | Genta 100 mg/ml | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Cattle, pig, horse declared as not being intended for slaugther for human consumption, cat, dog |
| Germany | Bela-Pharm GmbH & Co. KG<br>Lohner Str. 19<br>49377 Vechta<br>Germany | Gentacin | Gentamicin (as gentamicin sulphate) | 50 mg/ml | Solution for injection | Cattle, pig, horse declared as not being intended for slaugther for human consumption, cat, dog |
| Germany | aniMedica GmbH<br>Im Südfeld 9<br>48308 Senden-Bösensell<br>Germany | Gentamicin 50 | Gentamicin (as gentamicin sulphate) | 50 mg/ml | Solution for injection | Cattle, pig, horse declared as not being intended for slaugther for human consumption, cat, dog |
| Germany | aniMedica GmbH<br>Im Südfeld 9<br>48308 Senden-Bösensell<br>Germany | Genta-Sulfat 81 | Gentamicin (as gentamicin sulphate) | 50 mg/ml | Solution for injection | Cattle, pig, horse declared as not being intended for slaugther for human consumption, cat, dog |

| Member State EU/EEA | Applicant/Marketing Authorisation Holder | Product name | INN | Strength | Pharmaceutical form | Animal species |
|---|---|---|---|---|---|---|
| Germany | aniMedica GmbH<br>Im Südfeld 9<br>48308 Senden-Bösensell<br>Germany | Vepha-Gent forte | Gentamicin (as gentamicin sulphate) | 50 mg/ml | Solution for injection | Cattle, pig, horse declared as not being intended for slaugther for human consumption, cat, dog |
| Germany | Bela-Pharm GmbH & Co. KG<br>Lohner Str. 19<br>49377 Vechta<br>Germany | Vetogent Inj. | Gentamicin (as gentamicin sulphate) | 50 mg/ml | Solution for injection | Cattle, pig, horse declared as not being intended for slaugther for human consumption, cat, dog |
| Iceland | Franklin Pharmaceuticals Ltd.<br>Athboy Road<br>Trim<br>Co. Meath<br>Ireland | Genta Equine | Gentamicin | 100 mg/ml | Solution for injection | Horses |
| Ireland | Franklin Pharmaceuticals Ltd.<br>Athboy Road<br>Trim<br>Co. Meath<br>Ireland | Gentaject 10% Solution for Injection | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Horses declared as not being intended for slaughter for human consumption. |
| Latvia | CP - Pharma Handelsges. mbH<br>Ostlalandring 13<br>31303 Burgdorf,<br>Germany | Genta 100 | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Cats, cattle, dogs, horses |
| Latvia | Huvepharma AD<br>33 James Boucher Blvd.<br>Sofia 1407<br>Bulgaria | Gentacin | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Pigs, cats, cattle, dogs, horses |

| Member State EU/EEA | Applicant/Marketing Authorisation Holder | Product name | INN | Strength | Pharmaceutical form | Animal species |
|---|---|---|---|---|---|---|
| Latvia | KELA N.V.<br>St. Lenaartseweg 48<br>2320 Hoogstraten<br>Belgium | Genta-kel 10% | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Pigs, cattle, dogs, horses |
| Latvia | Bela-pharm GmbH & Co.KG<br>Lohner Str. 19<br>49377 Vechta<br>Germany | Gentamycin 5 | Gentamicin (as gentamicin sulphate) | 85 mg/ml | Solution for injection | Pigs, cats, cattle, dogs, horses |
| Lithuania | CP - Pharma Handelsges. mbH<br>Ostlalandring 13<br>31303 Burgdorf<br>Germany | Genta 100 mg/ml, injekcinis tirpalas | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Cats, dogs, cattle, pigs, horses |
| Lithuania | Bela-pharm GmbH & Co.KG<br>Lohner Str. 19<br>49377 Vechta<br>Germany | Gentacin, injekcinis tirpalas | Gentamicin (as gentamicin sulphate) | 85 mg/ml | Solution for injection | Horse, foal, cattle, calf, pig, piglet, weaner, dog and cat |
| Lithuania | Dopharma Research B.V.<br>Zalmweg 24m 4941 VX<br>Raamsdonksveer<br>the Netherlands | GENTA-JECT, injekcinis tirpalas | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Cattle, calves, pigs, piglets, horses, cats and dogs. |
| Lithuania | LABORATORIOS SYVA, S.A.<br>Av. Párroco Pablo Díez, 49-57<br>24010, León<br>Spain | GENTAYET 40 mg/ml injekcinis tirpalas arkliams, galvijams, kiaulėms, šunims ir katėms | Gentamicin | 40 mg/ml | Solution for injection | Bovine, equine, pigs, dogs and cats |

