# Annex I

## List of the names, pharmaceutical form, strengths of the veterinary medicinal products, animal species, withdrawal period, marketing authorisation holders in the member states

| Member State EU/EEA | Marketing Authorisation Holder | Name | INN | Strengths | Pharmaceutical form | Animal species | Withdrawal period (meat and milk) |
|---|---|---|---|---|---|---|---|
| Austria | Pfizer Corporation Austria GmbH<br>Floridsdorfer Hauptstraße 1<br>1210 Wien<br>Austria | Synulox comp - Injektoren für Kühe | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat and offal: 4 days,<br>milk: 3 days |
| Bulgaria | Pfizer Animal Health MA EEIG<br>Ramstage Road<br>Sandwich<br>Kent CT13 9NJ<br>United Kingdom | Synulox Lactating Cow | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk: 60 hours<br>In combination with SYNULOX RTU:<br>Meat: 42 days.<br>Milk: 60 hours. |
| Cyprus | PFIZER HELLAS AE<br>243 Mesogeion Ave.<br>154 51 Neo Psichiko<br>Athens<br>Greece | SYNULOX LC | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Edible tissues:<br>4 days<br>Milk: 72 Hours |
| Czech Republic | Pfizer, spol. s r.o.<br>Veterinární divize – Anumal Health<br>Stroupežnického 17<br>150 00 Praha 5<br>Czech Republic | SYNULOX LC 260 mg intramam. suspension for cattle | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk 84 hours<br>(7 milkings) |
| France | PFIZER<br>23/25 Avenue Du Docteur Lannelongue<br>75014 Paris<br>France | SYNULOX INTRAMAMMAIRE | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk: 2 days |
| Greece | PFIZER HELLAS A.E<br>Mesogion Av 242<br>15451 N.Psichiko<br>Greece | SYNULOX LC | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 3 days<br>Milk: 72 hours |

| Member State EU/EEA | Marketing Authorisation Holder | Name | INN | Strengths | Pharmaceutical form | Animal species | Withdrawal period (meat and milk) |
|---|---|---|---|---|---|---|---|
| Hungary | Pfizer Kft.<br>Alkotás u. 53.<br>1123 Budapest<br>Hungary | SYNULOX LC tőgyinfúzió | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Edible tissues: 4 days<br>Milk: 60 hours |
| Ireland | Pfizer Healthcare Ireland, Trading as Pfizer Animal Health<br>Ringaskiddy<br>County Cork<br>Ireland | Synulox Lactating Cow Intramammary suspension. | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat and offal:<br>7 Days<br>Milk: 60 Hours<br>Meat: 7 days<br>Milk (cows milked twice daily): 60 hours (i.e. at the 5th milking) after the last treatment. When any other milking routine is followed milk may be taken for human consumption only after the same period from the last treatment (e.g. with 3 times a day milking, milk for human consumption may only be taken at the 8th milking).<br>In combination with SYNULOX RTU:<br>Meat: 42 days.<br>Milk: 80 hours. |
| Italy | PFIZER ITALIA<br>Via Valbiondone 113<br>00188 Roma<br>Italy | SYNULOX ENDOMAMMARIO | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat : 4 days<br>Milk : 108 hours |

| Member State EU/EEA | Marketing Authorisation Holder | Name | INN | Strengths | Pharmaceutical form | Animal species | Withdrawal period (meat and milk) |
|---|---|---|---|---|---|---|---|
| Latvia | Pfizer Animal Health MA EEIG<br>Ramsgate Road<br>Sandwich, Kent<br>CT13 9NJ<br>United Kingdom | Synulox LC Suspensija ievadīšanai tesmenī laktējošām govīm | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk (cows milked twice daily): 60 hours (i.e. at the 5th milking) after the last treatment. When any other milking routine is followed milk may be taken for human consumption only after the same period from the last treatment (e.g. with 3 times a day milking, milk for human consumption may only be taken at the 8th milking).<br>In combination with SYNULOX RTU:<br>Meat: 42 days.<br>Milk: 60 hours. |
| Lithuania | Pfizer Animal Health MA EEIG<br>Ramstage Road<br>Sandwich<br>Kent CT13 9NJ<br>United Kingdom | SYNULOX LC, intramaminė suspensija | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk: 60 hours<br>In combination with SYNULOX RTU:<br>Meat: 42 days.<br>Milk: 60 hours. |
| Norway | Pfizer Oy<br>Animal Health<br>Tietokuja 4<br>00330 Helsinki<br>Finland | Synulox comp. vet | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary emulsion | Cattle | Meat: 6 days<br>Milk: 5 days |

