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	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml solution for injection for pigs	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Belgium	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Belgium	Ceva Sante Animale NV Metrologielaan 6 1130 Brussel Belgium	GABBROVET	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Czech Republic	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml solution for injection for pigs	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Denmark	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Estonia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
France	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml solution injectable pour porcins	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Germany	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml solution for injection	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Greece	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Ireland	Huvepharma NV	Parofor	Paromomycin	175 mg/ml	solution for	pigs	intramuscular

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
	Uitbreidingstraat 80 2600 Antwerpen Belgium				injection		use
Italy	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml soluzione iniettabile per suini	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Latvia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Luxembourg	Ceva Sante Animale NV Metrologielaan 6 1130 Brussel Belgium	GABBROVET	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
The Netherlands	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml, oplossing voor injectie	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Poland	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml solution for injection	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Portugal	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml solution for injection	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Portugal	Ceva Saúde Animal - Produtos Farmacêuticos e Imunológicos, Lda. Rua Doutor António Loureiro Borges, 9/9A, 9ºA Miraflores- 1495-131 Algés Portugal	Gabbrocol injectável 250 mg/ml para bovinos e suínos	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Slovak Republic	Huvepharma NV Uitbreidingstraat 80	Parofor	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
	2600 Antwerpen Belgium						
Slovenia	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml raztopina za injiciranje za prašiče	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
Spain	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml solution for injection	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use
United Kingdom	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Parofor 175 mg/ml Solution for Injection for Pigs	Paromomycin	175 mg/ml	solution for injection	pigs	intramuscular use

Annex II

Scientific conclusions and grounds for suspension of the marketing authorisations

Overall summary of the scientific evaluation of Veterinary medicinal products containing paromomycin to be administered parenterally to pigs (see Annex I)

1. Introduction

Paromomycin belongs to the group of aminoglycoside antibiotics. Paromomycin has broad spectrum activity against numerous Gram-positive and Gram-negative bacteria and acts in a concentration-dependent manner. It may be administered by parenteral route.

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 for the veterinary medicinal product 'Parofor 175 mg/ml solution for injection', with Belgium as Reference Member State (BE/V/0027/003/DC). The reference product is 'Gabbrovet solution injectable', which has been authorised in a few Member States. The reference product is authorised in Belgium since 1985.

During the aforementioned decentralised procedure, it has been noted that there are different approved indications, posology and withdrawal periods for veterinary medicinal products containing paromomycin to be administered parenterally to pigs across the European Union (EU). Belgium therefore 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.

2. Discussion of data available

Efficacy data

The veterinary medicinal products involved in this referral contain 250 mg/ml paromomycin sulfate as active substance (equivalent to 175 mg/ml paromomycin base or to a paromomycin activity of 175,000 IU/ml). The target species are pigs and the route of administration is intramuscular.

The currently authorised indications are unspecific and no specific pathogens are mentioned, i.e. for the treatment of bacterial infections caused by pathogens which are susceptible to paromomycin or for bacterial infections of the respiratory tract, uro-genital tract, mastitis, enteritis, abscess, wounds, canine leishmaniosis and surgery.

Within this referral procedure, one of the marketing authorisation holders proposed the following indications as an amendment to the current indications:

- Treatment of *E. coli* involved in swine colibacillosis (neonatal diarrhoea, post-weaning diarrhoea, oedema disease) and against *Actinobacillus pleuropneumoniae* strains with a MIC ≤ 4 mg/l.

The same marketing authorisation holder provided data in order to justify the use of 'Gabbrovet solution injectable' in pigs at a dose of 14 mg paromomycin base/kg bodyweight for 5 consecutive days.

The mechanism of action of paromomycin has been well described as well as the mechanisms of antimicrobial resistance to paromomycin.

A pharmacokinetic study was carried out in target animals at the recommended dose (14 mg/kg bodyweight of paromomycin). The product showed no accumulation during the treatment period (5 days). Moreover, the product was well tolerated.

In order to justify efficacy of the product, susceptibility data were provided for *E. coli* and *A. pleuropneumoniae* and a pharmacokinetics/pharmacodynamics (PK/PD) analysis was performed.

The sampling size in target strains was not optimal to distinguish between wild type and a population with acquired resistance determinants.

For antimicrobials like paromomycin, whose efficacy is concentration-dependent, high plasma concentration levels relative to the MIC of the pathogen (C_{max}/MIC ratio, also known as the inhibitory quotient or IQ) are a major determinant of clinical efficacy; a C_{max}/MIC ratio > 8-10 is suggested to achieve optimal efficacy.