| Member State EU/EEA | Applicant/Marketing Authorisation Holder | Product name | INN | Strength | Pharmaceutical form | Animal species |
|---|---|---|---|---|---|---|
| Malta | Laboratorios Calier S.A<br>Barcelones<br>26 Place del Ramass<br>Les Franqueses del valles<br>Barcelona<br>Spain | GENTACALIER | Gentamicin | 40 mg/ml | Solution for injection | Dog, cat, pig, piglets, cattle, calves, horses |
| Portugal | IAPSA PORTUGUESA PECUÁRIA, LDA<br>Avenida do Brasil nº 88 7º Esq<br>1700-073 Lisboa<br>Portugal | GENTAYET 40 mg/ml solução injectável | Gentamicin | 40 mg/ml | Solution for injection | Cattle, horses, dogs and cats |
| Slovakia | Fatro S.p.A.<br>Via Emilia 285<br>Ozzano Emília<br>Bologna<br>Italy | Aagent 50 mg/ml injekčný roztok | Gentamicin | 50 mg/ml | Solution for injection | Foals, calves, sucklings - the first month of life |
| Spain | SUPER´S DIANA, S.L<br>Ctra. Barcelona - Ripoll, Km 17<br>08150 Parets del Vallès<br>Barcelona<br>Spain | GENDIAN-400 | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |
| Spain | SUPER´S DIANA, S.L<br>Ctra. Barcelona - Ripoll, Km 17<br>08150 Parets del Vallès<br>Barcelona<br>Spain | GENDIAN-600 | Gentamicin (as gentamicin sulphate) | 60 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |
| Spain | FATRO IBERICA, S.L.<br>Constitución, 1 Planta baja 3<br>08960 Sant Just Desvern<br>Barcelona<br>Spain | GENTA 50 | Gentamicin (as gentamicin sulphate) | 50 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |

| Member State EU/EEA | Applicant/Marketing Authorisation Holder | Product name | INN | Strength | Pharmaceutical form | Animal species |
|---|---|---|---|---|---|---|
| Spain | Franklin Pharmaceuticals Ltd.<br>Athboy Road<br>Trim<br>Co. Meath<br>Ireland | Genta Equine 100 mg/ml Solution for injection | Gentamicin (as gentamicin sulphate) | 100 mg/ml | Solution for injection | Horses (non food producing horse). |
| Spain | LABORATORIOS CALIER, S.A.<br>C/ Barcelonés, 26<br>08520 Les Franqueses del Valles<br>Barcelona<br>Spain | GENTACALIER | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |
| Spain | POLICHEM S.L.U.<br>C/ Prudenci Bertrana, 5<br>Polígono Industrial Agro-Reus Reus<br>43206 Tarragona<br>Spain | GENTACHEM | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |
| Spain | B.BRAUN VETCARE, S.A.<br>Crta. Tarrasa, 121<br>Rubí<br>Barcelona<br>Spain | GENTAMICINA 6% BRAUN USO VETERINARIO | Gentamicin (as gentamicin sulphate) | 60 mg/ml | Solution for injection | Equine not intended for human consumption, dogs, cats |
| Spain | Industrial Veterinaria, S.A.<br>Esmeralda, 19<br>08950 Esplugues de Llobregat<br>Barcelona<br>Spain | GENTAMICINA GANADEXIL | Gentamicin (as gentamicin sulphate) | 35 mg/ml | Solution for injection | Horses, cattle, dogs and cats |
| Spain | Laboratorios e Industrias IVEN, S.A.<br>Polígono Industrial de Vallecas.<br>C/ Luis I s/n.<br>28031 Madrid<br>Spain | GENTAMICIVEN | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |

| Member State EU/EEA | Applicant/Marketing Authorisation Holder | Product name | INN | Strength | Pharmaceutical form | Animal species |
|---|---|---|---|---|---|---|
| Spain | LABIANA LIFE SCIENCE, S.A.<br>C/ Venus, 26<br>Can Parellada Industrial Terrassa<br>08228 Barcelona<br>Spain | GENTASOL 80 | Gentamicin (as gentamicin sulphate) | 80 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |
| Spain | MEVET, S.A.U<br>Poligono Industrial El Segre, Parcela 409-410<br>25191 Lérida<br>Spain | GENTAVALL 40 MG/ML SOLUCIÓN INYECTABLE | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |
| Spain | LABORATORIOS SYVA, S.A.U.<br>Avda. Parroco Pablo Diez, 49-57<br>24010 León<br>Spain | GENTAYET | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Non food-producing horses, cattle, pigs, dogs and cats |
| Spain | LABORATORIOS MAYMO, S.A.<br>Via Augusta, 302<br>08017 Barcelona<br>Spain | MAYCOLI INYECTABLE | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Non food-producing horses, cattle and pigs |
| Spain | CENAVISA<br>Camí Pedra Estela s/n<br>43205 Reus<br>Tarragona)<br>Spain | PURMICINA 40 MG/ML SOLUCIÓN INYECTABLE | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Bovine (calves up to 250 kg), porcine (suckling pigs), equine not intended for human consumption, dogs and cats |
| Spain | Laboratorios e Industrias IVEN, S.A<br>Luis I, 56<br>Poligono Industrial Vallecas<br>28031 Madrid<br>Spain | VETERSAN GENTAMICINA | Gentamicin (as gentamicin sulphate) | 40 mg/ml | Solution for injection | Non food-producing horses, cattle, dogs and cats |

| Member State EU/EEA | Applicant/Marketing Authorisation Holder | Product name | INN | Strength | Pharmaceutical form | Animal species |
|---|---|---|---|---|---|---|
| Sweden | Franklin Pharmaceuticals Ltd.<br>Athboy Road<br>Trim<br>Co. Meath<br>Ireland | Gentaject vet | Gentamicin | 100 mg/ml | Solution for injection | Horse |
| United Kingdom | Franklin Pharmaceuticals Ltd.<br>Athboy Road<br>Trim<br>Co. Meath<br>Ireland | Genta-Equine 100 mg/ml Solution for Injection for Horses | Gentamicin | 100 mg/ml | Solution for injection | Horses (non-food producing) |

# Annex II

# Scientific conclusions and grounds for amendment of the summaries of product characteristics, labelling and package leaflets

# Overall summary of the scientific evaluation of veterinary medicinal products containing gentamicin presented as solutions for injection to be administered to horses (see Annex I)

## 1. Introduction

Gentamicin is an aminoglycoside antibiotic indicated for the treatment of a variety of bacterial infections. It is normally used as the sulphate salt. In veterinary medicine gentamicin is used mainly as a solution for injection for pigs, cattle and horses and as an oral solution for poultry. It is also used in human medicine, usually as a solution for injection for intramuscular administration. It is currently included in the list of essential medicines for human use of the World Health Organisation (WHO).

An application for the product Genta Equine 10% solution for injection for horses, containing gentamicin as the active substance was submitted to Denmark as a concerned Member State in a mutual recognition procedure (MRP) under the legal basis of Article 13(1) of Directive 2001/82/EC, i.e. a generic application. The reference product is Gentaject 10% solution for injection for horses which has been authorised in Ireland since 1988 (VPA 10976/2/1; Franklin Pharmaceuticals Ltd). Since the reference product is only authorised in Ireland, the concept of the European reference product has been applied in this MRP. During this MRP Denmark noted that the originator and the generic products have different indications and dosing regimens.

The relatively low approved dose and the target pathogens indicated for Gentaject 10% solution for injection gave grounds for Denmark to be concerned as to whether the proposed indications and dosage regimen for this product are supported by adequate data, given evidence from recent scientific publications. It was questioned whether the product is effective for these indications and if the low approved doses may in turn increase resistance rates among equine bacteria towards gentamicin. Furthermore, higher approved doses (e.g. Genta Equine 10% solution for injection) may pose a threat to target animal safety due to the known nephrotoxicity of gentamicin. Thus, the use of these products may present a serious risk to animal health in terms of lack of efficacy, as well as target animal safety. Additionally, development of antimicrobial resistance towards gentamicin would present a serious risk both to human and animal health.

It was understood that the indications would not be unique to these two products and other injectable veterinary medicinal products containing gentamicin for use in horses authorised in the EU have approved different doses, and the concers and considerations would apply equally to these.

Therefore, on 14 February 2014, Denmark presented to the European Medicines Agency ('the Agency') a referral notification under Article 35 of Directive 2001/82/EC, for all veterinary medicinal products containing gentamicin presented as solutions for injection to be administered to horses. The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to harmonise the indication(s) and dosing regimens of the concerned products, taking into account the available data and in particular with regard to target animal safety.

