Annex I

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

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Vana GmbH Wolfgang Schmälzl Gasse 6 1020 Wien Austria	Gentavan 5%-Durchstichflasche für Tiere	gentamicin	50 mg/ml	solution for injection	Cattle, calves, pigs, horses, foals, dogs, cats	SC, IM, slow IV
Belgium	EMDOKA bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium	Emdogent 100	gentamicin	100 mg/ml	solution for injection	Cattle, pigs, horses, dogs, cats	SC, IM, slow IV
Belgium	VMD nv Hoge Mauw 900 B-2370 Arendonk Belgium	Gentaveto 5	gentamicin	50 mg/ml	solution for injection	Pigs	IM
Belgium	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Genta-Kel 5%	gentamicin	50 mg/ml	solution for injection	Cattle (calves)	IM
Bulgaria	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	ГЕНТАМИЦИН 10% инжекционен разтвор GENTAMYCIN 10% solution for injection	gentamicin	100 mg/ml	solution for injection	Cattle, pigs, dogs, cats	IM, SC, IV

Bulgaria	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	ГЕНТАМИЦИН 4% инжекционен разтвор GENTAMYCIN 4% solution for injection	gentamicin	40 mg/ml	solution for injection	Cattle, pigs, dogs, cats	IM, SC, IV
Bulgaria	Interchemie werken "de Adelaar" B.V. Hosterweg 26a 5811 AC Castenray The Netherlands	ГЕНТА-100 GENTA-100	gentamicin	100 mg/ml	solution for injection	Cattle, calves, pigs	IM
Bulgaria	VetProm JSC 26, Otets Paisii Str 2400 Radomir Bulgaria	ГЕНТАМИЦИН 40 mg/ml инжекционен разтвор / GENTAMICIN 40 mg/ml solutio pro injectionibus	gentamicin	40 mg/ml	solution for injection	Calves, pigs, dogs, cats	IM, SC
Croatia	Krka - Farma d.o.o. Radnička cesta 48 10000 Zagreb Croatia	GENTAMICIN 80 mg/mL	gentamicin	80 mg/ml	solution for injection	Cattle, non-food producing horses, pigs, dogs, cats	IM (cattle, pigs), IV (horses), SC (dogs, cats)
Croatia	PROPHARMA VET d.o.o. Vijenac A. Cesarca 16 31000 Osijek Croatia	NEOGENT	gentamicin	80 mg/ml	solution for injection	Cattle, pigs, horses, dogs, cats	IM, SC
Cyprus	FATRO S.p.A. Via Emilia, 285 40064 Ozzano Emilia (Bologna) Italy	AAGENT, 50 mg/ml, solution for injection for calves and piglets up to one month old.	gentamicin	50 mg/ml	solution for injection	Calves and piglets up to one month old	IM, SC, slow IV

Cyprus	Dimitrios Christophorou 169 Tseriou Av. 2048 Strovolos Nicosia Cyprus	Gentamycin 5% 50mg/ml ενέσιμο διάλυμα για βοοειδή, σκύλους και γάτες	gentamicin	85.0 mg/ml	solution for injection	Cattle, dogs, cats	IM, SC, slow IV
Czech Republic	FATRO S.p.A. Via Emilia, 285 40064 Ozzano Emilia (Bologna) Italy	AAGENT 50 mg/ml injekční roztok	gentamicin	50 mg/ml	solution for injection	Calves, foals and piglets at the age of one month	IM, SC, slow IV
Czech Republic	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	GENTA-KEL 50 000 IU/ml injekční roztok	gentamicin	81 mg/ml	solution for injection	Calves, pigs, dogs	IM, IV
Estonia	Interchemie werken "De Adelaar" Eesti AS Vanapere tee 14, Pringi 74001 Viimsi Harju County Estonia	Genta-100 EE	gentamicin	100 mg/ml	solution for injection	Cattle, pigs, horses	IM
Estonia	Interchemie werken "De Adelaar" Eesti AS Vanapere tee 14, Pringi 74001 Viimsi Harju County Estonia	Genta-100	gentamicin	100 mg/ml	solution for injection	Cattle, pigs	IM
Estonia	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Genta-kel	gentamicin	50 mg/ml	solution for injection	Calves, dogs	IM, IV, SC

Estonia	Huvepharma AD 33 James Boucher Blvd. Sofia 1407 Bulgaria	Gentacin	gentamicin	100 mg/ml	solution for injection	Calves, dogs	IM, IV
France	VIRBAC 1ere Avenue 2065 MLID 06516 Carros Cedex France	PANGRAM 4 %	gentamicin	40000 UI/ml	solution for injection	Calves, dogs, cats	IM, IV
France	Vetoquinol SA Magny-Vernois 70200 Lure France	FORTICINE SOLUTION	gentamicin	40000 UI/ml	solution for injection	Calves	IM, IV
France	VIRBAC 1ere Avenue 2065 MLID 06516 Carros Cedex France	G.4	gentamicin	40000 UI/ml	solution for injection	Calves, dogs, cats	IM, IV
France	CEVA SANTE ANIMALE 10 Avenue de la Ballastiere 33500 Libourne France	VETRIGEN	gentamicin	50000 UI/ml	solution for injection	Calves, piglets	IM
Germany	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 31303 Burgdorf Germany	Genta 100 mg/ml	gentamicin	100 mg/ml	solution for injection	Cattle, pigs, horses declared as not intended for slaughter for human consumption, dogs, cats	IM, IV, SC

Germany	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Vepha-Gent forte	gentamicin	50 mg/ml	solution for injection	Cattle, pigs, horses declared as not intended for slaughter for human consumption, dogs, cats	IM, IV, SC
Germany	Bela-Pharm GmbH & Co. KG Lohner Str. 19 49377 Vechta Germany	Gentacin	gentamicin	50 mg/ml	solution for injection	Cattle, pigs, horses declared as not intended for slaughter for human consumption, dogs, cats	IM, IV, SC
Germany	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Gentamicin 50	gentamicin	50 mg/ml	solution for injection	Cattle, pigs, horses declared as not intended for slaughter for human consumption, dogs, cats	IM, IV, SC
Germany	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Genta-Sulfat 81	gentamicin	50 mg/ml	solution for injection	Cattle, pigs, horses declared as not intended for slaughter for human consumption, dogs, cats	IM, IV, SC

Germany	Bela-Pharm GmbH & Co. KG Lohner Str. 19 49377 Vechta Germany	Vetogent Inj.	gentamicin	85 mg/ml	solution for injection	Cattle, pigs, horses declared as not intended for slaughter for human consumption, dogs, cats	IM, IV, SC
Germany	Bremer Pharma GmbH Werkstr. 42 34414 Warburg Germany	Gentafromm	gentamicin	50 mg/ml	solution for injection	Cattle, dogs, cats	IM, IV, SC
Germany	Eurovet Animal Health B.V. Handelsweg 25 NL-5531 AE Bladel The Netherlands	Genta 5%	gentamicin	50 mg/ml	solution for injection	Cattle, pigs, dogs, cats, pet birds	IM, IV, SC
Greece	PROVET SA Aspropyrgos Attikis 19300 Greece	GENTAMICIN/PROVET	gentamicin	50 mg/ml	solution for injection	Calves, dogs, cats	IM
Greece	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	GENTAKEL	gentamicin	50 mg/ml	solution for injection	Calves, pigs, dogs	IM
Hungary	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Neogent 5 % injekció A.U.V.	gentamicin	50 mg/ml	solution for injection	Cattle, pigs, dogs	cattle, pigs: IM dogs: IM or SC

