

Annex I

List of the names, pharmaceutical form, strength of the veterinary medicinal products, animal species, route of administration, marketing authorisation holders in the Member States

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate H18 W620 Monaghan Ireland	Betamox long acting- Injektionssuspension für Tiere	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Austria	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml Injektionssuspension für Rinder, Schafe, Schweine, Hunde, Katzen	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Belgium	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Bulgaria	Asklep-Farma OOD j.k. Lyulin 7, bl. 711A, shop 3 Sofia Bulgaria	Betamox LA Injection	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Bulgaria	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml suspension for injection for cattle, sheep, pigs, dogs and cats	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Croatia	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA, 150 mg/mL, suspenzija za injekciju, za goveda, ovce, svinje, pse i mačke	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Croatia	GENERA d.d. Svetonedeljska cesta 2 Kalinovica 10436 Rakov Potok Croatia	Simivet retard, 150 mg/mL, suspenzija za injekciju, za goveda, ovce, svinje, pse i mačke	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Cyprus	Stavrinides Spyros Chemicals Ltd 28A Stasinou Ave Nicosia Cyprus	Betamox LA Injection, 150 mg/ml Ενέσιμο Εναιώρημα	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Cyprus	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml Ενέσιμο εναιώρημα για βοοειδή, πρόβατα, χοίρους, σκύλους, γάτες	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Czech Republic	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland	Betamox LA 150 mg/ml injekční suspenze	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Denmark	ScanVet Animal Health A/S Kongevejen 66 3480 Fredensborg Denmark	Betamox Vet.	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Denmark	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Estonia	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Finland	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox vet	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Finland	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox vet	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml Suspension for Injection for Cattle, Sheep, Pigs, Dogs, Cats	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Germany	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150mg/ml suspension for injection	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Greece	Hellafarm A.E Fleming 15 15123, Marousi Greece	Betamox L.A	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Greece	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox L.A	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Hungary	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox LA 150 mg/ml szuszpenziós injekció A.U.V.	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Hungary	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml suspension for injection	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Hungary	Bayer Hungária Kft. 1123 Budapest Alkotás u. 50. Hungary	Amoxysol LA 150 mg/ml szuszpenziós injekció szarvasmarhák, sertések és juhok részére A.U.V.	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs	Intramuscular and/or subcutaneous use
Ireland	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland	Betamox LA 150 mg/ml Suspension for Injection	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Ireland	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150mg/ml suspension for injection	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox LA, 150 mg/ml sospensione iniettabile per bovini, suini, cani e gatti	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Italy	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trimox LA 150 mg/ml, sospensione iniettabile per bovini, ovini, suini, cani e gatti	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Latvia	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml suspensija injekcijām liellopiem, aitām, cūkām, suņiem, kaķiem	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Latvia	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox LA 150 mg/ml suspensija injekcijām liellopiem, aitām, cūkām, suņiem, kaķiem	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Lithuania	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox LA, 150 mg/ml, injekciné suspensija galvijams, kiaulēms, avims, šunims ir katēms	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Lithuania	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml Suspension for Injection for Cattle, Sheep, Pigs, Dogs, Cats	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Norway	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox Vet	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
The Netherlands	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml suspensie voor injectie voor runderen, schapen, varkens, honden, katten	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Poland	Scanvet Poland Sp. z o.o. ul. Kizkowska 9 Gniezno 62-200 Poland	Betamox L.A.	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Nordpharm Poland Sp. z o.o. Al. Jerozolimskie 99 lok. 39 02-001 Warszawa Poland	Amoxyvet LA	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Poland	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Portugal	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland	Betamox LA 150 mg/ml Suspension for Injection	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Portugal	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml suspension for injection	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Romania	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox LA, 150 mg/ml	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Slovak Republic	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox LA 150 mg/ml injekčná suspenzia	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Slovak Republic	Zoetis Česká republika, s.r.o náměstí 14. října 642/17 150 00 Prague 5 Czech Republic	Duphamox LA 150 mg/ml injekčná suspenzia	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Slovak Republic	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml Suspension for Injection for Cattle, Sheep, Pigs, Dogs, Cats	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Slovenia	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml suspension for injection for cattle, sheep, pigs, dogs and cats	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovenia	GENERA SI d.o.o. Parmova ulica 53 1000 Ljubljana Slovenia	Simivet retard 150 mg/ml suspenzija za injiciranje	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
Spain	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox LA	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs	Intramuscular and/or subcutaneous use
Sweden	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox vet	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
United Kingdom	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Betamox LA 150 mg/ml Suspension for Injection	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs	Intramuscular and/or subcutaneous use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Norbrook Laboratories Limited Station Works Camlough Road Newry, Co. Down BT35 6JP Northern Ireland United Kingdom	Amoxycare LA Suspension for Injection 15% w/v	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use
United Kingdom	Univet Ltd Tullyvin Cootehill Co. Cavan Ireland	Trymox LA 150 mg/ml Suspension for Injection for Cattle, Sheep, Pigs, Dogs, Cats	Amoxicillin trihydrate	150 mg/ml	Suspension for injection	Cattle, sheep, pigs, dogs, cats	Intramuscular and/or subcutaneous use

