

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Parofor 70 000 IU/g powder for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 1 gram:

Active substance:

70 000 IU of paromomycin activity (as paromomycin sulfate)

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for use in drinking water, milk or milk replacer
A white to almost white powder.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (pre-ruminant calves), pig.

4.2 Indications for use, specifying the target species

Treatment of gastro-intestinal infections caused by *Escherichia coli* susceptible to paromomycin.

4.3 Contraindications

Do not use in cases of hypersensitivity to paromomycin, other aminoglycosides or any of the excipients.

Do not use in cases with impaired function of the kidneys or liver.

Do not use in ruminating animals.

Do not use in turkeys due to the risk of selection for antimicrobial resistance in intestinal bacteria.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water/milk animals should be treated parenterally using a suitable injectable product following the advice of the veterinarian.

The use of the product should be combined with good management practices e.g. good hygiene, proper ventilation, no overstocking.

Since the product is potentially ototoxic and nephrotoxic, it is recommended to assess kidney function. Special care should be taken when considering administration of the product to newborn animals due to the known higher gastrointestinal absorption of paromomycin in neonates. This higher absorption could lead to an increased risk of oto- and nephrotoxicity. The use of the product in neonates should be

based on benefit-risk assessment by the responsible veterinarian. Prolonged or repeated use of the product should be avoided by improving management practices and through cleansing and disinfection.

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria. Official, national and regional antimicrobial policies should be taken into account when the product is used.

Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to paromomycin and may decrease the effectiveness of treatment with aminoglycosides due to the potential for crossresistance.

Aminoglycosides are considered as critical in human medicine. Consequently, they should not be used as a first line treatment in veterinary medicine.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

This product contains paromomycin, which can cause allergic reactions in some people. Anyone with known hypersensitivity (allergy) to aminoglycosides should avoid contact with the veterinary medicinal product. If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Personal protective equipment consisting of protective clothing and impervious gloves should be worn when handling the veterinary medicinal product.

Do not eat, drink and smoke when handling the product. Wash hands after use. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician.

When handling this product, inhalation of the dust must be avoided by wearing a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143.

Use in a well-ventilated area. Avoid inhaling the powder while preparing the medicated water or milk replacer. Avoid contact with the skin and eyes. In the event of accidental contact with the skin or eyes, rinse with plenty of water and seek medical attention if irritation persists.

4.6 Adverse reactions (frequency and seriousness)

Aminoglycoside antibiotics such as paromomycin can cause oto- and nephrotoxicity.

On rare occasions soft faeces has been observed.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rat and rabbit have not produced any evidence of teratogenic, foetoxic or maternotoxic effects. The use is not recommended during the pregnancy.

4.8 Interaction with other medicinal products and other forms of interaction

General anaesthetics and muscle relaxants increase the neuro-blocking effect of aminoglycosides, which can lead to acute paralysis and apnoea.

Do not use concurrently with loop diuretics and potentially oto- or nephrotoxic substances.

4.9 Amounts to be administered and administration route

Oral use

Pre-ruminant cattle: administration in milk/milk replacer

Pigs: administration in drinking water.

Duration of treatment: 3-5 days

Pre-ruminant cattle: 17500 – 35000 IU per kg BW/day (equivalent to 2.5-5 g of product/10 kg BW/day)

Pigs: 17500 – 28000 IU per kg BW/day (equivalent to 2.5-4 g of product/10 kg BW/day)

For the administration through the drinking water milk or milk replacer, the exact daily amount of product should be calculated, based on the recommended dose, and the number and weight of the animals to be treated, according to the following formula:

$$\frac{\text{mg product / kg body weight / day} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water/milk/milk replacer consumption (litre) per animal}} = \dots \text{ mg product per litre drinking water /milk/milk replacer}$$

To ensure a correct dosage body weight should be determined as accurately as possible.

The uptake of medicated water/milk /milk replacer depends on several factors including clinical conditions of the animals and the local conditions such as ambient temperature and humidity. In order to obtain the correct dosage, drinking water/milk/milk replacer uptake has to be monitored and the concentration of paromomycin has to be adjusted accordingly.

Medicated drinking water/milk/milk replacer and any stock solutions should be freshly prepared. Any remaining quantities of medicated fluids should be removed after 6 hours (in milk/milk replacer) or 24 hours (in water).

To assure administration of the exact daily amount of product suitably calibrated weighing equipment should be used.

For the administration of the product commercially available dosing pumps can be used. The solubility of the product has been tested at the maximum concentration of 95 g/L.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Paromomycin when administered orally is hardly absorbed systemically. Harmful effects due to accidental overdosing are highly unlikely.

4.11 Withdrawal period(s)

Pre-ruminant cattle

Meat and offal: 20 days

Pig

Meat and offal: 3 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: intestinal antiinfectives; antibiotics.

ATC vet code: QA07AA06.