| Member State EU/EEA | Marketing Authorisation Holder | Name | INN | Strengths | Pharmaceutical form | Animal species | Withdrawal period (meat and milk) |
|---|---|---|---|---|---|---|---|
| Poland | Pfizer Trading Polska Sp. z o. o.<br>ul. Rzymowskiego 34<br>02 – 697 Warszawa<br>Poland | SYNULOX L.C. (200mg + 50mg + 10mg)/3g, zawiesina dowymieniowa, bydło | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat and offal:<br>4 days<br>Milk: 60 hours |
| Portugal | Laboratórios Pfizer, Lda<br>Lagoas Park -Edifício 10<br>Porto Salvo<br>2470 Oeiras<br>Portugal | SYNULOX LC suspensão intramamária para bovinos em lactação | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat and offal:<br>14 days<br>Milk: 2 days |
| Romania | Pfizer Animal Health MA EEIG<br>Ramstage Road<br>Sandwich<br>Kent CT13 9NJ<br>United Kingdom | SYNULOX LC, amoxicilină, acid clavulanic, prednisolon, suspensie intramamara pentru vaci in lactatie | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat and offal:<br>7 days<br>Milk: 60 hours<br>In combination with SYNULOX RTU:<br>Meat: 42 days.<br>Milk: 14 days. |
| Slovak Republic | Pfizer Luxembourg SARL, o.z.<br>Pfizer AH<br>Pribinova 25<br>811 09 Bratislava<br>Slovak Republic | Synulox LC 260 mg intramammary suspension | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk: 84 hours<br>(7 milkings) |
| Slovenia | PFIZER Luxembourg SARL<br>51,Avenue J.F.Kennedy<br>1855 Luxembourg | SYNULOX LC intramamarna suspenzija za krave v laktaciji | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat and offal:<br>7 days<br>Milk: 60 hours |

| Member State EU/EEA | Marketing Authorisation Holder | Name | INN | Strengths | Pharmaceutical form | Animal species | Withdrawal period (meat and milk) |
|---|---|---|---|---|---|---|---|
| Spain | PFIZER, S.A.<br>Avd. Europa 20-B<br>Parque Empresarial<br>La Moraleja<br>28108 Alcobendas<br>(Madrid)<br>Spain | SYNULOX LC | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk: 60 hours or 5 milking |
| The Netherlands | Pfizer<br>Rivium Westlaan 142<br>2909 LD Capelle a/d Ijssel<br>The Netherlands | Avuloxil | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk: 4 days |
| United Kingdom | Pfizer Ltd<br>Ramsgate Road<br>Sandwich<br>Kent CT13 9NJ<br>United Kingdom | Synulox Lactating Cow Intramammary Suspension | Amoxicillin (as amoxicillin trihydrate)<br>Clavulanic acid (as potassium clavulanate)<br>Prednisolone | 200 mg<br>50 mg<br>10 mg | Intramammary suspension | Cattle | Meat: 7 days<br>Milk (cows milked twice daily): 60 hours (i.e. at the 5th milking) after the last treatment. When any other milking routine is followed milk may be taken for human consumption only after the same period from the last treatment (e.g. with 3 times a day milking, milk for human consumption may only be taken at the 8th milking).<br>In combination with SYNULOX RTU:<br>Meat: 42 days.<br>Milk: 60 hours. |

# Annex II

## Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

# Overall summary of the scientific evaluation of Synulox Lactating Cow and associated names (see Annex I)

## 1. Introduction

Synulox Lactating Cow and associated names is a pale cream/buff coloured oily suspension containing amoxicillin, clavulanic acid and prednisolone in a base designed to disperse rapidly in milk. The product is presented in disposable intramammary syringes containing 200 mg amoxicillin as amoxicillin trihydrate, 50 mg clavulanic acid as potassium clavulanate and 10 mg prednisolone in 3 g suspension.