Annex II

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

Overall summary of the scientific evaluation of Betamox LA 150 mg/ml suspension for injection and associated names, and generics products thereof (see Annex I)

1. Introduction

Amoxicillin is a broad-spectrum antibiotic of the β -lactam family belonging to the aminopenicillin group. This active substance has time-dependent bactericidal activity and acts against Gram-positive and some Gram-negative microorganisms.

Betamox LA 150 mg/ml suspension for injection (hereafter named Betamox LA) and associated names, and generic products thereof are suspensions for injection which contain 150 mg amoxicillin (as amoxicillin trihydrate) per 1 ml for use in cattle, sheep, pigs, dogs and cats. The recommended dosage rate is 15 mg amoxicillin per kg body weight to be repeated if necessary, after 48 hours.

An application was submitted under Article 13(1) of Directive 2001/82/EC, i.e. a generic application, for a marketing authorisation under the decentralised procedure (UK/V/0681/001/DC) for the veterinary medicinal product Trymox LA 150 mg/ml suspension for injection for cattle, sheep, pigs, dogs and cats, with the United Kingdom as reference Member State. The European reference product is Betamox LA which has been authorised in several EU Member States for decades (e.g. in the United Kingdom since 1986).

Based on the similarity of the formulation between the reference product Betamox LA and the generic product Trymox LA 150 mg/ml suspension for injection, the withdrawal period of the reference product was applied to the generic product. No residue depletion data for the generic product were provided. Considering that the reference and the generic product are qualitatively and quantitatively similar in regard of the active substance and excipients, bioequivalence was accepted.

During the assessment the reference Member State provided some summaries of residue depletion data on which the withdrawal periods of the reference product were based. However, within these residue depletion studies none of the animals received the maximal injection volume of 20 ml per injection site as mentioned in the product information.

Within the decentralised procedure, the reference Member State reviewed the withdrawal period of the reference product and stated that for meat and offal in all species, the safety factor added has been increased from 10% to 30% to compensate for the low body weight of the animals.

The volume of 20 ml per injection site leads to a 2 to 6-fold higher dose at the injection site for the veterinary medicinal products compared to the doses tested in residue depletion studies. Furthermore, the product is an oily formulation resulting in a slow resorption and possible retention of residues at injection sites. Additionally, as depletion at the injection site is influenced by both dose and the volume of injection, a higher dose could influence reactions at the injection site (tissue damage) and lead to changes in surface-to-mass ratio and a shift of depletion to zero-order kinetics. This typically leads to a slower resorption from the injection site. Germany considered that the addition of a safety factor to account for the intended higher dose/volume at the injection site was therefore not adequate; and without a limit on the injection volume to volumes covered by the residue depletion studies, consumer safety cannot be assured.

In addition, it has been noted that for Betamox LA there were differences between the established withdrawal periods for cattle, sheep and pigs in the Member States. Therefore, Germany considered that it is necessary to refer the matter to the CVMP in the interests of animal health and protecting consumer safety in the Union.

Germany requested the CVMP to review all available residue depletion data for Betamox LA 150 mg/ml suspension for injection and associated names, and generic products thereof, and recommend appropriate withdrawal periods for treated cattle, sheep and pigs. The CVMP was also requested to consider whether other risk management measures are possible for the veterinary medicinal products under consideration (e.g. limit the injection volume per injection site).

2. Discussion of data available

Qualitative and quantitative composition

Information was received regarding the composition of the concerned products. The formulations being very similar, it is expected that all formulations have the same behaviour with regards to absorption at the injection site. Consequently, the CVMP considered that a common withdrawal period could be applied to the veterinary medicinal products concerned by this referral procedure.

Residue depletion data

Residue depletion in cattle meat and offal

The dataset contained a project consisting of three residue depletion studies conducted in 1995 which was considered as historic and informative only, as well as a recent study conducted in 2019 which is in accordance with current guidelines and was used for withdrawal period determination.

