

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

PERMAWAY 600 mg intramammary suspension for cattle

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each intramammary syringe (3.6 g) contains:

### **Active substance:**

Cloxacillin (as benzathine).... 600 mg

### **Excipients:**

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Intramammary suspension.

Shiny white to off-white viscous suspension.

## **4. CLINICAL PARTICULARS**

### **4.1 Target species**

Dairy cattle (dry cows).

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

For the treatment of subclinical mastitis at dry-off and prevention of new intramammary infections occurring during the dry period, caused by *Trueperella pyogenes*, *Staphylococcus* spp., *Streptococcus agalactiae*, *Streptococcus dysgalactiae* and *Streptococcus uberis*, susceptible to cloxacillin.

### **4.3 Contraindications**

Do not use in cases of known hypersensitivity to penicillins, cephalosporins, or to any of the excipients. Do not use in cows with clinical mastitis outside the dry period.

### **4.4 Special warnings for each target species**

None.

### **4.5 Special precautions for use**

This product does not contain any antimicrobial preservatives.

#### **Special precautions for use in animals**

Use of the product should be based on susceptibility testing of bacteria isolated from milk samples obtained from the udder quarter(s) of each cow to be dried off. If this is not possible, therapy should be based on local (regional, farm level) risk based epidemiological information about the expected pathogen challenge, and susceptibility of target bacteria.

Use of the product deviating from the instructions given in the SPC may contribute to the development of bacterial resistance to cloxacillin which may also decrease the effectiveness of treatment with other beta-lactamase resistant penicillins. Dry cow therapy protocols should take local and national policies on antimicrobial use into consideration, and undergo regular veterinary review.

The feeding of waste milk containing residues of cloxacillin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

The efficacy of the product has only been established for target organisms listed in section 4.2. Consequently, the occurrence of a severe mastitis after drying-off (sometimes fatal) due to other organisms, especially *Pseudomonas aeruginosa*, is possible. To reduce this risk it is important to observe strict aseptic technique for the administration of the product.

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

Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reaction to these substances may occasionally be serious.

People with known hypersensitivity to penicillins or cephalosporins should avoid any contact with the veterinary medicinal product.

Handle this product with great care to avoid exposure. Wear gloves during administration of the product and wash hands after use.

In case of accidental contact with skin or eyes, wash immediately with clean water.

If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

**4.6 Adverse reactions (frequency and seriousness)**

Immediate allergic reactions have been described in some animals (agitation, tremor, edema of the udder, eyelids and lips) which can lead to the death of the animals.

**4.7 Use during pregnancy, lactation or lay**

Do not use this medicinal product in the lactating cows.

The product is intended to be used during gestation. The safety of the medicinal product in dairy cows during gestation has not been shown. However, the amounts of cloxacillin absorbed by the intramammary route being low, the use of this drug during gestation does not pose any particular problem.

**4.8 Interaction with other medicinal products and other forms of interaction**

The safety of the concomitant use of this medicinal product with other intramammary medicinal products has not been established, so simultaneous use is discouraged.

**4.9 Amounts to be administered and administration route**

For single intramammary use

600 mg of cloxacillin i.e. the content of one syringe should be infused once into each quarter via the teat canal immediately after the last milking of the lactation.

Milk out thoroughly before starting administration. Before administering the medicinal product, the teats should be thoroughly cleaned and disinfected, and care should be taken to avoid contamination of the syringe nozzle. Administer the full content of a syringe in each quarter. Massage after administration. After administration it is recommended to immerse the teat in an approved disinfectant bath. Do not milk after treatment.

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

No adverse reactions are expected in case of accidental overdose.

#### **4.11 Withdrawal period(s)**

Meat and offal: 28 days

Milk: Interval between treatment and calving is 42 days or longer: 4 days after calving.

Interval between treatment and calving is less than 42 days: 46 days after treatment.

### **5. PHARMACOLOGICAL PROPERTIES**

Pharmacotherapeutic group: beta-lactam antibiotics, penicillins, for intramammary use.  
ATCvet code: QJ51CF02.

#### **5.1 Pharmacodynamic properties**

Cloxacillin is a beta-lactamase resistant penicillin antibiotic with antibacterial activity. Its antibacterial effects target bacterial cell wall synthesis. Cloxacillin impairs the development of the bacterial cell wall by interfering with transpeptidases, the enzymes responsible for the cross-linkage of peptidoglycans chains, resulting in osmotic lysis of the cell wall.