Ireland	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Genta 50 mg/ml solution for injection.	gentamicin	50 mg/ml	solution for injection	Cattle	IM
Italy	FATRO S.p.A. Via Emilia, 285 40064 Ozzano Emilia (Bologna) Italy	Aagent	gentamicin	50 mg/ml	solution for injection	Calves, piglets (in the 1st month of life)	IM, SC, slow IV
Italy	FATRO S.p.A. Via Emilia, 285 40064 Ozzano Emilia (Bologna) Italy	Aagent 10%	gentamicin	100 mg/ml	solution for injection	Calves, piglets (in the 1st month of life)	IM, SC, slow IV
Italy	Industria Italiana Integratori Trei S.p.A. Via Affarosa, 4 42010 Rio Saliceto (Reggio Emilia) Italy	Gentabiotic	gentamicin	100 mg/ml	solution for injection	Calves, piglets, dogs, cats	IM, IV, endo peritoneal
Latvia	Huvepharma EOOD 3A Nikolay Haytov street Sofia 1113 Bulgaria	Gentacin	gentamicin	100 mg/ml	solution for injection	Cattle, pigs, horses, dogs, cats	IM, IV, SC
Latvia	Bela-Pharm GmbH & Co. KG Lohner Str. 19 49377 Vechta Germany	Gentamycin 5	gentamicin	85 mg/ml	solution for injection	Cattle, pigs, horses, dogs, cats	IM, IV, SC

Latvia	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 31303 Burgdorf Germany	Genta- 100	gentamicin	100 mg/ml	solution for injection	Cattle, horses, dogs, cats	IM, IV, SC
Latvia	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Genta-kel 10%	gentamicin	100 mg/ml	solution for injection	Cattle, pigs, horses, dogs	IM, IV, SC
Latvia	Industrial Veterinaria, S.A. Esmeralda, 19 E-08950 Esplugues de Llobregat (Barcelona) Spain	Gentaprim	trimethoprim gentamicin sulphate sulfadi-methoxinum	40 mg/ml 30 mg/ml 200 mg/ml	solution for injection	Cattle, pigs, horses, dogs, cats	IM
Latvia	Bremer Pharma GmbH Werkstr. 42 34414 Warburg Germany	Gentamicin BREMER PHARMA	gentamicin	50 mg/ml	solution for injection	Cattle, dogs, cats	IM, SC, slow IV
Latvia	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	Genta-kel 5%	gentamicin	50 mg/ml	solution for injection	Cattle, pigs, dogs	IM, SC, slow IV
Latvia	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 31303 Burgdorf Germany	Genta	gentamicin	100 mg/ml	solution for injection	Cattle, horses, dogs, cats	IM, SC, slow IV

Lithuania	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 31303 Burgdorf Germany	Genta 100 mg/ml, injekcinis tirpalas	gentamicin	100 mg/ml	solution for injection	Cattle, pigs, horses, dogs, cats	IM, IV, SC
Lithuania	Dopharma Research B.V. Zalmweg 24m 4941 VX Raamsdonksveer The Netherlands	GENTA-JECT, injekcinis tirpalas	gentamicin	100 mg/ml	solution for injection	Cattle, calves, pigs, piglets, horses, dogs, cats	IM, IV, SC
Lithuania	Bela-Pharm GmbH & Co. KG Lohner Str. 19 49377 Vechta Germany	Gentacin, injekcinis tirpalas	gentamicin	85 mg/ml	solution for injection	Cattle, calves, pigs, piglets, weaners, horses, foals, dogs, cats	IM, IV, SC
Lithuania	Interchemie werken "de Adelaar" B.V. Hosterweg 26a 5811 AC Castenray The Netherlands	GENTA 100 mg/ml injekcinis tirpalas galvijams ir kiaulėms	gentamicin	100 mg/ml	solution for injection	Cattle, calves, pigs	IM
Malta	CENAVISA, S.L. Camí Pedra Estela s/n 43205 Reus (Tarragona) Spain	Gentacen	gentamicin	100 mg/ml	solution for injection	Calves up to 13 weeks	IM
Malta	Industrial Veterinaria, S.A. Esmeralda, 19 E-08950 Esplugues de Llobregat (Barcelona) Spain	Gentaprim	trimethoprim gentamicin sulfa-dimethoxin	40 mg/ml 30 mg/ml 200 mg/ml	solution for injection	Cattle, pigs	IM

Malta	Laboratorios Calier, S.A. Barcelones, 26 - El Ramassar 08520 Les Franqueses del Valles (Barcelona) Spain	GENTACALIER	gentamicin	40 mg/ml	solution for injection	Cattle, calves, pigs, piglets	IM, slow IV
Portugal	IAPSA PORTUGUESA PECUÁRIA, LDA Avenida do Brasil nº 88 7º Esq 1700-073 Lisboa Portugal	GENTAYET 40 mg/ml solução injectável	gentamicin	40 mg/ml	solution for injection	Cattle, horses, dogs, cats	IM, slow IV
Portugal	KELA NV Sint Lenaartseweg 48 2320 Hoogstraten Belgium	GENTA-kel 05, solução injectável para bovinos, suínos, cães, gatos	gentamicin	50 mg/ml	solution for injection	Cattle, pigs, dogs, cats	IM, SC (only dogs)
Portugal	VETLIMA - SOC. DISTRIBUIDORA DE PROD. AGRO-PECUÁRIOS, SA Centro Empresarial da Rainha, Lote 27 2050-501 Vila Nova da Rainha Portugal	GENTAVET solução injectavel	gentamicin	40 mg/ml	solution for injection	Cattle (calves), pigs (piglets), birds (chicks, turkeys), dogs, cats	IM, slow IV
Romania	Alapis SA 19 300 Aspropyrgos mailbox 26 Athens Greece	GENTAMICIN 5% Gentamicin Provet 50mg/ml	gentamicin	50 mg/ml	solution for injection	Calves, piglets, dogs, cats	IM