In this Good laboratory practice (GLP) compliant residue depletion study twenty mixed breed cattle (10 males and 10 females) at an age of 9-13 months and a body weight of 269-371 kg, were allocated to five groups of four animals (two males and two females) per group. Betamox LA was administered by intramuscular injection into the neck and rump muscle at the recommended dose of 15 mg amoxicillin per kg body weight (i.e. 1 ml product per 10 kg body weight) on two occasions, with an interval of 48 hours. The maximum dose volume was 15 ml per injection site, so that each animal received at least two injections.

The animals were slaughtered at 6, 12, 18, 24 and 30 days after the final intramuscular administration. Tissue samples (loin muscle, liver, peri-renal fat, kidney and injection site (core and surrounding)) were collected and analysed by a validated Liquid chromatography with tandem mass spectrometry (LCMS/MS) system, with a lower limit of quantification (LLOQ) of 20 ng/g for all tissues.

All non-injection site samples (loin muscle, liver, peri-renal fat and kidney) harvested at all slaughter times contained amoxicillin concentrations lower than the LLOQ (20 ng/g). Injection site samples showed residues above the maximum residue limit (MRL) value of 50 µg/kg at day 6, 12, 18 and 24 after administration; at day 30, all levels were below the MRL.

The injection site was considered the determining tissue for withdrawal period calculation with residue concentrations above the MRL until day 24 after administration. On day 12 and 24, one sample each showed a significantly higher residue concentration in the surrounding sample than in the core sample. According to the CVMP guideline on injection site residues (EMA/CVMP/542/2003)¹, in such a case the point should not be included in the statistical calculations and an alternative approach might be followed. Based on the overall data available, the CVMP concluded that the alternative approach described in the CVMP guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012)² should be used and a 30% safety span should be added, leading to a withdrawal period for cattle meat and offal of 39 days.

¹ CVMP guideline on injection site residues (EMA/CVMP/542/2003) – [link](#)

² CVMP guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012 – Rev. 1) – [link](#)

In addition, for intramuscular administration, the CVMP concluded that the maximum injection volume per injection site in cattle should be restricted to 15 ml (i.e. the highest tested volume).

Residue depletion in sheep meat and offal

The dataset contained a project consisting of three residue depletion studies conducted in 1995 which was considered as historic and informative only, as well as a recent study conducted in 2019 which is in accordance with current guidelines and was used for withdrawal period determination.

In this GLP-compliant residue depletion study thirty mixed breed sheep (15 males and 15 females) at approximately 5 months of age and a body weight of 36.0-47.4 kg, were allocated to five groups of six animals (three males and three females) per group. Betamox LA was administered by intramuscular injection into the neck and rump muscle at the recommended dose of 15 mg amoxicillin per kg body weight (i.e. 1 ml product per 10 kg body weight) on two occasions, with an interval of 48 hours. The maximum dose volume was 4 ml per injection site, so that each animal received at least two injections.

The animals were slaughtered at 8, 16, 24, 32 and 40 days after the final intramuscular administration. Tissue samples (loin muscle, liver, peri-renal fat and kidney, injection site (core and surrounding)) were collected and analysed using a validated LCMS/MS system, with a LLOQ of 20 ng/g for all tissues.

All non-injection site samples (loin muscle, liver, peri-renal fat and kidney) and the surrounding sample of the injection site harvested at all slaughter times contained amoxicillin concentrations lower than the LLOQ (20 ng/g). Injection site samples showed residues above the MRL at day 8 and 16 after administration. From day 24 onwards all residue concentrations were below the MRL.

The injection site was considered the determining tissue for withdrawal period calculation with residue concentrations above the MRL until day 16 after administration. As there were not enough time points with measured residue values, the statistical approach cannot be used and instead the alternative approach as described in the aforementioned CVMP guideline (EMA/CVMP/SWP/735325/2012) would be applicable. Based on the overall data available, the CVMP concluded that the alternative approach should be used and a 20% safety span should be added, leading to a withdrawal period for sheep meat and offal of 29 days.

In addition, for intramuscular administration, the CVMP concluded that the maximum injection volume per injection site in sheep should be restricted to 4 ml (i.e. the highest tested volume).

Residue depletion in pig meat and offal

The dataset contained a project consisting of three residue depletion studies conducted in 1995 which was considered as historic and informative only, as well as a recent study conducted in 2019 which is in accordance with current guidelines and was used for withdrawal period determination.

