Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal products, animal species, applicants / marketing authorisation holders in the Member States

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Belgium	Merial Belgium SA Culliganlaan 1c 1831 Diegem Belgium	Captalin	Spiramycin	1 000 000 IU/ml	Solution for injection	Cattle
Bulgaria	Ceva Animal Health Bulgaria Ltd 26 Elemag Str., ent.B, app.1 Sofia 1113 Bulgaria	Spirovet 600 000 IU/ml инжекционен разрвор за говеда и свине/ Spirovet 600 000IU/ml solution for injection for cattle and pigs	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Czech Republic	Merial 29 avenue Tony Garnier 69007- Lyon France	SUANOVIL 20 injekční roztok	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Czech Republic	Ceva Sante Animale Z.I. La Ballastiere Libourne France	SPIROVET 600 000 IU/ml solution for injection for cattle and pigs	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Estonia	Merial 29 avenue Tony Garnier 69007 Lyon France	Suanovil 20	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Estonia	Ceva Sante Animale 10 avenue de la Ballastiere 33500 Libourne France	Spirovet	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Product name	INN	Strength	Pharmaceutical form	Animal species
France	Merial 29 avenue Tony Garnier 69007 Lyon France	Suanovil 20	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
France	Merial 29 avenue Tony Garnier 69007 Lyon France	Captalin	Spiramycin	1 000 000 IU/ml	Solution for injection	Cattle
France	Ceva Sante Animale 10 avenue de la Ballastiere 33500 Libourne France	Spirovet	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
France	Ceva Sante Animale 10 avenue de la Ballastiere 33500 Libourne France	Spiramycine CEVA 600 000 UI/ML solution injectable pour bovins et porcins	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Greece	Merial 29 avenue Tony Garnier 69007 Lyon France	Suanovil 20	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Hungary	Merial 29 avenue Tony Garnier 69007 Lyon France	Suanovil 20% injekció	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Hungary	Ceva-Phylaxia Zrt. Szállás u. 5 1107 Budapest Hungary	Spirovet 600 000 NE/ml, injekció szarvasmarha és sertés részére	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Ireland	Ceva Sante Animale 10 avenue de la Ballastiere 33500 Libourne France	SPIROVET 600 000 IU/ml solution for injection for cattle and pigs	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Italy	Merial Italia S.p.A. Via Vittor Pisani 16 20124 Milano Italy	Captalin	Spiramycin	1 000 000 IU/ml	Solution for injection	Cattle
Italy	Merial Italia S.p.A. Via Vittor Pisani 16 20124 Milano Italy	Spiramin	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Italy	Ceva Salute Animale S.p.A. Viale Colleoni, 15 20864 Agrate Brianza (MB) Italy	Spiravet 20	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Latvia	Merial 29 avenue Tony Garnier 69007 Lyon France	Suanovil 20	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Lithuania	Ceva Sante Animale Z.I. La Ballastière 33500 Libourne France	SPIROVET 600 000 TV/ml, injekcinis tirpalas galvijams ir kiaulėms	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Portugal	Merial Portuguesa - Saúde Animal, LDA Av. Maria Lamas, lote 19 - BL. A Piso 2 Parque Industrial e Comercial Serra das Minas 2635-432 Rio de Mouro Portugal	Suanovil 20	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Portugal	Ceva Saúde Animal - Produtos Farmacêuticos e Imunológicos, Lda. Rua Doutor António Loureiro Borges, 9/9A, 9ºA Miraflores 1495-131 Algés Portugal	SPIROVET 600 000 UI/ml solução injetável para bovinos e suínos	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Romania	Ceva Sante Animale Z.I. de la Ballastiere, BP 126 33500 Libourne Cedex FRANCE	Spirovet	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Romania	Merial Rue de Bourgelat 17 69002 Lyon France	Suanovil 20	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Slovakia	Merial 29 avenue Tony Garnier 69007 Lyon France	Suanovil 20 injekčný roztok	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
Slovenia	Ceva Sante Animale 10 avenue de la Ballastiere 33500 Libourne France	SPIROVET 600 000 IU/ml raztopina za injiciranje za govedo in prašiče	Spiramycin	600000 IU/ml	Solution for injection	Cattle Pigs

Member State EU/EEA	Applicant/Marketing Authorisation Holder	Product name	INN	Strength	Pharmaceutical form	Animal species
Spain	Merial Laboratorios S.A. Tarragona, Nº 161 - Locales D/E 08820 Barcelona Spain	Suanovil 20	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs
United Kingdom	Ceva Animal Health Ltd Unit 3 Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB United Kingdom	Spirovet	Spiramycin	600 000 IU/ml	Solution for injection	Cattle Pigs

Annex II

Scientific conclusions and grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Overall summary of the scientific evaluation of Suanovil 20 and associated names, Captalin and associated names and generic products thereof (see Annex I)

1. Introduction

The veterinary medicinal products Suanovil 20 solution for injection and its generic product Spirovet are solutions for injection which contain 20 g spiramycin per 100 ml, corresponding to 600 000 IU spiramycin per ml.