Romania	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	GENTA-JECT 10%	gentamicin	100 mg/ml	solution for injection	Cattle, pigs	IV, IM, SC
Romania	PASTEUR - Filiala Filipesti SRL Str. Principala nr. 944 Filipestii de Padure Jud. Prahova Romania	GENTAMICINA FP 10%	gentamicin	100 mg/ml	solution for injection	Cattle, pigs, dogs, cats	IM, slow IV, SC
Slovak Republic	FATRO S.p.A. Via Emilia, 285 40064 Ozzano Emilia (Bologna) Italy	Aagent 50 mg/ml injekčný roztok	gentamicin	50 mg/ml	solution for injection	Calves and piglets in the first month of life, horses declared as not intended for slaughter for human consumption	IM, SC, slow IV
Slovenia	KRKA, d.d. Novo mesto, Šmarješka cesta 6 8501 Novo mesto Slovenia	GENTAMICIN KRKA 80 mg/ml raztopina za injiciranje za govedo, prašiče, pse in mačke	gentamicin	80 mg/ml	solution for injection	Cattle, pigs, dogs, cats	IM
Spain	Laboratorios Maymo, S.A. Via Augusta, 302 08017 Barcelona Spain	MAYCOLI INYECTABLE - 306 ESP	gentamicin	40 mg/ml	solution for injection	Cattle (calves up to 250 kg), non-food-producing horses	IM, slow IV

Spain	MEVET, S.A.U. Poligono Industrial El Segre Parcela 409-410 25191 Lérida Spain	GENTAVALL 40 MG/ML SOLUCIÓN INYECTABLE - 307 ESP	gentamicin	40 mg/ml	solution for injection	Cattle (calves up to 250 kg), non-food-producing horses, dogs, cats	IM, slow IV
Spain	Laboratorios Calier, S.A. Barcelones, 26 - El Ramassar 08520 Les Franqueses del Valles (Barcelona) Spain	GENTACALIER - 397 ESP	gentamicin	40 mg/ml	solution for injection	Cattle (calves up to 250 kg), non-food-producing horses, dogs, cats	IM, slow IV
Spain	Laboratorios e Industrias Iven, S.A. Luis I, 56 Poligono Industrial Vallecas 28031 Madrid Spain	VETERSAN GENTAMICINA - 637 ES	gentamicin	40 mg/ml	solution for injection	Cattle (calves up to 250 kg), non-food-producing horses, dogs, cats	IM, slow IV
Spain	LABIANA LIFE SCIENCES, S.A. Venus, 26. Can Parellada Industrial 08228 Terrassa (Barcelona) Spain	GENTASOL 80 - 638 ESP	gentamicin	80 mg/ml	solution for injection	Cattle (calves up to 250 kg), non-food producing horses, dogs, cats	IM, slow IV
Spain	Laboratorios e Industrias Iven, S.A. Luis I, 56 Poligono Industrial Vallecas 28031 Madrid Spain	GENTAMICIVEN - 641 ESP	gentamicin	40 mg/ml	solution for injection	Cattle (calves up to 250 kg), non-food-producing horses, dogs, cats	IM, slow IV

Spain	SUPER´S DIANA, S.L. Ctra. C-17, Km 17 08150 Parets del Valles (Barcelona) Spain	GENDIAN 60mg/ml SOLUCIÓN INYECTABLE - 690 ESP	gentamicin	60 mg/ml	solution for injection	Cattle (calves up to 250 kg), non-food-producing horses, dogs	IM, slow IV
Spain	CENAVISA, S.L. Camí Pedra Estela s/n 43205 Reus (Tarragona) Spain	PURMICINA 40 MG/ML SOLUCIÓN INYECTABLE - 2922 ESP	gentamicin	40 mg/ml	solution for injection	Cattle (calves up to 250 kg), pigs (suckling pigs), horses not intended for human consumption, dogs, cats	IM, slow IV
Spain	CENAVISA, S.L. Camí Pedra Estela s/n 43205 Reus (Tarragona) Spain	GENTACEN 100mg/ml SOLUCIÓN INYECTABLE - 2583 ESP	gentamicin	100 mg/ml	solution for injection	Calves (up to 13 weeks of age)	IM
Spain	S.P. VETERINARIA, S.A. Ctra Reus Vinyols, km 4.1 Riudoms (Tarragona) 43330 Spain	GENTAVIN 100mg/ml SOLUCIÓN INYECTABLE - 2584 ESP	gentamicin	100 mg/ml	solution for injection	Calves (up to 13 weeks of age)	IM
Spain	MEVET, S.A.U. Poligono Industrial El Segre Parcela 409-410 25191 Lérida Spain	GENTAVALL 5mg/ml SOLUCIÓN INYECTABLE - 304 ESP	gentamicin	5 mg/ml	solution for injection	Piglets, dogs, cats	IM

Spain	LABORATORIOS HIPRA, S.A. Avda. la Selva 135 Amer (Girona) 17170 Spain	GENTIPRA - 305 ESP	gentamicin	50 mg/ml	solution for injection	Cattle (calves up to 250kg)	IM, slow IV
The Netherlands	Dopharma Research B.V. Zalmweg 24m 4941 VX Raamsdonksveer The Netherlands	Genta-ject 10%	gentamicin	100 mg/ml	solution for injection	Calves up to 13 weeks of age	IM

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics

Overall summary of the scientific evaluation of veterinary medicinal products containing gentamicin presented as solutions for injection to be administered to cattle and pigs (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 sulfate salt. In veterinary medicine gentamicin is used mainly as a solution for injection for cattle, pigs, horses, cats and dogs.

Following a marketing authorisation application to the Belgian Federal Agency for Medicines and Health Product, under Article 13(1) of Directive 2001/82/EC as amended, i.e., a generic application, it appeared that no product-specific residue data were generated in support of the cattle and pigs' meat and offal withdrawal periods for the reference product Genta 100 mg/ml, as authorised in Germany. Using the data available in the CVMP EPMAR for gentamicin (EMEA/MRL/803/01)[1], it was not possible for Belgium to confirm that the withdrawal periods of 95 days for cattle and 60 days for pigs are safe. Furthermore, data available in Belgium for comparable products clearly indicate that residue levels can be above the maximum residue limits (MRLs) at the proposed withdrawal periods. Therefore, Belgium considered that consumer safety is not ensured by the withdrawal periods set for the reference product Genta 100 mg/ml (marketing authorisation holder (MAH): CP-Pharma) and consequently, for its generic product Emdogent 100 (applicant: Emdoka).

Belgium also noted that there are different approved withdrawal periods for cattle and pigs for veterinary medicinal products containing gentamicin presented as solutions for injection across the European Union, e.g. cattle meat and offal from 28 days to 210 days; cattle milk from 2 to 7 days, with some of the products stating 'do not use in cows whose milk is intended for human consumption'; and pigs meat and offal from 28 days to 150 days.

Therefore, on 8 January 2016, Belgium initiated a procedure under Article 35 of Directive 2001/82/EC, for veterinary medicinal products containing gentamicin presented as solutions for injection to be administered to cattle and pigs. The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to review all available residue depletion data and recommend withdrawal periods for cattle (meat and milk) and pigs.

2. Discussion of data available

Residue depletion in cattle meat and offal

In all residue depletion studies submitted, gentamicin was used as an injectable aqueous solution and was administered by the intramuscular route.