In this GLP-compliant residue depletion study thirty mixed breed pigs (15 males and 15 females) at an age of approximately 3 months and a body weight of 51.8-69.2 kg, were allocated to five groups of six animals (three males and three females) per group. Betamox LA was administered by intramuscular injection into the neck and rump muscle at the recommended dose of 15 mg amoxicillin per kg body weight (i.e. 1 ml product per 10 kg body weight) on two occasions, with an interval of 48 hours. The maximum dose volume was 4 ml per injection site, so that each animal received at least two injections.

The animals were slaughtered at 8, 16, 24, 32 and 40 days after the final intramuscular administration. Tissue samples (loin muscle, liver, fat with skin, kidney and injection site (core and

surrounding)) were collected and analysed using a validated LCMS/MS system, with a LLOQ of 20 ng/g for all tissues.

For all non-injection site samples (loin muscle, liver, kidney and fat with skin) amoxicillin concentrations were below the LLOQ (20 ng/g) at all time points. Injection site samples showed residues above the MRL at day 8 and 16 after administration. From day 24 onwards all residue concentrations were below the MRL.

The injection site was considered the determining tissue for withdrawal period calculation with residue concentrations above the MRL until day 16 after administration. However, on day 8 three surrounding samples had higher residue concentrations than the corresponding core sample and on day 24 two surrounding samples had higher residue concentration than the corresponding core sample. According to the above-mentioned CVMP guideline on injection site residues (EMA/CVMP/542/2003), in such a case the point should not be included in the statistical calculations and an alternative approach might be followed. Based on the overall data available, the CVMP concluded that the alternative approach as described in the aforementioned CVMP guideline (EMA/CVMP/SWP/735325/2012) should be used and a 30% safety span should be added, leading to a withdrawal period for pig meat and offal of 42 days.

In addition, for intramuscular administration, the CVMP concluded that the maximum injection volume per injection site in pigs should be restricted to 4 ml (i.e. the highest tested volume).

Residue depletion in cattle milk

One GLP/QA-compliant residue depletion study conducted in 1993 was provided, in which eight Friesian cows at an age of 3-8 years and with a body weight range of 480-620 kg were used. Betamox LA was administered intramuscularly at a dose rate of 15 mg amoxicillin per kg body weight (i.e. 1 ml product per 10 kg body weight) on two occasions, 48 hours apart. The maximum dose volume per injection site was 20 ml and 3-4 sites were used per animal. They were milked twice daily with an interval of 10-14 hours. Milk samples were taken from the total milk production of each animal for 5 days and analysed using a microbiological assay with an LOQ of 0.003 µg/ml.

Residue concentrations were below the LOQ from the 72 hours' time point onwards. Based on the time to safe concentration (TTSC) method as described in the CVMP note for guidance on determination of withdrawal periods for milk (EMA/CVMP/473/1998)³, a withdrawal period of 9 milkings, i.e. 108 hours (4.5 days) for milk of treated cattle was proposed.

This milk residue depletion study was not conducted in accordance with the aforementioned CVMP guideline (EMA/CVMP/473/1998). Only 8 animals were used and the LOQ of 3 µg/kg is near the MRL value of 4 µg/kg. However, the used TTSC approach takes into account the uncertainty due to the small sample size, since it is based on tolerance limits (a smaller sample size results in larger tolerance limits). Furthermore, the TTSC approach only uses the information whether observations are above or below the MRL, but does not rely on the exact value of an observation. Consequently, the closeness of LOQ to MRL is not considered critical for this approach. Therefore, a 108-hour (4.5 days) withdrawal period for cattle milk was considered acceptable.

Residue depletion in sheep milk

No residue data for sheep milk were provided and a proposal was made to include a statement in the product information in order to exclude the use in sheep producing milk for human consumption.

The CVMP guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market

³ CVMP note for guidance on determination of withdrawal periods for milk (EMA/CVMP/473/1998) – [link](#)

(EMA/CVMP/SWP/66781/2005–Rev.1)⁴ contains a provision for the extrapolation of milk withdrawal periods from major to minor species, i.e. in this case from cattle milk to sheep milk. However, in addition to the lack of product specific residue depletion data in sheep milk for the veterinary medicinal products concerned by this referral procedure, no pharmacokinetic data nor residue depletion data are available in the CVMP MRL Summary report for amoxicillin⁵ in order to compare pharmacokinetics or residues between species. Therefore, CVMP concluded that it was not possible to establish a safe withdrawal period for sheep milk for the veterinary medicinal products involved in this referral procedure.