Referral procedures on the basis of Article 35 of Directive 2001/82/EC require a clearly formulated question referred to the Committee. The CVMP notes that pursuant to Article 36 of the Directive, its obligation is to consider the matter concerned and issue a reasoned opinion within the appropriate time limit. The scope of referral procedures is limited to evaluation of quality, safety and efficacy of veterinary medicinal products. Thus only the scientific questions posed to the CVMP in the referral notification have been considered and are reported below.

The CVMP notes that there is no MRL for gentamicin for horses. The marketing authorisations of the products concerned by this referral procedure are assumed to have been granted by the national competent authorities on the basis of Article 6(3) of Directive 2001/82/EC. The interpretation of the EU legislation and consideration of compliance with the legal provisions of Article 6(3) of the Directive are not within the remit of the Committee and therefore these issues are not addressed in the assessment of the referral procedure.

# 2. Discussion of the data available

Currently injectable veterinary medicinal products containing gentamicin for use in horses are authorised in the EU for the treatment of a variety of indications, including broad ones such as infections of the respiratory tract, gastrointestinal, and genito-urinary tract, caused by various target pathogens. This is primarily due to its fast bacteriocidal effect against Gram-negative bacteria for which there are only limited treatment choices available, its chemical stability and synergy with beta-lactam antibiotics. The approved dosing regimens vary widely, ranging between doses of 2–10 mg/kg bw at intervals of 8–24 hours over 3–5 days.

Most of the injectable products for horses containing gentamicin were initially approved in the 1980s and 1990s, and (compared to current requirements) only very limited data are available to support indications or dosing regimens in horses.

## *Indications*

As only very limited data are available to support all the current indications in horses the CVMP focused in their review mainly on the assessment of current scientific literature and minimum inhibitory concentration (MIC) data.

The Committee concluded that most of the current broad indications would not be supported by data. The lack of data and limited scientific evidence would only support a narrow indication, i.e. “For the treatment of infections of the lower respiratory tract in horses caused by aerobic Gram-negative bacteria susceptible to gentamicin.” This indication is consistent with the distribution pattern of gentamicin, which is primarily in the extracellular fluid.

The Committee considered that for any other indications for horses for injectable products contaning gentamicin, applicants/marketing authorisation holders (MAHs) would need to submit appropriate data, following up-to-date requirements.

## *Dosing regimen*

Only one proprietary study in support of the approved dosing regimen for a product included in the scope of this referral was provided.The CVMP considered this study was of limited value to their assessment. All other dosing regimens appear to be approved based on expert reports, scientific publications and PK/PD characteristics. In addition, gentamicin is known to be one of the most nephrotoxic aminoglycosides, with a very narrow margin of safety, which is of particular concern in young aninmals, i.e. foals. However, no target animal safety studies using a substantiated scientific study design, as recommended in the VICH guideline 43[1] on target animal safety have been conducted covering the authorised dosing regimens and routes of administration in adult horses and foals, in particular in regard to gentamicin-induced nephrotoxicity. The CVMP Antimicrobials Working Party (AWP) and Efficacy Working Party (EWP) were consulted on several aspects of a safe dosing regimen of gentamicin in horses.

[1] VICH GL 43: Guideline on target animal safety for veterinary pharmaceutical products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004361.pdf

Based on all available evidence, the CVMP considered that a single daily dose of 6.6 mg gentamicin/kg bw, administered intravenously, would provide an efficacious dose, taking into account the desired PK/PD characteristics for a concentration-dependent antibiotic, i.e. optimal maximum serum concentration ($C_{max}$) to MIC ratio of 8–10, and assuming a bacterial MIC ≤2 µg/ml. The CVMP considered that this dose was supported by clinical experiences, taking into account that a single daily administration would reduce the risk of nephrotoxicity in adult horses (compared to more frequent daily administrations) and also the risk of the theoretical concept of adaptive resistance.

The Committee therefore concluded that a single dose of 6.6 mg gentamicin/kg bw given intravenously once daily for 3–5 consecutive days would provide an efficacious dose for adult horses, when used according to the SPC.

However, foals, especially neonates, were recognised as significantly different from adult horses with regard to both an effective dosing regimen and target animal safety. Pharmacokinetics of gentamicin change considerably in the first 2 weeks of a foal's life — plasma concentrations of gentamicin are more difficult to achieve in neonatal foals and gentamicin is retained longer in the body, especially kidneys, compared to adults leading to a higher likelihood of gentamicin-induced nephrotoxicity. The target animal safety of injectable gentamicin products for horses is considered not proven for use in foals. Therefore, the use of the products in foals is not recommended.