A GLP-compliant study in calves was submitted concerning the product Aagent 50 mg/ml solution for injection (MAH: Fatro). The study design is in accordance with current standards. The study involved calves of less than 1 month of age. Groups of 5 animals were treated at a dose of 4 mg/kg body weight (bw) once a day for 3 days, and slaughtered at days 30, 40, 50, 60, 70, 80 and 90 after the last administration. Kidney, liver, fat, muscle, and injection site (core and surrounding) were analysed using a validated HPLC/MS-MS method. Analysis of the results for each tissue leads to a maximum withdrawal period of 103 days, relating to residue depletion in the liver, and obtained using the

[1] CVMP EPMAR for gentamicin (EMEA/MRL/803/01) - http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500014350.pdf

statistical method as per CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95)[2].

The product Aagent 50 mg/ml solution for injection was also tested in a depletion studies in adult cattle. The study is GLP-compliant; it is considered by the MAH (Fatro) as a preliminary study. No surrounding control injection site was sampled. The residue measured (gentamicin) was not the established marker residue, and the lower limit of quantification (LLOQ) of the HPLC-MS/MS method was equal to the MRL for muscle and fat. No stability data were presented. The study involved groups of 4 animals receiving a dose of 4 mg/kg bw once a day for 5 days, which were slaughtered at days 21, 35, 49 and 70 after the last administration. Kidney, liver, fat, muscle, and injection site were analysed. At day 70, the last sampling point, the concentration of gentamicin still exceeded the MRLs in all liver and kidney samples, with some values amounting to more than 2x the current MRL in kidney and more than 3x in liver. No reliable withdrawal period can be established from these data.

A GLP compliant study conducted with Gentamicina 4% solucion inyectabile (applicable for Gentacalier 40 mg/ml, Maycoli inyectable 40 mg/ml, Gentavall 40 mg/ml, Vetersan gentamicina 40 mg/ml, Gentamiciven 40 mg/ml and Purmicina 40 mg/ml (MAHs: Laboratorios Calier, Laboratorios Maymo, Super's Diana, Mevet, Laboratorios e Industrias Iven and Cenavisa)) was provided. The study meets current standards, although fat and muscle (other than injection site) were not analysed. However in view of the overall data available on gentamicin residue depletion, it is known that fat and muscle (except injection site muscle) are not limiting tissues. The enrolled animals were 6-7 month old ruminating calves. Groups of 4 animals were treated at a dose of 4 mg/kg bw every 12 hours for 3 days, and slaughtered at days 80, 100, 130, and 170 after the last administration. Kidney, liver, and the injection site (core and surrounding) were analysed using a validated HPLC/MS-MS method. Analysis of the results for each tissue leads to a maximum withdrawal period of 192 days, relating to residue depletion in the liver and calculated with the statistical method.

Another study in calves was submitted in relation to the product Vetrigen (MAH: Ceva Sante Animale), but is not GLP-compliant. The study concerns non-ruminating animals weighing approximately 50-60 kg. Groups of only 3 animals were treated at a dose of 4 mg/kg bw every 12 hours for 4.5 days (9 injections), and slaughtered at days 15 and 60 after the last administration. Kidney, liver, fat, muscle and the injection site, with no control surrounding sample, were analysed using a microbiological method, for which no adequate validation data are available. At the last slaughter point i.e. day 60, residue levels were below the MRL in liver and kidney, but no firm conclusion can be drawn as to fat, muscle and in particular the injection site, since the relating sensitivity limit was twice the MRL. Overall, a withdrawal period cannot be derived from this study.

A GLP compliant study conducted with Genta-ject 10% (MAH: Dopharma), was provided. The study meets current standards, although the analytical method was microbiological and no control surrounding injection site sample was collected (on the other hand, two injection sites per animal, one on each side, were analysed). The microbiological assay was adequately validated. The enrolled animals were non-ruminating calves of approximately 3 months, reported to have been fed solid feed during the study. Groups of 4 animals were treated at a dose of 2 mg/kg bw every 12 hours for 3 days, and slaughtered at days 76, 90, 104, and 126 after the last administration. Kidney, liver, muscle, fat and the injection site were analysed. The statistical method could not be applied as, for all edible tissues, an insufficient number of data points were available. Using the alternative method, applied to data in kidney, and with a 10% safety margin, leads to a withdrawal period of 139 days.

The products Forticine Solution 1% and 4% (MAH: Vetoquinol), were investigated in one main study focusing kidney, liver and muscle, and using the 1% solution, and one confirmatory study using the

[2] CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004428.pdf

4% solution, after demonstration of plasma bioequivalence to the 1% strength, and where only the injection site was analysed. In both studies, calves of maximum 1.5 months, presumably non-ruminating, were involved. The studies were either not GLP-compliant, or the status is unknown.

In the main study, the dose administered was 4 mg/kg bw once, followed by three injections of 2 mg/kg bw every 12 hours. The analytical method used liquid-liquid chromatography with fluorometric detection but data demonstrating the validity of the method were not available; only 3 of the 4 recommended gentamicin marker residue components were monitored. Only two animals per slaughter time were involved (14 hours, 7 days, 14 days, 28 days). Due to a LLOQ which is unclear and possibly higher than the respective MRLs no conclusion can be drawn as to residues in muscle and liver. In kidney, at the last time point i.e., 28 days after the last administration, all residue concentrations were below the current MRL value, although they remained relatively close to the MRL (680 and 700 µg/kg). Overall, a withdrawal period cannot be derived from this study.

In the confirmatory, injection site study no control surrounding sample was collected but 3 injection sites per animal were used, in 6 animals. The dose received was 3 mg/kg bw every 8 hours for 3 days. The analytical method was a bacteriological assay for which adequate validation data were not available, with a LLOQ of 100 µg/kg, i.e., twice the current applicable MRL (50 µg/kg for muscle). For that reason it is not possible to use the study to demonstrate a safe withdrawal period, despite the fact that no residues above the sensitivity limit of 100 µg/kg were detected.

A further GLP study concerning both cattle and pigs was conducted with Gentamicin 40 mg/ml solution for injection (MAH: Vetprom), using an enzyme-linked immunoassay as the analytical method. The study is not provided as a full report but rather as a summary. No complete validation data are available. Residue depletion was only followed in kidney and liver; notably the injection site was not analysed. Only two animals per slaughter point were involved. The study was conducted in ruminating cattle (350-380 kg). The dose administered was 4 mg/kg bw at a 12-hour interval on the first day, and afterwards at 24-hour intervals, until day 5 included. Groups of cattle were slaughtered 60, 70, 80 and 90 days after the last administration. Residues in both kidney and liver fall below the MRL at day 80. However in view of shortcomings in the study a reliable withdrawal period cannot be derived from this study.