The product is intended for the treatment of bovine clinical mastitis in lactating cows, including cases of infections associated with the following pathogens:

- Staphylococci (including β-lactamase producing strains);
- Streptococci (including *S. agalactiae*, *S. dysgalactiae* and *S. uberis*);
- *Escherichia coli* (including β-lactamase producing strains).

Due to the divergent national decisions taken by Member States concerning the authorisation of Synulox Lactating Cows and associated names and differences between the summary of product characteristics (SPC) of the product as authorised in the Member States, the issue was referred on 26 March 2010 by Belgium and Denmark to the CVMP under Article 34(1) of Directive 2001/82/EC.

The reason for divergent national decisions regarding the authorisation of the products was mainly the justification of the combination of amoxicilline/clavulanic acid/prednisolone for the treatment of bovine mastitis.

The CVMP was asked to address the following specific points:

1. to assess if efficacy of Synulox Lactating Cow and associated names has been demonstrated for bovine mastitis in lactating cows,
2. if efficacy is confirmed, to assess if efficacy of amoxicilline/clavulanic acid/prednisolone combination is superior to treatment with amoxicilline/clavulanic acid alone,
3. to consider whether the benefit/risk balance of this product is positive and, if not, whether the marketing authorisations should be (i) amended, (ii) revoked or (iii) suspended on grounds of safety and efficacy.

The main sections of disharmony of the existing SPCs related to:

- Indications;
- Posology;
- Withdrawal periods.

## 2. Discussion of the data available

#### Efficacy against the target pathogens

The combination of amoxicillin and clavulanic acid has a broad spectrum antimicrobial activity including β-lactamase producing organisms. According to the provided pharmacodynamic data, the claimed

pathogens are sensitive to the clavulanic acid / amoxicillin combination. Based on the past and recent data, the incidence of pathogens producing β-lactamase, *i.e. Staphylococcus aureus* and *Escherichia coli* from cases of bovine mastitis can be considered as high in some regions.

The Minimum Inhibitory Concentration (MIC) of a number of different mastitis pathogens from a range of EU Member States and therefore from a range of husbandry conditions were reviewed. Globally, the *in vitro* susceptibility of most mastitis pathogens was very high. Clavulanic acid is a valuable addition to amoxicillin for efficacy against mastitis pathogens and caused the MIC of target pathogens to amoxicillin only to be greatly reduced.

Pharmacokinetic studies, performed with the finished product revealed individual concentrations of amoxicillin in milk above the $MIC_{90}$ (2 µg/ml) for *Staphylococcus aureus* until 12 hours after the last infusion. For *Escherichia coli* $MIC_{90}$ (16 µg/ml), individual milk levels in amoxicillin were above the $MIC_{90}$ for the period covering the first 2 infusions. After the third infusion, the $MIC_{90}$ of *Escherichia coli* was covered well for 10 hours and the levels were partially acceptable at 12 hours. After 24 hours, the levels were too low in comparison with the $MIC_{90}$.

Two clinical trials have been provided for Synulox Lactating Cow and associated names:

- The efficacy of the product for the treatment of clinical mastitis in lactating dairy cows was compared with another veterinary medicinal product authorised in the United Kingdom. The comparator product was authorised for similar indications (Staphylococci, Streptococci, *Escherichia coli*), but has a different composition (penethamate, dihydrostreptomycin, framycetin and prednisolone) and a different interval of administration (24 hours for the comparator instead of 12 hours for Synulox Lactating Cow). No statistical difference was shown clinically and bacteriologically between both products. Synulox Lactating Cow was non-inferior to the comparator. However it was noted that the self-cure effect was not considered regarding *Escherichia coli* cases.
- In another study the efficacy of Synulox Lactating Cow for the treatment of clinical mastitis in the lactating dairy cow was compared with another veterinary medicinal product authorised in France. The comparator product had a different composition (cloxacillin-ampicillin combination). Synulox Lactating Cow was non-inferior to the comparator clinically and bacteriologically for efficacy against *Staphylococcus aureus*, *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis* and Gram negative bacteria.