5.1 Pharmacodynamic properties

Paromomycin belongs to the group of aminoglycoside antibiotics. Paromomycin changes the reading of messenger-RNA, which disrupts protein synthesis. The bactericidal activity of paromomycin is mainly attributed to its irreversible binding to ribosomes. Paromomycin has broad spectrum activity against numerous Gram-positive and Gram-negative bacteria, including *E. coli*.

Paromomycin acts in a concentration-dependant manner. Five mechanisms of resistance have been identified: changes of the ribosome due to mutations, reduction of permeability of bacterial cell wall or active efflux, inactivation of aminoglycosides by enzymes and enzymatic substitution of the molecular target. The first three resistance mechanisms arise from mutations of certain genes on chromosomes. The fourth and fifth resistance mechanisms only occurs following intake of a transposon or plasmid coding for resistance. Paromomycin selects for resistance and cross-resistances at high frequency against a variety of other aminoglycosides among intestinal bacteria.

5.2 Pharmacokinetic properties

Following oral administration of paromomycin, hardly any absorption takes place and the molecule is eliminated unchanged via the faeces.

5.3 Environmental properties

The active ingredient paromomycin sulfate is very persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous
Glucose monohydrate

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.

Shelf life after first opening the immediate packaging: 6 months.

Shelf life after reconstitution in drinking water: 24 hours

Shelf life after reconstitution in milk/milk replacer: 6 hours

6.4 Special precautions for storage

Store below 25°C.

Keep the sachet tightly closed.

6.5 Nature and composition of immediate packaging

Block-bottom polyethylene/aluminium/polyethylene terephthalate sachet of 1000 g - 500 g – 250 g
Sachet of polyethylene foil/aluminium/polypropylene foil of 25 g, placed into a cardboard box, 40 sachets per box.

Not all pack sizes may be marketed.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton box 40 x 25 g

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Parofor 70 000 IU/g powder for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs.

Paromomycin (as sulfate).

2. STATEMENT OF ACTIVE SUBSTANCES

Per gram:

70 000 IU of paromomycin activity (as paromomycin sulfate)

3. PHARMACEUTICAL FORM

Powder for use in drinking water, milk or milk replacer.

4. PACKAGE SIZE

40 x 25 g

5. TARGET SPECIES

Cattle (pre-ruminant calves), pig.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Pre-ruminant cattle

Meat and offal: 20 days

Pig

Meat and offal: 3 days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use

10. EXPIRY DATE

EXP

Shelf life after first opening: 6 months. Once opened use by....

Medicated drinking water should be refreshed or replaced every 24 hours

Shelf life after reconstitution in milk/milk replacer: 6 hours

11. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Keep the sachet tightly closed.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read the package leaflet.

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Sachet of 1000 g - 500 g - 250 g – 25 g

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Parofor 70 000 IU/g powder for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs.
Paromomycin (as sulfate).

2. STATEMENT OF ACTIVE SUBSTANCES

Per gram:

70 000 IU of paromomycin activity (as paromomycin sulfate)

3. PHARMACEUTICAL FORM

Powder for use in drinking water, milk or milk replacer.

4. PACKAGE SIZE

1000 g
500 g
250 g
25 g

5. TARGET SPECIES

Cattle (pre-ruminant calves), pig.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Pre-ruminant cattle
Meat and offal: 20 days
Pig
Meat and offal: 3 days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use

10. EXPIRY DATE

EXP

Shelf life after first opening: 6 months. Once opened use by....

Medicated drinking water should be refreshed or replaced every 24 hours

Shelf life after reconstitution in milk/milk replacer: 6 hours

11. SPECIAL STORAGE CONDITIONS

Store below 25°C.

Keep the sachet tightly closed.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read the package leaflet.

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

16. MARKETING AUTHORISATION NUMBER(S)**17. MANUFACTURER'S BATCH NUMBER**

Lot:

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Parofor 70 000 IU/g powder for use in drinking water, milk or milk replacer
for pre-ruminant cattle and pigs.

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

Manufacturer responsible for batch release:

Biovet JSC
39 Petar Rakov Str
4550 Peshtera
Bulgaria

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Parofor 70 000 IU/g powder for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs.
Paromomycin (as sulfate)

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Per gram:

70 000 IU of paromomycin activity (as paromomycin sulfate)

Excipients:

Silica, colloidal anhydrous
Glucose monohydrate

A white to almost white powder.

4. INDICATION(S)

Treatment of gastro-intestinal infections caused by *Escherichia coli* susceptible to paromomycin

5. CONTRAINDICATIONS

Do not use in cases of hypersensitivity to paromomycin, other aminoglycosides or any of the excipients.

Do not use in cases with impaired function of the kidneys or liver.

Do not use in ruminating animals.

Do not use in turkeys due to the risk of selection for antimicrobial resistance in intestinal bacteria.

6. ADVERSE REACTIONS

On rare occasions soft faeces has been observed.