In renewal assessment reports as assessed by the Belgian NCA, a study was identified supporting the withdrawal period for Genta-kel 5% in calves (MAH: Kela). No full study report and analytical method validation report are available. The GLP status of the study is not known. The study involves non ruminating calves of 8-11 weeks of age, which received 3 mg/kg bw gentamicin twice a day for 3 consecutive days. Animals were slaughtered at 4, 11, 20, and 89 days after the last administration, in groups of 4 to 5. Kidney, liver, fat, muscle, injection site (with no control surrounding sample) were analysed for residue depletion, using an LC-MS/MS method. At the last time point i.e., day 89, residues above the MRL were still detected in the liver (2 in 5 samples). Use of the statistical method for evaluation of the liver data is not considered appropriate, as the homoscedasticity assumption is not met. For the other tissues, the alternative method could be applied. However, in view of the residues above the MRL in liver at day 89, and given that no full study report is available and no analytical method validation report is available, it is not possible to derive a withdrawal period from the study.

Withdrawal periods for cattle meat and offal

Overall for the species cattle, three studies allow derivation of withdrawal periods of 103 days for Aagent 50 mg/ml (MAH: Fatro), 192 days for Gentacalier 40 mg/ml, Maycoli inyectable 40 mg/ml, Gentavall 40 mg/ml, Vetersan gentamicina 40 mg/ml, Gentamiciven 40 mg/ml and Purmicina 40 mg/ml (MAHs: Laboratorios Calier, Laboratorios Maymo, Super's Diana, Mevet, Laboratorios e Industrias Iven and Cenavisa), and 139 days for Genta-ject 10% (MAH: Dopharma).

It is not appropriate to pool the residue data in order to calculate an overall withdrawal period for all products as different dosing regimens were applied in the studies.

It is considered that the withdrawal periods of 103, 192 and 139 days should be applied to the aforementioned specific products used in the corresponding studies, insofar as the recommended dosing regimen is identical to the one applied in the relevant study, or amounts to a lesser or equivalent dosing in terms of total exposure.

For those products mentioned in the above paragraph that have maximum recommended doses that exceed those used in the corresponding residue studies, the worst case withdrawal period derived directly from residue data, i.e. 192 days, should be applied provided the total dose as per the SPC recommendations does not exceed the total dose administered in the study that yielded this withdrawal period (i.e. 24 mg gentamicin base per kg bw).

For the products where the residues depletion study provided does not cover the recommended dosing regimen, or for products where no data have been provided, the worst case withdrawal period calculated directly from residue depletion data, i.e., 192 days, should apply. This relates to a dosing regimen of 4 mg/kg bw each 12 hours for 3 days, and an injection volume of 20 ml for a concentration of 40 mg/ml. It can be considered that this withdrawal period is sufficient to cover differences in product composition that could have an impact on the residue depletion pattern. Any such impact is likely to remain limited in view of the available product compositions, given the very long period over which depletion takes place, and given that all products concerned by this referral are aqueous solutions. The withdrawal period of 192 days cannot be applied to products for which the total recommended dose exceeds the dose used in the residues study, i.e., 24 mg gentamicin base per kg bw.

For products where the total dose exceeds that for which reliable residues data are available (i.e., for products administered at total doses of greater than 24 mg gentamicin base per kg bw in cattle) the CVMP agreed to extrapolate withdrawal periods based on pharmacokinetic principles. This is not a standard approach and is not referred to in CVMP guidance. However, in the context of this referral procedure, where products are already authorised and where limited residue depletion data are available, use of this pragmatic approach was considered to be an acceptable way to maintain the availability of medicinal products while ensuring consumer safety. The pharmacokinetic approach uses the observed terminal depletion half-life in tissues, the withdrawal period established based on data, and the dose to be administered to allow derivation of withdrawal periods, according to the following formula:

$$WP_{new} = WP_{old} + \{log_2(D_{new}/D_{old}) \times T_{1/2}(final\ phase)\}^{\ rounded\ up}$$

Where: WP_{new} is the withdrawal period for the product for which a withdrawal period is to be derived; WP_{old} is the withdrawal period for the product from which extrapolation is proposed; D_{new} is the dose of the product for which a withdrawal period is to be derived; D_{old} is the dose of the product from which extrapolation is proposed; $T_{1/2}$(final phase) is the terminal half-life.

This calculation is applicable provided that the depletion kinetics are linear and that when residues deplete below the MRLs, the tissue distribution is complete. The mean half-life calculated is 20.41 days. The method leads to a recommended extrapolated withdrawal period of 214 days based on the maximum recommended total dose for most concerned products, i.e., 50 mg gentamicin base per kg bw. Only one product (Gentamicin Bremer Pharma, authorised in Latvia, MAH: Bremer Pharma) recommends a higher total dose, of 80 mg gentamicin base per kg bw. In that case an extrapolated withdrawal period of 228 days is recommended.

It should be emphasised that the extrapolation method used is a pragmatic approach aimed at preserving product availability while in the same time ensuring consumer safety. It is acknowledged

that there are some uncertainties in the data with respect to the terminal half-life and dose linearity of the depletion kinetics, both being conditions, that have to be fulfilled for a correct use of the extrapolation. The intention is to address those products concerned by this procedure for which the maximum recommended dose is high and for which no withdrawal period can be set in a conventional manner based on residue data. For products for which the maximum recommended dose is below that used in the worst case residues studies (24 mg gentamicin base per kg bw), use of this extrapolation approach is not considered appropriate, as using the highest calculated withdrawal period has the effect of incorporating an overall safety margin to cover the lack of specific and adequate data.

Some of the concerned products may be used in older animals than those used in the studies, leading to higher total injection volumes, which may entail a slowest depletion rate due to the decreased surface/volume ratio of the injection site bolus. Therefore, the withdrawal periods cannot be extrapolated to higher injection volumes than those applied in the studies. However, it appears from all the data taken together that, at least for an injection volume of up to 20 ml in calves, the injection site is not the limiting tissue and therefore, it may be considered that the risk for the consumer in relation to higher injection volumes would remain low.

The 192 days withdrawal period was established in ruminating animals; however the Committee considers that it is applicable also to non-ruminating calves. Indeed, the concerned products are for parenteral injection and therefore the impact of digestive physiology is likely limited. Furthermore, the comparison of the studies with Aagent 50 mg/ml solution for injection (MAH: Fatro) and Genta-ject 10% (MAH: Dopharma) shows that residue depletion is not slower in very young animals, since the withdrawal period is lower (103 days) for calves less than one month of age receiving a milk replacer and a solid supplement, than for older calves receiving solid food. This is confirmed to some extent by the rapid depletion observed with Forticine Solution 1% (MAH: Vetoquinol), also conducted in young calves fed with milk replacer. Moreover the residue depletion period is long for gentamicin, and will in most cases cover a period where animals will at least partly, be ruminating.

Residue depletion in pig meat and offal

In all residue depletion studies provided, gentamicin was used as an injectable aqueous solution and was administered by the intramuscular route.

A study is available concerning the product Aagent 50 mg/ml solution for injection (MAH: Fatro). That study in piglets is GLP-compliant; the design is in accordance with current standards. The piglets used were less than 1 month of age. Groups of 5 animals were treated at a dose of 4 mg/kg bw once a day for 3 days, and slaughtered at days 30, 40, 50 and 60 after the last administration. Kidney, liver, skin+fat, muscle, and injection site (core and surrounding) were analysed using a validated HPLC/MS-MS method. Analysis of the results for each tissue leads to a maximum withdrawal period of 66 days, relating to residue depletion in skin+fat and in the injection site and obtained using the alternative calculation method.