Synulox Lactating Cow was shown to be efficacious regarding the main mastitis pathogens: Staphylococci, Streptococci and *Escherichia coli*. However, the self-cure effect for the *Escherichia coli* infections was not considered.

The review of literature on the current level of resistance to amoxycillin/clavulanic acid among clinically significant mastitis pathogens indicates that resistance remains low.

The overall review indicates that over the six years covered by the data from the Netherlands, there was no evidence of significant and consistent increases in MIC levels of amoxycillin/clavulanic acid and cephalosporins.

There is little evidence of a real increase in amoxycillin/clavulanic acid resistance among the mastitic *E. coli* isolated in a number of European countries. The identified isolates of ESBL carrying strains, particularly from mastitis pathogens does not appear to be increasing at a rate to cause major concern.

In regard to public health risk, gastrointestinal bacteria are not significantly exposed to antimicrobial after this intramammary administration and milk is (nearly always) pasteurised prior to human consumption so the risk to human health from potential resistant pathogens after intramammary treatment is far lower than that which would arise following systemic use.

Notwithstanding the conclusions on the efficacy of prednisolone, the combination was deemed efficacious against the claimed pathogens. Regarding the efficacy against *Escherichia coli*, it is recognised that the product may not be indicated in case of self-cure.

Consequently the CVMP agreed on the following indications for the product:

> *"For use in clinical cases of mastitis including cases associated with infections with the following pathogens:*
> *Staphylococci (including β-lactamase producing strains)*
> *Streptococci (including S.agalactiae, S.dysgalactiae and S.uberis)*
> *Escherichia coli (including β-lactamase producing strains)"*

As it is generally recommended to treat clinical mastitis in the first instance with a narrow spectrum antimicrobial and where possible after bacteriological diagnosis, recommendations on prudent use were proposed to be included in the SPC.

Consequently the CVMP considered that the recommendations for prudent use in the SPC under section 4.5 Special precautions for use, should be amended as follows:

> *"The product should be used for treatment of clinical mastitis only. Use of the product should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria and take into account official and local antimicrobial policies. The use of the product should preferably be based on susceptibility tests. Avoid use of the product in herds where no β-lactamase producing Staphylococci strains have been isolated. Veterinarians should strive to use narrow spectrum antibiotics if possible. Inappropriate use of the product may increase the prevalence of bacteria resistant to ß-lactam antibiotics and may decrease the effectiveness of treatment with ß-lactam antibiotics, due to the potential for cross-resistance."*

Regarding the possibility for combined therapy with Synulox RTU, data to support this recommendation were not provided. Therefore the marketing authorisation holders' proposal to remove such a recommendation from the product information was accepted by the CVMP.

**Added value of prednisolone in the combination**

The current SPC indicates that prednisolone has an anti-inflammatory action which helps to reduce the potentially destructive swelling and inflammation associated with mastitis, without affecting the white cell response to infection. A pharmacokinetic study demonstrated that prednisolone does not have a prolonged residence time in the milk/udder (about 8-10 hours post infusion, levels of prednisolone were less than 1µg/ml).

Experimental studies have been provided to support this statement.

In a *Streptococcus uberis* challenge, a single administration of the product reduced the udder swelling 4 and 6 hours post treatment, but no significant action was seen on the cellular response.

Prednisolone administered before *Escherichia coli* endotoxin challenge may reduce the quarter size at some time points within 8 hours.

In a *Staphylococcus aureus* challenge, a reduction of udder induration, udder swelling and inflammation was observed at some time-points following the product administration. The mean differential white blood cell counts were not significantly different at sampling times post treatment suggesting that the low levels of prednisolone did not markedly affect white blood cell counts.

While these experimental studies showed a positive effect of prednisolone on udder inflammation at some time-points following treatment, there were statistical deficiencies (small numbers of cows

included, no grouped statistical analyses of sets of data) that meant that conclusions could not be drawn on the significance of the observed effects.

Based on the two clinical trials described above it was not possible to draw a conclusion on the added value of prednisolone, because there was no comparison with a product including amoxicilline/cavulanic acid without prednisolone.