# 3. Benefit-risk assessment

Currently injectable veterinary medicinal products containing gentamicin for use in horses are authorised in the EU for the treatment of a variety of indications, including broad ones such as infections of the respiratory tract, gastrointestinal, and genito-urinary tract, caused by various target pathogens. The approved dosing regimens vary widely, ranging between doses of 2–10 mg/kg bw at intervals of 8–24 hours over 3–5 days.

Only very limited data are available to support the range of indications and dose regimens and the CVMP was asked to review the data available and to recommend scientifcally justified indications and a safe and efficacious dosing regimen in horses.

**Benefit assessment**

Gentamicin is used for first or second choice treatments in a variety of clinical situations in horses. This is primarily due to its fast bacteriocidal effect against Gram-negative bacteria, its chemical stability and synergy with beta-lactam antibiotics.

In addition, there are only limited choices available for the treatment of Gram-negative infections in horses, and clinical experience has shown that gentamicin is effective in adult horses at a single daily dose of 6.6 mg/kg bw (intravenously) over 3–5 days.

There are insufficient data available to support the currently approved indications. The CVMP considered that the lack of data and limited scientific evidence would only support a narrow indication, i.e. "For the treatment of infections of the lower respiratory tract in horses caused by aerobic Gram-negative bacteria susceptible to gentamicin."

**Risk assessment**

Nephrotoxicity is the main risk to the target animal from gentamicin that could occur within therapeutic doses. Studies on the margin of safety of the currently approved dosing regimens were neither submitted by the MAHs nor could be identified in the scientific literature. The CVMP recommended a dosing regimen for adult horses of 6.6 mg/kg once daily for 3-5 days, accompanied by strong warnings in the product literature about the lack of target animal safety data. Nephrotoxicity is especially a

concern in foals. Therefore, the CVMP considers that no dosing regimen should be specified for foals, and currently approved dosing regimens for foals should be deleted from the product information, due to lack of target animal safety data especially concerning nephrotoxicity.

Over-use of gentamicin products might result in an increased risk of the theoretical concept of adaptive resistance.

**Risk management or mitigation measures**

The use of the products has been limited to an indication for which gentamicin is considered efficacious on the basis of the data and information available.

A harmonised dosing regimen to be used in adult horses is proposed, that conforms to the desired PK/PD characteristics of a concentration-dependent antibiotic and reflects data available in horses.

Warning sentences and advice for safe use have been included in the product information, which reflect the lack of target animal safety data in horses and foals.

**Evaluation of the benefit-risk balance**

The CVMP considered the benefit-risk balance for injectable veterinary medicinal products containing gentamicin for horses positive for the following indication:

“For the treatment of infections of the lower respiratory tract in horses caused by Gram-negative bacteria susceptible to gentamicin.”

The CVMP also considered the benefit-risk balance for injectable veterinary medicinal products containing gentamicin for horses positive when the posology for adult horses (with appropriate warnings and advice on dosing) is changed to:

“Single dose of 6.6 mg/kg bw given intravenously once daily for 3–5 consecutive days.

To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid under- or over-dosing. The dosing regimen must not be exceeded.”

The CVMP considered the benefit-risk balance for injectable veterinary medicinal products containing gentamicin for horses negative for use in foals. Therefore, the use of the products in foals is not recommended.

## Grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Whereas:

- on the basis of the available data, the CVMP considered that the indication as provided in Annex III were justified;
- on the basis of the available data, the CVMP considered that the dosage regimen should be amended as described in Annex III;
- on the basis of the available data, the CVMP considered that all other indications and dosage regimens in horses should be deleted from the product information;
- the CVMP considered that the overall benefit-risk balance is positive for the veterinary medicinal products (see annex I), subject to amendments in the product information;

the CVMP recommended variations of the marketing authorisations for veterinary medicinal products containing gentamicin presented as solutions for injection to be administered to horses, in order to amend the summaries of product characteristics, labelling and package leaflets as set out in Annex III.

# Annex III

## Amendments in the relevant sections of the summary of product characteristics, labelling and package leaflet

# Summary of product characteristics

With relation to the already approved target species horses, the wording below should be used:

### 4.1 Target species

Horses (non food-producing horses).

### 4.2 Indications for use, specifying the target species

For the treatment of infections of the lower respiratory tract in horses caused by aerobic Gram-negative bacteria susceptible to gentamicin.