The product Aagent 50 mg/ml solution for injection was also tested in depletion studies in adult pigs. This study is GLP-compliant and it is considered by the MAH (Fatro) as a preliminary study. No control injection site surrounding sample was analysed. No combined skin+fat sample was analysed, as only fat was sampled. The residue measured, gentamicin, was not the marker residue, and the LLOQ of the HPLC-MS/MS method was equal to the MRL for muscle and fat. No stability data were presented. Groups of 4 adult pigs receiving a dose of 4 mg/kg bw once a day for 5 days, were slaughtered at days 7, 21, 35, and 49 after the last administration, and kidney, liver, fat, muscle, and injection site were analysed. At day 49, the last sampling point, levels in kidney and liver were above the MRLs in all samples, with some values being more than 2x MRL in kidney and more than 3x MRL in liver. In addition, for the injection site, one concentration was still slightly above the MRL at day 49. Therefore, no reliable withdrawal period can be established from these data.

Another study in pigs is available in relation to the product Vetrigen (MAH: Ceva Sante Animale). The study is not GLP-compliant. The study concerns animals weighing 23 to 27 kg. Groups of only 3 animals were treated at a dose of 4 mg/kg bw every 12 hours for 4.5 days (9 injections), and slaughtered at days 15 and 60 after the last administration. Kidney, liver, fat, muscle and the injection site, with no control surrounding sample, were analysed using a microbiological method, for which no adequate validation data are available. At the last slaughter point i.e. day 60, residue levels were below the MRL in liver and kidney, but no firm conclusion can be drawn for fat, muscle and in particular the injection site, since the relating sensitivity limit was twice the MRL. A reliable withdrawal period cannot be derived from this study.

A study conducted with Gentavall 5 mg/ml (MAH: Mevet), was not clearly GLP-compliant (the study used a surprisingly low dose of 5 mg per animal, in newborn piglets (3-5 days old), administered once). Otherwise, it can be regarded as meeting current standards, although muscle (other than injection site) and fat were not analysed; this can be accepted as these tissues are recognised as not limiting with regard to gentamicin residue depletion. A validated HPLC-MS/MS analytical method was used. Groups of 4 animals were slaughtered at days 40, 45 and 50 after the last administration. Kidney, liver, and the injection site were analysed. Due to the size of the animals no control surrounding injection site sample could be collected. As expected in view of the dose administered, depletion appears rapid in all tissues and levels were below the MRL at the first time point, i.e. 40 days. The withdrawal period derived from those data, based on the alternative method with a 10% safety span, and relating to a single dose of 5 mg/animal, is 44 days for piglets.

A GLP study concerning both cattle and pigs was conducted with Gentamicin 40 mg/ml solution for injection (MAH: Vetprom), using an enzyme-linked immunoassay as the analytical method. The study is not provided as a full report, but rather as a summary. No complete validation data are available. Residue depletion was only followed in kidney and liver; notably the injection site was not analysed. Only two animals per slaughter point were involved. The study was conducted in ruminating cattle (350-380 kg) and pigs of 35-40 kg. The dose administered was 4 mg/kg bw with a 12 hours interval on the first day, and afterwards at 24 hours intervals, until day 5 inclusive. Groups of pigs were slaughtered 14, 28, 35 and 40 days after the last administration. Residues in both kidney and liver fall below the MRL at day 28. However, in view of study shortcomings a reliable withdrawal period could not be derived from this study.

In renewal assessment reports as assessed by the Belgian NCA, two studies were identified, respectively supporting the withdrawal periods for Genta-kel 5% (MAH: Kela), and for Gentaveto-5 in calves (MAH: VMD). No full report is available for the study with Genta-kel 5%, while the study with Gentaveto-5 was provided as a full report.

The study for Genta-kel 5% (MAH: Kela) in piglets used a dose of 3 mg/kg bw twice daily; the treatment duration could not be identified. Groups of 4 to 5 animals were slaughtered at days 3, 10, 17, 27, 67 and 89 after the last administration. Kidney, liver, fat, muscle and injection site (with no surrounding sample) were analysed using a validated LC-MS/MS method; however the results for fat are not available. No withdrawal period can be drawn from the study since residues above the MRL were detected in all tissues for which adequate data were available at the last time point i.e., 89 days after the last administration.

The study for Gentaveto-5 (MAH: VMD) was conducted in pigs weighing 3.75 to 8 kg, and dosed at 5 mg/kg bw, every 12 hours for 5 days. Groups of 5 animals each were slaughtered at 14, 42, 70 and 112 days after the last administration. Kidney, liver, skin+fat and injection sites were analysed for residue depletion, using a validated LC-MS/MS method. No control surrounding sample was collected for the injection site, but 2 sites per animal were analysed and the sites were considered as sufficiently close to each other. On day 112 after the last injection, the last time point, all concentrations were

below the MRL. The approved withdrawal period of 146 days was derived using the alternative method with a safety span of 30%, and can be considered as safe for the consumer.

Withdrawal periods for pigs

For the target species pigs, three studies were identified from which a sufficiently reliable withdrawal period could be drawn. Those are the studies conducted with the products Gentavall 5 mg/ml (MAH: Mevet), Aagent 50 mg/ml solution for injection (MAH: Fatro), and Gentaveto-5 (MAH: VMD). The withdrawal periods are, respectively, 44, 66 and 146 days. They do not relate to the same applied posology.

It is of note that the withdrawal period of 44 days in piglets based on the study with Gentavall 5 mg/ml (MAH: Mevet) corresponds to very particular conditions of use (one single 5 mg injection in neonates).

It is concluded that the withdrawal periods of 44, 66 and 146 days should be applied to the aforementioned products used in the corresponding studies, insofar as the recommended dosing regimen is identical to the one applied in the relevant study, or amounts to a lesser or equivalent dosing in terms of total exposure.

For those products mentioned in the above paragraph that have maximum recommended doses that exceed those used in the residue studies, the worst case withdrawal period derived directly from residue data, i.e. 146 days, should be applied provided the total dose as per the SPC recommendations does not exceed the total dose administered in the study that yielded this withdrawal period (i.e. 50 mg gentamicin base per kg bw).

The withdrawal period of 146 days can also be applied to other products, provided the total dose as per the recommendations does not exceed the total dose administered in the corresponding study (50 mg gentamicin base per kg bw). It is noted that the dose used in the relevant study (50 mg gentamicin base per kg bw) appears to cover all of the currently recommended dosing regimens. It can be considered that this worst case withdrawal period sufficiently covers possible effects arising from differences in product composition. Indeed, it appears from the available product compositions that products have very similar compositions, including common preservatives and buffer systems which are not likely to influence the absorption rate, and which are present in very low relative amounts. In addition the period over which depletion takes place is very long, and all products concerned by this referral are aqueous solutions.