Therefore, while clinical cure and bacteriological cure have been demonstrated for the formulation it was considered that the marketing authorisation holders had not demonstrated the efficacy of prednisolone in the combination.

The benefit of prednisolone is considered as indirect and is expected to be of short term. Intramammary administration of prednisolone seems not affect the functions of neutrophils. No immune modulating effects of prednisolone were observed.

The tolerance of the product formulation was acceptable.

As a conclusion, the marketing authorisation holders could not demonstrate the efficacy of prednisolone when included in the combination. Therefore a positive clinical anti-inflammatory impact of prednisolone remains questionable. However the presence of prednisolone in the product does not represent a risk for the animal or public health.

Consequently the CVMP considered that since the added value of prednisolone in the product has not been demonstrated, the following statement in the SPC under section 5. Pharmacological properties: "*Prednisolone is a glucocorticoid with anti-inflammatory properties. After intramammary infusion, prednisolone can lead to a reduction in the local signs of inflammation (swelling and subsequent size of the infected quarter)*" to be replaced with "*Prednisolone is an anti-inflammatory corticosteroid.*".

**Harmonisation of the posology**

The posology was supported by the two clinical trials performed in the United Kingdom and France (please see above).

The contents of one syringe should be infused into each affected quarter via the teat canal, immediately after milking, at 12 hour intervals for three consecutive milkings.

However, it is recognised that in cases of infections caused by *Staphylococcus aureus*, a longer course of antibacterial therapy may be required.

Considering that no product specific data have been provided in support of efficacy of an extended duration of treatment, the following recommendation has been included into the SPC under section 4.9 Amounts to be administered and administration route:

> *"In cases of infections caused by Staphylococcus aureus, a longer course of antibacterial therapy may be required. Therefore overall treatment length must be at the veterinarian's discretion but should be long enough to ensure complete resolution of intramammary infection."*

A longer duration of treatment would not impact the recommended withdrawal periods for meat and milk.

**Harmonisation of the withdrawal periods**

Meat and offal:

The withdrawal period was supported by a residue depletion study where 20 cows received an infusion of one injector per quarter of Synulox Lactating Cow in all 4 quarters of the udder at 12-hour intervals following 3 consecutive milkings. Animals were slaughtered at 12, 24, 36, 48 and 72 hours after the last treatment. The tissue samples were analysed for amoxicillin, clavulanic acid and prednisolone by the validated HPLC method. Amoxicillin residues were the limiting factor in liver and kidney. While a withdrawal period of 3 days could have been derived from the dataset, a withdrawal time of 7 days was recommended by the marketing authorisation holders. The longer than necessary withdrawal period provides a margin of safety that covers any concerns relating to cases of prolonged duration of treatment.

Milk:

The milk withdrawal period was supported by two residue depletion studies. In the first study performed in 8 lactating dairy cows, amoxicillin was the limiting active substance to determine the withdrawal period which, according to these data, should be set at 7 milkings (84 hours).

In the second study 20 healthy lactating dairy cows were treated 3 times, by the intramammary route, with the test product at the dosage of 1 syringe infused into each quarter via the teat canal, immediately after milking, for 3 consecutive milkings. Milk samples were collected from each animal immediately before the administration of the test product, then for the following 16 milkings, starting 12 hours after the last treatment. Analytical determinations of the marker residues were carried out by high-performance liquid chromatography. Amoxicillin was the limiting active substance to determine the withdrawal period in milk. Values were below the maximum residue limits from the 5$^{th}$ milking and the half-life was estimated to be less than 12 hours.

By using the most conservative method of calculating the time to safe concentration and including the 5$^{th}$ milking in the calculations, a withdrawal period of 6.1 milkings or 73.4 hours was calculated which is rounded to 7 milkings or 84 hours.

Based on the worst-case scenario where all quarters were treated according to the recommended posology, the withholding time of 84 hours or 7 milkings as claimed by the marketing authorisation holders was considered acceptable. Since no bio-accumulation in milk has been observed, a longer duration of treatment would have no impact on the withdrawal period.