In the case of *E. coli*, the PK/PD analysis was only favourable for strains with MICs equal to or below 4.44 µg/ml. Hence, the veterinary medicinal product could be expected to be effective against *E. coli* as shown by the sensitivity results of a recent study, where 76% of the strains would be sensitive. This result, however is likely to overestimate the efficacy of paromomycin at the recommended dose since the % binding of paromomycin to plasma proteins was not determined, which would reduce the portion of paromomycin in plasma able to work against *E. coli*.

Moreover, this model holds true only for target strains in plasma or tissue sites with equivalent paromomycin distribution, no predictability can be expected against the pathogen located in other tissues.

Furthermore, neither dose determination, nor dose confirmation studies have been made available to confirm the results of the PK/PD analysis and no field trial was made available.

Finally the PK/PD model does not allow justifying the duration of treatment.

Therefore, the indication against colibacillosis based on an overestimated success from a theoretical modelling, against *E. coli* strictly located in plasma, for an unjustified duration of treatment and not confirmed by clinical data, is not acceptable.

The marketing authorisation holder also considered that the veterinary medicinal product could be used to treat Mastitis-Metritis-Agalactia (MMA) syndrome associated with *E. coli,* but acknowledged that further data are needed to assess the correct dose regimen in adult animals. However, there are no pre-clinical and clinical data supporting the indication for the treatment of MMA in sows.

Regarding *A. pleuropneumoniae,* the PK/PD analysis based on the inhibitory quotient (C_{max}/MIC >8 to 10) shows that only 10% of the target bacterial population would be sensitive to paromomycin administered at the recommended posology. This already poor result is in addition likely to overestimate the efficacy of paromomycin at the recommended dose since the % binding of paromomycin to plasma proteins was not determined, which would reduce the portion of paromomycin in plasma able to work against *A. pleuropneumoniae*. Furthermore, the duration of treatment has not been justified and no clinical data have been provided by the marketing authorisation holder to justify the recommended dose.

In conclusion, the CVMP considered that the efficacy of these veterinary medicinal products was not supported for any indication and posology.

In the absence of adequate data to support indications and posology, there is a risk that product administration at the currently recommended dose and duration of treatment will lead to ineffective treatment and a potential unnecessary suffering in the treated animals. Moreover, product administration at an inappropriate dose poses an added risk of resistance development.

Residue data

The residue depletion study was performed in pigs with the intramuscular administration of the maximum recommended dose of 14 mg paromomycin/kg bodyweight/day for 5 consecutive days.

Both the animal and analytical phases of the study were in compliance with GLP requirements and European guidelines. Samples from treated animals were collected at 4, 8, 12, 16, 20, 24 and 28 days after the end of treatment.

The quantification of paromomycin in tissues was carried out by validated HPLC-MS/MS analytical methods.

The statistical evaluation to establish withdrawal period was carried out following the CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95)[1].

The most relevant tissues for the presence of paromomycin residue were muscle at the injection site and kidney. Muscle of injection site is not the most reliable tissue for withdrawal time calculation, as it is often characterised by a high variability in residues levels, confirmed also in this case by the limited number of samples with concentrations above limit of quantification (2/4 on Day 12).

One of the marketing authorisation holders proposed a withdrawal time of 16 days based on a linear regression with kidney as limiting tissue, and 16 days with muscle of injection site by using the 'alternative' method, in line with CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95).

However, a number of deficiencies in the study were noted related to the storage of the samples, the stability of the residues in storage conditions, the wide range of recovery in muscle and the absence of a ring-shaped control surrounding the excised injection site core sample.

Due to the deficiencies noted in the study, a withdrawal period cannot be covered by any safety margin. Therefore a withdrawal period cannot be reliably estimated.

3. Benefit-risk assessment

Introduction

The CVMP was requested to review all available pre-clinical, clinical and residue depletion data for veterinary medicinal products containing paromomycin to be administered parenterally to pigs and recommend appropriate indications, dosing recommendations and withdrawal periods. The CVMP was also asked to recommend whether in view of the elements described in the referral notification the marketing authorisations for the veterinary medicinal products concerned should be maintained, varied, suspended, or withdrawn.

Benefit assessment

The currently authorised indications are unspecific and no specific pathogens are mentioned i.e. for the treatment of bacterial infections caused by pathogens which are susceptible to paromomycin or for bacterial infections of the respiratory tract, uro-genital tract, mastitis, enteritis, abscess, wounds, canine leishmaniosis and surgery.