In the case of pigs, all withdrawal periods determined relate to a maximum injected volume of 1 ml, for a concentration of 50 mg/ml, and cannot be directly extrapolated either to larger volumes or to larger doses per injection site. Therefore, the injection volume should be limited to a maximum of 1 ml per injection site, or to 50 mg gentamicin per injection site for products with a strength exceeding 50 mg gentamicin per ml.

Residue depletion data in cattle milk

The only residue depletion in cow milk is provided with Aagent 50 mg/ml solution for injection (MAH: Fatro), although the product is not authorised for use in lactating cows. The study is considered by the MAH as a pilot study and involves only 8 animals. The residue measured (gentamicin) did not correspond to the established marker residue, and the available data are not sufficient to allow verification of the validity of the HPLC-MS/MS analytical method. The dose administered was 4 mg/kg bw once a day for a duration of 5 days. Residue concentrations in milk were determined 12, 24, 36, 48, 60, 72, 84 and 96 hours after the last administration. The low number of animals and data points did not allow analysis of the results using the TTSC (time to safe concentration) or SCLR (safe concentrations, based on linear regression, and allowing for measurements below the limit of quantification) statistical methods, as per CVMP Note for guidance for the determination of withdrawal

periods for milk (EMEA/CVMP/473/98)[3]. The SCPM (safe concentrations, based on data per time point, allowing for data below the limit of quantification) method resulted in a calculated withdrawal period of 72 hours, which corresponds to the first time points where all concentrations are below the MRL, although residues were below the MRL for 7 out of 8 animals at 48 hours after the last administration. Overall the data from this study were not considered adequate for the purpose of deriving a milk withdrawal period.

In the milk residue study described in the CVMP EPMAR for gentamicin (EMA/CVMP/619817/2015)[4], five lactating cows were treated with repeated intramuscular doses of 4 mg gentamicin/kg bw/day for 3 days. Milk samples were collected up to 90 hours after the last administration. Gentamicin residues in edible tissues and milk were determined by a microbiological assay with a limit of quantification being 50 µg/kg (1/2 MRL). No antimicrobial active residues could be detected in any milk sample collected, which is indicative of an overall very rapid depletion.

Taking a pragmatic approach intended to preserve product availability in lactating cows while ensuring consumer safety, it is considered appropriate to apply to the maximum milk withdrawal period currently authorised, i.e., 7 days, to all products that have lactating cows as an indicated species. This withdrawal period includes a wide safety margin with regard to the available data.

General considerations

Based on the information made available to the CVMP it appears that there are several products for which unclear dosing instructions are given in the product information. It is the responsibility of each National Competent Authority to apply the recommendations of this opinion based on the recommended maximum dose as per the approved SPC, and to take action in case the recommendations in the product information cannot be properly interpreted.

It is considered that the intravenous route is unlikely to lead to higher residue levels in comparison to the intramuscular route and consequently the withdrawal periods derived based on subcutaneous administration can also be recommended for intravenous administration. However, the subcutaneous route should no longer be recommended for cattle and pigs since the depletion kinetics from the injection site remains unknown and may be limiting.

The same rationale used as a basis for the withdrawal periods for products containing gentamicin as the sole active substance may also be applied to gentamicin in combination with trimethoprim and sulfadimethoxine. Indeed, given the especially long persistence of gentamicin in tissues, which is not the case for the other substances in combination products, in view of the withdrawal periods generally approved for products containing trimethoprim and sulphonamides, there is no reason to expect any long-term effect on residues due to interaction.

Finally, a repeated course of treatment within a certain timescale is highly likely to lead to accumulation of gentamicin residues in liver, kidneys, and potentially injection sites of treated animals, and therefore it should be made clear in product information that any repeated course of treatment during the withdrawal period must be avoided.

3. Benefit-risk assessment

Quality, target animals safety, user safety, environmental risk and efficacy have not been assessed in this referral procedure.

[3] CVMP Note for guidance for the determination of withdrawal periods for milk (EMEA/CVMP/473/98) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004496.pdf
[4] CVMP EPMAR for gentamicin (EMA/CVMP/619817/2015) - http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2016/03/WC500203742.pdf

The withdrawal periods for cattle (meat and milk) and pigs should be amended as recommended to provide assurance for consumer safety.

The subcutaneous route should no longer be recommended for cattle and pigs since the depletion kinetics from the injection site remains unknown and may be limiting.

A warning sentence should be added to the product information to advise that any repeated course of treatment during the withdrawal period must be avoided.

The overall benefit-risk balance of the products under this procedure was deemed positive subject to the recommended amendments in the product information (see Annex III).

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- on the basis of the residue depletion data in cattle and pigs, the CVMP considered the withdrawal periods for cattle (meat and milk) and pigs should be amended to provide assurance for consumer safety;
- in the absence of residue depletion data with subcutaneous route of administration, the CVMP considered the subcutaneous route for cattle and pigs should be removed from the product information;
- a repeated course of treatment within a certain timescale is highly likely to lead to accumulation of gentamicin residues in liver, kidneys, and potentially injection sites of treated animals, the CVMP considered that a warning sentence should be added to the product information to advise that any repeated course of treatment during the withdrawal period must be avoided;
- the CVMP considered that the overall benefit-risk balance for the products under this procedure remains positive subject to amendments in the product information;

the CVMP has recommended variations of the marketing authorisations for veterinary medicinal products containing gentamicin presented as solutions for injection to be administered to cattle and pigs (see Annex I) in order to amend the summaries of product characteristics, labelling and package leaflets in line with recommended changes in the product information as set out in Annex III.

Annex III

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

A. For Aagent 50 mg/ml listed in Annex I (Marketing Authorisation Holder: Fatro S.p.A.)

Where the maximum total dose, as recommended in the product information, does not exceed 12 mg gentamicin base per kg bw in cattle and pigs, the wording below should be used:

Summary of product characteristics

4.9 Amounts to be administered and administration route

Delete, where applicable, any references to subcutaneous use in calves and piglets.

In pigs do not administer more than 1 ml per injection site.

Repeated injections should be made at different injection sites.

4.11 Withdrawal period(s)

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Calves:

Intramuscular or intravenous use: Meat and offal: 103 days.

Piglets:

Meat and offal: 66 days.

Labelling:

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Delete, where applicable, any references to subcutaneous use in calves and piglets.

8. WITHDRAWAL PERIOD

Calves:

IM, IV: Meat and offal: 103 days.

Piglets:

Meat and offal: 66 days.

Package leaflet:

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

Delete, where applicable, any references to subcutaneous use in calves and piglets.

In pigs do not administer more than 1 ml per injection site.

Repeated injections should be made at different injection sites.

10. WITHDRAWAL PERIOD

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Calves:

Intramuscular or intravenous use: Meat and offal: 103 days.

Piglets:

Meat and offal: 66 days.

B. For Genta-ject 10% listed in Annex I (Marketing Authorisation Holder: Dopharma Research B.V.)

Where cattle and/or pigs have already been approved as target species and provided that the maximum total dose, as recommended in the product information, does not exceed 12 mg gentamicin base per kg bw in cattle and 50 mg gentamicin base per kg bw in pigs, the wording below relating to the relevant species should be used:

Summary of product characteristics

4.9 Amounts to be administered and administration route

Delete, where applicable, any references to subcutaneous use in cattle and pigs.