Cloxacillin shows *in vitro* activity against Gram-positive bacteria, including *Staphylococcus* spp., *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus uberis* and *Trueperella pyogenes* (formerly known as *Arcanobacterium pyogenes* or *Corynebacterium pyogenes* or *Actinomyces pyogenes*).

*Escherichia coli* is not susceptible to cloxacillin.

The following MIC (VetPath) of cloxacillin against mastitis pathogens have been described:

<b>Bovine mastitis bacteria</b>	<b><math>\text{MIC}_{50}</math> (<math>\mu\text{g/mL}</math>)</b>	<b><math>\text{MIC}_{90}</math> (<math>\mu\text{g/mL}</math>)</b>
<i>Staphylococcus aureus</i>	0.25	0.5-1
<i>Streptococcus agalactiae</i>	1	2
<i>Streptococcus dysgalactiae</i>	0.06-0.125	0.12-0.25
<i>Streptococcus uberis</i>	0.5-2	4
<i>Trueperella pyogenes</i>	0.25	2

The main resistance mechanism to cloxacillin was described in *Staphylococci*, notably in methicillin resistant isolates and is due to the production of the penicillin binding protein 2a (PBP2a) which has low affinity to the majority of  $\beta$ -lactams. PBP2a gene is harboured by the mobile genomic island **SCCMec** (staphylococcal cassette chromosome *mec*) which can carry resistance genes to other classes of antibiotics.

## **5.2 Pharmacokinetic particulars**

Intramammary administration of cloxacillin benzathine results in negligible systemic absorption of the active substance. The small fraction of cloxacillin that reaches the systemic circulation is excreted mainly via the kidneys (and to a lesser extent via the bile duct).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Stearic Acid  
Aluminium Stearate  
Liquid Paraffin

### **6.2 Major incompatibilities**

Not applicable.

### **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: use immediately.

### **6.4. Special precautions for storage**

Do not store above 25°C.

### **6.5 Nature and composition of immediate packaging**

Low density polyethylene (LDPE) white intramammary syringe with a LDPE cap and a LDPE plunger.

Pack sizes:

Cardboard box of 24 intramammary syringes.  
Cardboard box of 48 intramammary syringes.  
Cardboard box of 96 intramammary syringes.

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 product should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

## **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**

**Cardboard box (24 intramammary syringes, 48 intramammary syringes, 96 intramammary syringes)**

**1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

PERMAWAY 600 mg intramammary suspension for cattle  
Cloxacillin (benzathine)

**2. STATEMENT OF ACTIVE SUBSTANCES**

Cloxacillin (as benzathine) 600 mg /intramammary syringe

**3. PHARMACEUTICAL FORM**

Intramammary suspension

**4. PACKAGE SIZE**

24 intramammary syringes  
48 intramammary syringes  
96 intramammary syringes

**5. TARGET SPECIES**

Dairy cattle (dry cows)

**6. INDICATION(S)****7. METHOD AND ROUTE(S) OF ADMINISTRATION**

For single intramammary use.

Read the package leaflet before use.

**8. WITHDRAWAL PERIOD(S)**

Meat and offal: 28 days  
Milk: Interval between treatment and calving is 42 days or longer: 4 days after calving.  
Interval between treatment and calving is less than 42 days: 46 days after treatment.

**9. SPECIAL WARNING(S), IF NECESSARY**

Read the package leaflet before use.

**10. EXPIRY DATE**

EXP {month/year}

Once opened use immediately

**11. SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.

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

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

Lot {number}

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

intramammary Syringe of 3.6 g

**1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

PERMAWAY 600 mg intramammary suspension for cattle  
Cloxacillin (benzathine)

**2. QUANTITY OF THE ACTIVE SUBSTANCE(S)**

Cloxacillin (as benzathine) 600 mg / intramammary syringe

**3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES**

3.6 g

**4. ROUTE(S) OF ADMINISTRATION**

Single intramammary use

**5. WITHDRAWAL PERIOD(S)**

Meat and offal: 28 days

Milk: Interval between treatment and calving is 42 days or longer: 4 days after calving.

Interval between treatment and calving is less than 42 days: 46 days after treatment.

**6. BATCH NUMBER**

Lot {number}

**7. EXPIRY DATE**

EXP {month/year}

Once opened use immediately.

**8. THE WORDS "FOR ANIMAL TREATMENT ONLY"**

For animal treatment only.