3. Benefit-risk assessment

Introduction

The CVMP was requested to review all available residue depletion data for Betamox LA 150 mg/ml suspension for injection and associated names, and generic products thereof, and to recommend appropriate withdrawal periods (milk, meat and offal) for treated cattle, sheep and pigs.

Benefit assessment

While the efficacy of the concerned products in cattle, sheep and pigs has not been specifically assessed as part of this referral, the products under assessment are considered to be effective.

Risk assessment

Quality, target animal safety, user safety, and the environmental risk for the concerned veterinary medicinal products have not been assessed in this referral procedure. Furthermore, for generic products bioequivalence was not evaluated, as this has been done within the respective marketing authorisation procedures.

A risk has been identified regarding the length of the authorised withdrawal periods for cattle, sheep and pigs, which, for some products, may be insufficient to allow residues of amoxicillin to fall below the respective MRLs in edible tissues and milk, thereby posing a risk to consumers.

Risk management or mitigation measures

Based on the available data, revised withdrawal periods for Betamox LA 150 mg/ml suspension for injection, its associated names, and generic products thereof have been established following intramuscular use:

Cattle

Meat and offal: 39 days

Milk: 108 hours (4.5 days)

Pigs

Meat and offal: 42 days

Sheep

Meat and offal: 29 days

Milk: Not authorised for use in sheep producing milk for human consumption

⁴ CVMP guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (EMA/CVMP/SWP/66781/2005–Rev.1) – [link](#)

⁵ CVMP MRL Summary report on penicillins – [link](#)

No data has been presented to support a safe withdrawal period following subcutaneous or any other route of administration. Therefore, it should be clearly stated in the product information that only intramuscular use is approved for food-producing species.

In addition, the maximum injection volume per injection site should be restricted to 15 ml for cattle and 4 ml for sheep and pigs.

These measures were considered adequate to ensure consumer safety.

Evaluation and conclusions on the benefit-risk balance

Having considered the grounds for referral and the available data, the CVMP concluded that the withdrawal periods for cattle, sheep and pigs should be amended as recommended and that the maximum injection volume should be limited to provide assurance for consumer safety.

The overall benefit-risk balance for the veterinary medicinal products Betamox LA 150 mg/ml suspension for injection, its associated names, and generic products thereof remains positive, subject to the recommended changes in the product information.

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

Whereas

- on the basis of the available residue depletion data, the CVMP considered that the withdrawal periods for milk, meat and offal derived from treated cattle, sheep and pigs should be amended to provide assurance for consumer safety;
- on the basis of the available residue depletion data, the CVMP considered that a limitation of the injection volumes is necessary;
- 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 the amendment of the marketing authorisations for Betamox LA 150 mg/ml suspension for injection and associated names, and generics products thereof as referred in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

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

Where cattle, sheep and/or pigs have already been approved as target species the wording below relating to the relevant species should be used:

Summary of product characteristics

4.9 Amounts to be administered and administration route

...

Cattle, sheep and pigs - By intramuscular injection only.

...

Dose volume is equivalent to 1 ml per 10 kg body weight. If dose volume exceeds 15 ml in cattle and 4 ml in sheep and pigs, it should be divided and injected into two or more sites.

...

4.11 Withdrawal period(s)

Cattle:

Meat and offal: 39 days

Milk: 108 hours (4.5 days)

Pigs:

Meat and offal: 42 days

Sheep:

Meat and offal: 29 days

Milk: Not authorised for use in sheep producing milk for human consumption.

Labelling

7. METHOD AND ROUTE(S) OF ADMINISTRATION

...

Cattle, sheep and pigs - By intramuscular injection only.

...

Dose volume is equivalent to 1 ml per 10 kg body weight. If dose volume exceeds 15 ml in cattle and 4 ml in sheep and pigs, it should be divided and injected into two or more sites

...

8. WITHDRAWAL PERIOD(S)

Cattle:

Meat and offal: 39 days

Milk: 108 hours (4.5 days)

Pigs:

Meat and offal: 42 days

Sheep:

Meat and offal: 29 days

Milk: Not authorised for use in sheep producing milk for human consumption.

Package leaflet

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

...

Cattle, sheep and pigs - By intramuscular injection only.

...

Dose volume is equivalent to 1 ml per 10 kg body weight. If dose volume exceeds 15 ml in cattle and 4 ml in sheep and pigs, it should be divided and injected into two or more sites.

...

10. WITHDRAWAL PERIOD(S)

Cattle:

Meat and offal: 39 days

Milk: 108 hours (4.5 days)

Pigs:

Meat and offal: 42 days

Sheep:

Meat and offal: 29 days

Milk: Not authorised for use in sheep producing milk for human consumption.