In pigs do not administer more than 50 mg gentamicin per injection site.

Repeated injections should be made at different injection sites.

4.11 Withdrawal period(s)

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use: Meat and offal: 139 days.

Pigs:

Meat and offal: 146 days.

Labelling:

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Delete, where applicable, any references to subcutaneous use in cattle and pigs.

8. WITHDRAWAL PERIOD

Cattle:

IM, IV: Meat and offal: 139 days.

Pigs:

Meat and offal: 146 days.

Package leaflet:

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

Delete, where applicable, any references to subcutaneous use in cattle and pigs.

In pigs do not administer more than 50 mg gentamicin per injection site.

Repeated injections should be made at different injection sites.

10. WITHDRAWAL PERIOD

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use: Meat and offal: 139 days.

Pigs:

Meat and offal: 146 days.

C. For Gentavall 5 mg/ml listed in Annex I (Marketing Authorisation Holder: Mevet S.A.U.)

Where the maximum total dose, as recommended in the product information, does not exceed 5 mg gentamicin base per animal in pigs, the wording below should be used:

Summary of product characteristics

4.11 Withdrawal period(s)

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Piglets:

Meat and offal: 44 days.

Labelling:

8. WITHDRAWAL PERIOD

Piglets:

Meat and offal: 44 days.

Package leaflet:

10. WITHDRAWAL PERIOD

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Piglets:

Meat and offal: 44 days.

D. For Gentaveto-5 (50 mg/ml) listed in Annex I (Marketing Authorisation Holder: V.M.D. n.v.)

Where the maximum total dose, as recommended in the product information, does not exceed 50 mg gentamicin base per kg bw in pigs, the wording below should be used:

Summary of product characteristics

4.9 Amounts to be administered and administration route

Repeated injections should be made at different injection sites.

In pigs do not administer more than 1 ml per injection site.

4.11 Withdrawal period(s)

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Pigs:

Meat and offal: 146 days.

Labelling:

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Repeated injections should be made at different injection sites.

8. WITHDRAWAL PERIOD

Pigs:

Meat and offal: 146 days.

Package leaflet:

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

Repeated injections should be made at different injection sites.

In pigs do not administer more than 1 ml per injection site.

10. WITHDRAWAL PERIOD

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Pigs:

Meat and offal: 146 days.

E. For Gentamicin Bremer Pharma listed in Annex I (Marketing Authorisation Holder: Bremer Pharma GmbH)

Where the maximum total dose, as recommended in the product information, is up to 80 mg gentamicin base per kg bw in cattle, the wording below should be used:

Summary of product characteristics

4.9 Amounts to be administered and administration route

Delete, where applicable, any references to subcutaneous use in cattle.

Repeated injections should be made at different injection sites.

4.11 Withdrawal period(s)

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use: Meat and offal: 228 days.

Labelling:

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Delete, where applicable, any references to subcutaneous use in cattle.

8. WITHDRAWAL PERIOD

Cattle:

IM, IV: Meat and offal: 228 days.

Package leaflet:

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

Delete, where applicable, any references to subcutaneous use in cattle.

Repeated injections should be made at different injection sites.

10. WITHDRAWAL PERIOD

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use: Meat and offal: 228 days.

F. For all other products listed in Annex I for which the recommended total doses do not exceed 24 mg gentamicin base per kg bw for cattle and 50 mg gentamicin base per kg bw for pigs

Where cattle and/or pigs have already been approved as target species and provided that the maximum total dose of gentamicin, as recommended in the product information, does not exceed 24 mg gentamicin base per kg bw in cattle and 50 mg gentamicin base per kg bw in pigs, the wording below relating to the relevant species should be used:

Summary of product characteristics

4.9 Amounts to be administered and administration route

Delete, where applicable, any references to subcutaneous use in cattle and pigs.

For products with a strength up to 50 mg gentamicin per ml: In pigs do not administer more than 1 ml per injection site.

For products with a strength exceeding 50 mg gentamicin per ml: In pigs do not administer more than 50 mg gentamicin per injection site.

Repeated injections should be made at different injection sites.

4.11 Withdrawal period(s)

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use: Meat and offal: 192 days.

Pigs:

Meat and offal: 146 days.

Labelling:

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Delete, where applicable, any references to subcutaneous use in cattle and pigs.

8. WITHDRAWAL PERIOD

Cattle:

IM, IV: Meat and offal: 192 days.

Pigs:

Meat and offal: 146 days.

Package leaflet:

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

Delete, where applicable, any references to subcutaneous use in cattle and pigs.

For products with a strength up to 50 mg gentamicin per ml: In pigs do not administer more than 1 ml per injection site.

For products with a strength exceeding 50 mg gentamicin per ml: In pigs do not administer more than 50 mg gentamicin per injection site.

Repeated injections should be made at different injection sites.

10. WITHDRAWAL PERIOD

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use: Meat and offal: 192 days.

Pigs:

Meat and offal: 146 days.

G. For products listed in Annex I for which the recommended total dose is between 24 mg gentamicin base per kg bw and 50 mg gentamicin base per kg bw for cattle

Summary of product characteristics

4.9 Amounts to be administered and administration route

Delete, where applicable, any references to subcutaneous use in cattle.

Repeated injections should be made at different injection sites.

4.11 Withdrawal period(s)

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use: Meat and offal: 214 days.

Labelling:

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Delete, where applicable, any references to subcutaneous use in cattle.

8. WITHDRAWAL PERIOD

Cattle:

IM, IV: Meat and offal: 214 days.

Package leaflet:

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

Delete, where applicable, any references to subcutaneous use in cattle.

Repeated injections should be made at different injection sites.

10. WITHDRAWAL PERIOD

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use: Meat and offal: 214 days.

H. For products listed in Annex I for which lactating cows have already been approved as target species

Summary of product characteristics

4.9 Amounts to be administered and administration route

Delete, where applicable, any references to subcutaneous use in cattle.

Repeated injections should be made at different injection sites.

4.11 Withdrawal period(s)

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use:

Meat and offal: *as recommended in the relevant sections of Annex III above*.

Milk: 7 days.

Labelling:

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Delete, where applicable, any references to subcutaneous use in cattle.

8. WITHDRAWAL PERIOD

Cattle:

IM, IV:

Meat and offal: *as recommended in the relevant sections of Annex III above*.

Milk: 7 days.

Package leaflet:

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

Delete, where applicable, any references to subcutaneous use in cattle.

Repeated injections should be made at different injection sites.

10. WITHDRAWAL PERIOD

Due to accumulation of gentamicin in liver, kidneys and injection site, any repeated course of treatment during the withdrawal period must be avoided.

Cattle:

Intramuscular or intravenous use:

Meat and offal: *as recommended in the relevant sections of Annex III above*.

Milk: 7 days.