### 4.3 Contraindications

Do not use in known cases of renal dysfunction.
Do not use in cases of known hypersensitivity to the active substance or to any of the excipients.
Do not exceed the proposed dosing regimen.

### 4.5 Special precautions for use

**Special precautions for use in animals**

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.

### 4.7 Use during pregnancy, lactation or lay

The safety in pregnant horses is unknown. However, studies in laboratory animals have shown evidence of fetal nephrotoxicity. Use only based on the benefit-risk assessment by the responsible veterinarian.

### 4.9 Amounts to be administered and administration route

Horses:
Intravenous use.
Single dose of 6.6 mg/kg body weight given intravenously once daily for 3–5 consecutive days.
To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid under- or over-dosing. The dosing regimen must not be exceeded.
The use of gentamicin in foals and neonates is not recommended.

### 4.11 Withdrawal period(s)

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

## 5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, gentamicin.
ATCvet code: QJ01GB03

### 5.1 Pharmacodynamic properties

Gentamicin sulphate exerts concentration-dependent bacterial killing characteristics. Their rate of killing increases as the gentamicin concentration increases above the minimum concentration (MIC) for a given Gram-negative pathogen, with optimal maximum serum concentration ($C_{max}$) to MIC ratio of 8-10.
Gentamicin sulphate is bactericidal in action by irreversibly binding to 30S ribosomal subunits, and acts through two different mechanisms. In one mechanism, gentamicin can interfere with the correct amino acid polymerisation and elongation. This mechanism takes place at high concentrations. Another mechanism predominates at low concentrations in which amino acid codons are misread by tRNA and proof-reading is impaired. This leads to incorrect amino acid sequencing and nonsense proteins.
The substance is highly polar, hydrophilic and transport appears to be an active process closely linked to electron transport, oxidative phosphorylation and the respiratory quinones in the cell membrane.
Gentamicin is primarily distributed within extracellular fluids. Gentamicin does not distribute to the cerebrospinal fluid.
Gentamicin is best considered as a narrow-spectrum Gram-negative bactericidal antimicrobial (e.g. *E. coli*, *Proteus*, *Pseudomonas*). Gentamicin does not have 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. Gentamicin is eliminated unchanged by the kidney via glomerular filtration, including 85–95% of the dose.
There are several mechanisms by which various strains of bacteria have developed resistance against aminoglycosides like gentamicin. Enzymatic modification is the most common type of aminoglycoside resistance. Over 50 different enzymes have been identified. Enzymatic modification results in high-level resistance. The genes encoding for aminoglycoside modifying enzymes are usually found on plasmids and transposons.
There are three types of aminoglycoside modifying enzymes:

1. N-Acetyltransferases (AAC) – catalyses acetyl CoA-dependent acetylation of an amino group
2. O-Adenyltransferases (ANT) – catalyses ATP-dependent adenylation of hydroxyl group
3. O-Phosphotransferases (APH) – catalyses ATP-dependent phosphorylation of a hydroxyl group

Two other mechanisms of resistance include ribosomal mutations of the binding site of aminoglycosides, the 30S subunit, and the bacteria decreasing the permeability of aminoglycosides.

# Labelling:

With relation to the already approved target species horses, the wording below should be used:

**5. TARGET SPECIES**

Horses (non food-producing horses).

**8. WITHDRAWAL PERIOD**

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

# Package leaflet:

With relation to the already approved target species horses, the wording below should be used:

**4. INDICATIONS**

For the treatment of infections of the lower respiratory tract in horses caused by aerobic Gram-negative bacteria susceptible to gentamicin.

**5. CONTRAINDICATIONS**

Do not use in known cases of renal dysfunction.
Do not use in cases of known hypersensitivity to the active substance or to any of the excipients.
Do not exceed the proposed dosing regimen.

**7. TARGET SPECIES**

Horses (non food-producing horses).

**8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION**

Horses:
Intravenous use.
Single dose of 6.6 mg/kg body weight given intravenously once daily for 3–5 consecutive days.
To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid under- or over-dosing. The dosing regimen must not be exceeded.
The use of gentamicin in foals and neonates is not recommended.

**10. WITHDRAWAL PERIOD**

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

## 12. SPECIAL WARNINGS

Special precautions for use in animals:

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.

Pregnancy:

The safety in pregnant horses is unknown. However, studies in laboratory animals have shown evidence of fetal nephrotoxicity. Use only based on the benefit-risk assessment by the responsible veterinarian.