As a conclusion, the residue depletion data support the withdrawal periods of 84 hours for milk and 7 days for meat and offal.

# 3. Benefit-risk assessment

Synulox Lactating Cow and associated names is a pale cream/buff coloured oily suspension containing clavulanic acid, amoxicillin and prednisolone in a base designed to disperse rapidly in milk. It is presented in disposable intramammary syringes containing 50 mg clavulanic acid as potassium clavulanate; 200 mg amoxicillin as amoxicillin trihydrate and 10 mg prednisolone in 3 g suspension.

The product is formulated for the treatment of bovine clinical mastitis in lactating cows.

The product is efficacious regarding the claimed indications, treatment of bovine clinical mastitis in lactating cows, including cases of infections associated with the following pathogens:

- Staphylococci (including β-lactamase producing strains)
- Streptococci (including *S. agalactiae, S. dysgalactiae* and *S. uberis*)
- *Escherichia coli* (including β-lactamase producing strains)

A review of the susceptibility of the mastitis pathogens against amoxicillin-clavulanic acid indicates that the major bacterial causes of bovine mastitis continue to be susceptible to clavulanate potentiated amoxicillin.

In regard to public health risk, gastrointestinal bacteria are not significantly exposed to antimicrobials after this intramammary administration and milk is (nearly always) pasteurised prior to human consumption so the risk to human health from potential resistant pathogens after intramammary treatment is far lower than that which would arise following systemic use.

Regarding the risk to prednisolone, tolerance of the product formulation is acceptable. Intramammary administration of prednisolone seems not to affect the functions of neutrophils. No immune modulating effects of prednisolone were observed.

While the clinical added value of prednisolone in Synulox Lactating Cow remains questionable, no risk arising from its use has been identified from clinical trials and pharmacovigilance.

The withdrawal periods of 84 hours for milk and 7 days for meat and offal were adequately justified.

Appropriate recommendations for prudent use of the product were recommended.

Since the product has been shown to be efficacious for the claimed indication and no risk has been identified to its use from clinical trials and pharmacovigilance, the benefit/risk balance is deemed positive.

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

Whereas:

- the CVMP considered the primary scope of the referral regarding the efficacy of the product for the treatment of bovine mastitis in lactating cows and the added value of the prednisolone in the product;
- the CVMP reviewed the summary of products characteristics, labelling and package leaflet proposed by the marketing authorisation holders and considered all the overall submitted data;

the CVMP, concluded that the overall benefit/risk balance for this product remains positive subject to the recommended changes in the product information. Therefore the CVMP has recommended the variation of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Synulox Lactating Cow and associated names *(see Annex I)*.

# Annex III

# Summary of product characteristics, labelling and package leaflet

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

*"Product name" (to be completed nationally)*
Intramammary suspension for lactating cattle

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

*Active substances:*
One syringe (3 g) contains:

| | |
|---|---|
| Amoxicillin trihydrate equivalent to amoxicillin | 200 mg |
| Potassium clavulanate equivalent to clavulanic acid | 50 mg |
| Prednisolone | 10 mg |

For a full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Intramammary suspension.
Pale cream/buff coloured oily suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Target species

Cattle (lactating cows).

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

For use in clinical cases of mastitis including cases associated with infections with the following pathogens:
Staphylococci (including β-lactamase producing strains)
Streptococci (including *S.agalactiae, S.dysgalactiae and S.uberis*)
*Escherichia coli* (including β-lactamase producing strains)

### 4.3 Contraindications

Do not use in animals, which are known to be hypersensitive to ß-lactam antibiotics.

### 4.4 Special warnings

Do not use in cases associated with *Pseudomonas*.

### 4.5 Special precautions for use

**Special precautions for use in animals**
Swab teat end with appropriate disinfectant before treatment.

**Recommendations for prudent use**
The product should be used for treatment of clinical mastitis only.

Use of the product should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria and take into account official and local antimicrobial policies.
The use of the product should preferably be based on susceptibility tests.

Avoid use of the product in herds where no β-lactamase producing *Staphylococci* strains have been isolated. Veterinarians should strive to use narrow spectrum antibiotics if possible.
Inappropriate use of the product may increase the prevalence of bacteria resistant to ß-lactam antibiotics and may decrease the effectiveness of treatment with ß-lactam antibiotics, due to the potential for cross-resistance.