Aminoglycoside antibiotics such as paromomycin can cause oto- and nephrotoxicity.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon. Alternatively you can report via your national reporting system {national system details}

7. TARGET SPECIES

Cattle (pre-ruminant calves), pig.

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

Oral use

Pre-ruminant cattle: administration in milk/milk replacer

Pigs: administration in drinking water.

Duration of treatment: 3-5 days

Pre-ruminant cattle: 17500 – 35000 IU per kg BW/day (equivalent to 2.5-5 g of product/10 kg BW/day)

Pigs: 17500 – 28000 IU per kg BW/day (equivalent to 2.5-4 g of product/10 kg BW/day)

For the administration through the drinking water milk or milk replacer, the exact daily amount of product should be calculated, based on the recommended dose, and the number and weight of the animals to be treated, according to the following formula:

$$\frac{\text{mg product / kg body weight / day} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water/milk/milk replacer consumption (litre) per animal}} = \dots \text{ mg product per litre drinking water /milk/milk replacer}$$

To ensure a correct dosage body weight should be determined as accurately as possible.

The uptake of medicated water/milk /milk replacer depends on several factors including clinical conditions of the animals and the local conditions such as ambient temperature and humidity. In order to obtain the correct dosage, drinking water/milk/milk replacer uptake has to be monitored and the concentration of paromomycin has to be adjusted accordingly.

9. ADVICE ON CORRECT ADMINISTRATION

Medicated drinking water/milk/milk replacer and any stock solutions should be freshly prepared. Any remaining quantities of medicated fluids should be removed after 6 hours (in milk/milk replacer) or 24 hours (in water).

To assure administration of the exact daily amount of product suitably calibrated weighing equipment should be used. For the administration of the product commercially available dosing pumps can be used. The solubility of the product has been tested at the maximum concentration of 95 g/L.

10. WITHDRAWAL PERIOD

Pre-ruminant cattle

Meat and offal: 20 days

Pig

Meat and offal: 3 days

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Store below 25°C.

Keep the sachet tightly closed.

Do not use this veterinary medicinal product after the expiry date which is stated on the sachet after "EXP". The expiry date refers to the last day of that month.

Shelf life after first opening of the immediate packaging: 6 months

Shelf life after reconstitution in drinking water: 24 hours

Shelf life after reconstitution in milk/milk replacer: 6 hours

12. SPECIAL WARNING(S)

Special precautions for use in animals

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water/milk animals should be treated parenterally using a suitable injectable product following the advice of the veterinarian.

The use of the product should be combined with good management practices e.g. good hygiene, proper ventilation, no overstocking.

Since the product is potentially ototoxic and nephrotoxic, it is recommended to assess kidney function. Special care should be taken when considering administration of the product to newborn animals due to the known higher gastrointestinal absorption of paromomycin in neonates. This higher absorption could lead to an increased risk of oto- and nephrotoxicity. The use of the product in neonates should be based on benefit-risk assessment by the responsible veterinarian.

Prolonged or repeated use of the product should be avoided by improving management practices and through cleansing and disinfection.

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria. Official, national and regional antimicrobial policies should be taken into account when the product is used.

Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to paromomycin and may decrease the effectiveness of treatment with aminoglycosides due to the potential for cross-resistance. Paromomycin selects for resistance and cross-resistances at high frequency against a variety of other aminoglycosides among intestinal bacteria.

Aminoglycosides are considered as critical in human medicine. Consequently, they should not be used as a first line treatment in veterinary medicine.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

This product contains paromomycin, which can cause allergic reactions in some people. Anyone with known hypersensitivity (allergy) to aminoglycosides should avoid contact with the veterinary medicinal product. If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Personal protective equipment consisting of protective clothing and impervious gloves should be worn when handling the veterinary medicinal product.

Do not eat, drink and smoke when handling the product. Wash hands after use. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician

When handling this product, inhalation of the dust must be avoided by wearing a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143.

Use in a well-ventilated area. Avoid inhaling the powder while preparing the medicated water or milk replacer. Avoid contact with the skin and eyes. In the event of accidental contact with the skin or eyes, rinse with plenty of water and seek medical attention if irritation persists.

Pregnancy

Laboratory studies in rat and rabbit have not produced any evidence of teratogenic, foetoxic or maternotoxic effects. The use is not recommended during the pregnancy.

Interaction with other medicinal products and other forms of interaction

General anaesthetics and muscle relaxants increase the neuro-blocking effect of aminoglycosides, which can lead to acute paralysis and apnoea. Do not use concurrently with loop diuretics and potentially oto- or nephrotoxic substances.

Overdose

Paromomycin when administered orally is hardly resorbed. Harmful effects due to accidental overdosing is highly unlikely.

Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

The active ingredient paromomycin sulfate is very persistent in the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

Pack size: sachet of 1000 g – 500 g – 250 g – 25 g

Not all pack sizes may be marketed.