Risk assessment

While target animal safety was not in the scope of this referral, there are no known adverse events in pigs.

In the absence of adequate data to support indications and posology, there is a risk that product administration at the currently recommended dose will lead to ineffective treatment and a potential unnecessary suffering in the treated animals. Moreover, product administration at an inappropriate dose poses an added risk of resistance development.

[1] CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95) - link

The withdrawal period was determined in animals with a mean weight of 37.2 kg (range of 32 to 42.8 kg) treated according to the recommended posology at the longest duration of treatment.

Samples of the target tissues were analysed by HPLC method coupled with MS/MS detection.

The most relevant tissues for the presence of paromomycin residue were muscle at the injection site and kidney.

For kidney, a withdrawal time rounded to 16 days was determined based on linear regression using the 'statistical' method, in line with CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95).

For injection site, a rounded withdrawal period of 16 days was calculated using the 'alternative' method, in line with CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95).

However, the deficiencies noted in the study (absence of data on storage stability, the wide recovery rates in muscle samples and the absence of ring sample in the sampling of the injection site) cannot be covered by any safety span. Therefore a withdrawal period cannot be reliably estimated.

Risk management or mitigation measures

As no adequate data are available to support indications, posology and withdrawal periods, the CVMP is not able to recommend any appropriate indications, dosage and withdrawal periods for the concerned veterinary medicinal products.

Evaluation and conclusions on the benefit-risk balance

Therefore, the Committee considers that in the absence of adequate pre-clinical, clinical and residue depletion data and because the use of these medicinal products could pose a potential risk to animal and human health, the benefit-risk balance for the concerned veterinary medicinal products containing paromomycin to be administered parenterally to pigs is not favourable. Consequently, the Committee recommends the suspension of the existing marketing authorisations for the concerned veterinary medicinal products containing paromomycin to be administered parenterally to pigs.

Grounds for suspension of the marketing authorisations

Whereas

- the CVMP considered that the use of veterinary medicinal products containing paromomycin to be administered parenterally to pigs is not supported by pre-clinical, clinical and residue depletion data and the currently recommended indications, dosing regimens and withdrawal period could pose a potential risk to animal and human health;
- the CVMP concluded that the benefit-risk assessment for veterinary medicinal products containing paromomycin to be administered parenterally to pigs is negative because there were inadequate data to support efficacy of these veterinary medicinal products for the proposed indications at the recommended treatment dose and that this deficiency poses a risk of ineffective treatment and antimicrobial resistance development;

the CVMP has recommended the suspension of the marketing authorisations for veterinary medicinal products containing paromomycin to be administered parenterally to pigs as referred in Annex I.

The conditions to lift the suspension of the marketing authorisations are set out in Annex III.

Annex III

Conditions for lifting the suspension of the marketing authorisations

The national competent authorities shall ensure that the following conditions are fulfilled by the concerned marketing authorisation holders:

- To provide adequate clinical data in support of an indication against colibacillosis at the recommended dose and duration of treatment. Considering that colibacillosis is a disease complex (including neonatal diarrhoea, post-weaning diarrhoea, oedema disease, septicemia, polyserositis, coliform mastitis, and urinary tract infection) and is caused by different types of *Escherichia coli* (enteropathogenic *E. coli*, Shiga-toxin producing *E. coli*, enterotoxigenic *E. coli*, etc.), the marketing authorisation holders should define the clinical indication(s) as precisely as possible by including also the sub-category (age and production type) of the target animals. Justification of the dose and the duration of treatment are required. Relevant clinical data (including GCP, randomised, blinded field study) are required for each claim related to a specific type of *Escherichia coli*.
- To provide adequate clinical data (including GCP, randomised, blinded field study) in support of the treatment of pleuropneumonia caused by *Actinobacillus pleuropneumoniae* at the recommended dose and duration of treatment. Justification of the dose and the duration of treatment are required.
- A new residue depletion study is required regardless of whether the dosing regimen has changed or not. The withdrawal period should be based on robust and complete data (animal phase and validation of the analytical method) in accordance with the guidelines in force.
- If efficacy is demonstrated for a different dosage regimen compared to the authorised dosage regimen at the time of marketing authorisation suspension, the following points should be reviewed from a safety point of view:
    - Environmental impact assessment;
    - Potential effect(s) on the user safety;
    - Potential effects on target animal tolerance.
- To provide a benefit-risk assessment outlining that the clinical benefits of these veterinary medicinal products outweigh potential risks relating to animal health and the development of resistance, and (if applicable) environmental and user risks.