**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 reactions to these substances may occasionally be serious.
Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
Handle this product with great care to avoid exposure, taking all recommended precautions.
If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty with breathing, are more serious symptoms and require urgent medical attention.
Wash hands after use.

## 4.6 Adverse reactions (frequency and seriousness)

None known.

## 4.7 Use during pregnancy, lactation or lay

No special precautions.

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

None known.

## 4.9 Amounts to be administered and administration route

Before the infusion is made, the teat end should be cleaned and disinfected.
The contents of one syringe should be infused into each affected quarter via the teat canal, immediately after milking, at 12 hour intervals for three consecutive milkings.
In cases of infections caused by *Staphylococcus aureus*, a longer course of antibacterial therapy may be required. Therefore overall treatment length must be at the veterinarian's discretion but should be long enough to ensure complete resolution of intramammary infection.

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

No adverse reactions are to be expected from an accidental overdose.

## 4.11 Withdrawal period(s)

Meat and offal: 7 days
Milk: 84 hours. With cows milked twice daily, milk for human consumption may only be taken the 7$^{th}$ milking after the last treatment. Where any other milking routine is followed, milk may be taken for human consumption only after the same period from the last treatment (e.g. with 3 times a day milking, milk may be taken for human consumption at the 11$^{th}$ milking).

## 5. PHARMACOLOGICAL PROPERTIES

Amoxicillin is a broad spectrum bactericidal β-lactam antibiotic. Clavulanic acid inactivates β-lactamases. This combination is effective against β-lactamase producing organisms.

Prednisolone is an anti-inflammatory corticosteroid.
*In vitro* clavulanic acid and amoxicillin in combination are active against a wide range of clinically important bacteria including the following organisms which are commonly associated with bovine mastitis:
Staphylococci (including β-lactamase producing strains)
Streptococci (including *S. agalactiae*, *S. dysgalactiae* and *S. uberis*)
Arcanobacteria (including *A. pyogenes*)
*Escherichia coli* (including β-lactamase producing strains)

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Calcium Sodium Aluminosilicate (dried)
Mineral Oil (Formula A)

Formula A:
Emulsifying Wax
White Soft Paraffin
Liquid Paraffin Light

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.

### 6.4 Special precautions for storage

Do not store above 25°C.
Store in a dry place.

### 6.5 Nature and composition of immediate packaging

Low density polyethylene syringes packed in cartons containing 3, 12, 24 or 300 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, if appropriate

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

*To be completed nationally*

## 8. MARKETING AUTHORISATION NUMBER

*To be completed nationally*

## 9. DATE OF RENEWAL OF THE AUTHORISATION

*To be completed nationally*

## 10. DATE OF REVISION OF THE TEXT

*To be completed nationally*

**LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**

**Carton box**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

*"Product name" (to be completed nationally)*
Intramammary suspension for lactating cattle

## 2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One syringe (3 g) contains:
**Active substances:**

| | |
|---|---|
| Amoxicillin trihydrate (equivalent to amoxicillin) | 200 mg |
| Potassium clavulanate (equivalent to clavulanic acid) | 50 mg |
| Prednisolone | 10 mg |

## 3. PHARMACEUTICAL FORM

Intramammary suspension

## 4. PACKAGE SIZE

3 syringes
12 syringes
24 syringes
300 syringes
350 syringes

## 5. TARGET SPECIES

Cattle (lactating cows).

## 6. INDICATION(S)

For use in clinical cases of mastitis including cases associated with infections with the following pathogens:
Staphylococci (including β-lactamase producing strains)
Streptococci (including *S. agalactiae, S. dysgalactiae and S. uberis*)
*Escherichia coli* (including β-lactamase producing strains).

## 7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramammary use.

Read the package leaflet before use.

## 8. WITHDRAWAL PERIOD

Withdrawal period:
Meat and offal: 7 days.
Milk: 84 hours, i.e. 7 milking times with 2 times a day milking or 11 milking times with 3 times a day milking.