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET:**  
**PERMAWAY 600 mg intramammary suspension for cattle**

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

Marketing authorisation holder and manufacturer responsible for batch release:

Vetoquinol Biowet Sp. z o.o.  
ul. Kosynierów Gdyńskich 13-14 66-400 Gorzów Wlkp.  
POLAND

**2. NAME OF THE VETERINARY MEDICINAL PRODUCT**

PERMAWAY 600 mg intramammary suspension for cattle  
Cloxacillin (benzathine)

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

Each intramammary syringe (3.6 g) contains:

**Active substance:**

Cloxacillin (as benzathine) 600 mg

**Excipients, q.s.**

Intramammary suspension  
Shiny white to off-white viscous suspension.

**4. INDICATION(S)**

For the treatment of subclinical mastitis at dry-off and prevention of new intramammary infections occurring during the dry period, caused by *Trueperella pyogenes*, *Staphylococcus spp.*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* and *Streptococcus uberis*, susceptible to cloxacillin.

**5. CONTRAINDICATIONS**

Do not use in cases of known hypersensitivity to penicillins, cephalosporins, or to any of the excipients. Do not use in cows with clinical mastitis outside the dry period.

**6. ADVERSE REACTIONS**

Immediate allergic reactions have been described in some animals (agitation, tremor, edema of the udder, eyelids and lips) which can lead to the death of the animals.

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

**7. TARGET SPECIES**

Dairy cattle (dry cows)



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

For single intramammary use.

600 mg of cloxacillin i.e. the content of one syringe should be infused once into each quarter via the teat canal immediately after the last milking of the lactation.

Milk out thoroughly before starting administration. Before administering the medicinal product, the teats should be thoroughly cleaned and disinfected, and care should be taken to avoid contamination of the syringe nozzle. Administer the full content of a syringe in each quarter. Massage after administration. After administration it is recommended to immerse the teat in an approved disinfectant bath. Do not milk after treatment.

## **9. ADVICE ON CORRECT ADMINISTRATION**

None.

## **10. WITHDRAWAL PERIOD(S)**

Meat and offal: 28 days

Milk: Interval between treatment and calving is 42 days or longer: 4 days after calving.

Interval between treatment and calving is less than 42 days: 46 days after treatment.

## **11. SPECIAL STORAGE PRECAUTIONS**

Keep out of the sight and reach of children.

Do not store above 25°C.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP.

The expiry date refers to the last day of that month.

Shelf life after first opening the container: use immediately.

## **12. SPECIAL WARNING(S)**

### Special precautions for use in animals:

Use of the product should be based on susceptibility testing of bacteria isolated from milk samples obtained from the udder quarter(s) of each cow to be dried off. If this is not possible, therapy should be based on local (regional, farm level) risk based epidemiological information about the expected pathogen challenge, and susceptibility of target bacteria.

Use of the product deviating from the instructions given in the package leaflet may contribute to the development of bacterial resistance to cloxacillin which may also decrease the effectiveness of treatment with other beta-lactamase resistant penicillins. Dry cow therapy protocols should take local and national policies on antimicrobial use into consideration, and undergo regular veterinary review.

The feeding of waste milk containing residues of cloxacillin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

The efficacy of the product has only been established for target organisms listed in the indications. Consequently, the occurrence of a severe mastitis after drying-off (sometimes fatal) due to other organisms, especially *Pseudomonas aeruginosa*, is possible. To reduce this risk it is important to observe strict aseptic technique for the administration of the product.

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

Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reaction to these substances may occasionally be serious.

People with known hypersensitivity to penicillins or cephalosporins should avoid any contact with the veterinary medicinal product.

Handle this product with great care to avoid exposure.

Wear gloves during administration of the product and wash hands after use.

In case of accidental contact with skin or eyes, wash immediately with clean water.

If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Pregnancy and lactation:

Do not use this medicinal product in the lactating cows.

The product is intended to be used during gestation. The safety of the medicinal product in dairy cows during gestation has not been shown. However, the amounts of cloxacillin absorbed by the intramammary route being low, the use of this drug during gestation does not pose any particular problem.

Interaction with other medicinal products and other forms of interaction:

The safety of the concomitant use of this medicinal product with other intramammary medications has not been established, so simultaneous use is discouraged.

Overdose (symptoms, emergency procedures, antidotes):

No adverse reactions are expected in case of accidental overdose.

Incompatibilities:

Not applicable.

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

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

**14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED**

**15 OTHER INFORMATION**

Pack sizes:

Cardboard box of 24 intramammary syringes.

Cardboard box of 48 intramammary syringes.

Cardboard box of 96 intramammary syringes.

Not all pack sizes may be marketed.