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

The product should be used for treatment of clinical mastitis only.
The use of the product should preferably be based on susceptibility tests.
Read the package leaflet before use.

## 10. EXPIRY DATE

EXP

## 11. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in a dry place.

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

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

## 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 REACH AND SIGHT OF CHILDREN"

Keep out of the reach and sight of children.

## 15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

*To be completed nationally*

## 16. MARKETING AUTHORISATION NUMBER(S)

*To be completed nationally*

## 17. MANUFACTURER'S BATCH NUMBER

Batch

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

**Polyethylene syringe**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

*"Product name" (to be completed nationally*
Intramammary suspension for lactating cows

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

| | |
|---|---|
| Amoxicillin | 200 mg |
| Clavulanic acid | 50 mg |
| Prednisolone | 10 mg |

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

One dose (3 g)

## 4. ROUTE(S) OF ADMINISTRATION

Intramammary use

## 5. WITHDRAWAL PERIOD

Withdrawal period:
Meat and offal: 7 days
Milk: 84 hours

## 6. BATCH NUMBER

Lot

## 7. EXPIRY DATE

EXP

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

For animal treatment only.

# PACKAGE LEAFLET

*"Product name" (to be completed nationally)* intramammary suspension for lactating 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:
*To be completed nationally*

## 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

*"Product name" (to be completed nationally)* intramammary suspension for lactating cattle

## 3. STATEMENT OF THE ACTIVE SUBSTANCES AND OTHER INGREDIENTS

***Active ingredients:***
One syringe (3 g) contains:

| | |
|---|---|
| Amoxicillin (as amoxicillin trihydrate): | 200 mg |
| Clavulanic acid (as potassium clavulanate): | 50 mg |
| Prednisolone: | 10 mg |

## 4. INDICATIONS

For use in clinical cases of mastitis including cases associated with infections with the following pathogens:
Staphylococci (including β-lactamase producing strains)
Streptococci (including *S.agalactiae, S.dysgalactiae and S.uberis*)
*Escherichia coli* (including β-lactamase producing strains)

## 5. CONTRAINDICATIONS

Do not use in animals, which are known to be hypersensitive to ß-lactam antibiotics.

## 6. ADVERSE REACTIONS

None known.
If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

## 7. TARGET SPECIES

Cattle (lactating cows)

## 8. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF ADMINISTRATION

The contents of one syringe should be infused into each affected quarter via the teat canal, immediately after milking, at 12 hour intervals for three consecutive milkings.
In cases of infections caused by *Staphylococcus aureus*, a longer course of antibacterial therapy may be required. Therefore overall treatment length must be at the veterinarian's discretion but should be long enough to ensure complete resolution of intramammary infection.

## 9. ADVICE ON CORRECT ADMINISTRATION

Before the infusion is made, the teat end should be cleaned and disinfected.

## 10. WITHDRAWAL PERIOD

Meat and offal: 7 days
Milk: 84 hours, i.e. 7 milking times with 2 times a day milking or 11 milking times with 3 times a day milking.

## 11. SPECIAL STORAGE PRECAUTIONS

Do not store above 25°C.
Store in a dry place.

Keep out of the reach and sight of children.
Do not use after the expiry date stated on the label after "EXP".

## 12. SPECIAL WARNINGS

**Recommendations for prudent use**
The product should be used for treatment of clinical mastitis only.
Use of the product should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria and take into account official and local antimicrobial policies.
The use of the product should preferably be based on susceptibility tests.

Avoid use of the product in herds where no β-lactamase producing *Staphylococci* strains have been isolated. Veterinarians should strive to use narrow spectrum antibiotics if possible.
Inappropriate use of the product may increase the prevalence of bacteria resistant to ß-lactam antibiotics and may decrease the effectiveness of treatment with ß-lactam antibiotics, due to the potential for cross-resistance.

**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 reactions to these substances may occasionally be serious.
Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
Handle this product with great care to avoid exposure, taking all recommended precautions.
If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty with breathing, are more serious symptoms and require urgent medical attention.

Wash hands after use.

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

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

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

*To be completed nationally*

## 15. OTHER INFORMATION

*To be completed nationally*