Captalin solution for injection contains 31.25 g spiramycin per 100 ml, corresponding to 1 000 000 IU spiramycin per ml.

Spiramycin is a macrolide antibiotic exerting bacteriostatic action against Mycoplasma, Gram-negative and Gram-positive bacteria which cause infections in cattle and pigs.

The veterinary medicinal product Suanovil 20 and its associated names has been authorised by several Member States for use in cattle for the treatment and prevention of respiratory infections and gastrointestinal infections, mastitis, metritis, omphalitis and omphalophlebitis, arthritis and interdigital abscesses at a dose of 30 000 IU/kg body weight once or twice in 24 hour interval for adult cattle and at 75 000 IU/kg body weight once or twice in 24 hour interval for calves. In pigs, the products has been authoresed for the treatment of respiratory infections, pig house cough, atrophic rhinitis, infections caused by *Streptococcus spp*., erysipelas, arthritis, treatment and prevention of mastitis, prevention of neonatal infections in piglets and infectious gastro-enteritis at 75 000 IU/kg body weight once or twice in 24 hour interval.

It should be noted that the generic product, Spirovet, has been authorised in several Member States for a restricted list of indications, only i.e. in adult cattle for the treatment of respiratory diseases, mastitis, metritis and interdigital necrobacillosis at a dose of 30 000 IU/kg once or twice in 24 hour interval. In sows has been authoresed for the treatment of mastitis at 75 000 IU/kg once or twice in 24 hour interval.

Captalin solution for injection has been authorised by severeal Member States for use in cattle for the treatment of respiratory diseases at a dose of 100 000 IU/kg body weight twice at 48 hour interval and for the metaphylaxis of respiratrory diseases at a single dose of 100 000 IU/kg body weight.

Due to concerns related to efficacy, antimicrobial resistance and withdrawal periods, on 12 September 2012, Germany presented to the Agency a referral notification under Article 35 of Directive 2001/82/EC for Suanovil 20 and associated names, Captalin and associated names, and generic products thereof. The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to give its opinion on the indications, dosing regimens and withdrawal periods in cattle and pigs, in order to ensure efficacious treatment and lower the risk of development of antimicrobial resistance to spiramycin taking into account the available data and also to harmonise the withdrawal periods in cattle and pigs for the concerned products.

2. Discussion of the data available

Efficacy issues

Cattle (calves)

Treatment of respiratory infections caused by Pasteurella multocida and Mannheimia haemolytica at a dose regime of 100 000 IU/kg body weight twice at 48 hours of interval.

The indication was substantiated by *in vitro* susceptibility data for *Pasteurella multocida* and *Mannheimia haemolytica* and by pharmacokinetic data of spiramycin in the target species, on the basis of which a detailed pharmacokinetic/pharmacodynamic (PK/PD) assessment has been performed. In addition, clinical efficacy data have been presented to support the aforementioned indication.

Earlier and more recent *in vitro* susceptibility data of the target pathogens had been derived from a large number of strains collected from cattle in several EU Member States. Although results from different laboratories can be compared only with reservation because of the different methods used, Minimum Inhibitory Concentrations (MIC) of spiramycin for the relevant respiratory tract pathogens such as *Pasteurella* and *Mannheimia spp.* were generally distributed in a mono-modal pattern on the right side of the MIC distribution curve with MIC_{90}-values around 64 µg/ml for bovine isolates, suggesting limited *in vitro* susceptibility of these bacteria to spiramycin.

The pharmacokinetic characteristics derived from specific studies demonstrated that in plasma relatively low spiramycin levels (Cmax: 6-10 IU/ml corresponding to 2–3 µg/ml) were reached with the treatment regime, whereas considerably higher spiramycin levels were reached in bronchoalveolar lavage (4-5-fold of the plasma levels) and in lung tissue (100-fold of the plasma levels). Lung levels determined following this treatment regime reached a multiple of the corresponding plasma levels from 4 hours after injection onwards and persisted on a high level for 32 hours after a single injection. Particularly high spiramycin concentrations were determined in lung macrophages. Spiramycin levels in tissues and fluids were further increased when spiramycin was injected for a second time after 48 hours.

By using the pharmacodynamic and pharmacokinetic data mentioned abobe, a detailed PK/PD assessment was performed, which was based on two parameters: the T>MIC (time during which the concentration exceeds the MIC), which is recommended for time-dependent antibiotics like the macrolides, and the AUC/MIC (area under the curve to MIC), which is recommended for specific macrolides like azithromycin. In a worst-case scenario a AUC/MIC-ratio of 100-125 hours as target for spiramycin has been proposed.

When applying these concepts it has been concluded that based on PK/PD-considerations in cattle, following 2 injections at 100 000 IU/kg body weight at 48 hours interval, the spiramycin concentrations in lung, macrophages and bronchoalveolar lavage reached the respiratory pathogens with MICs up to 128 µg/ml. It is assumed that compared to cattle the pharmacokinetic profile of spiramycin in calves would be similar or even more favourable.

For the treatment of bovine respiratory diseases several appropriate clinical studies from 1988 and 1989 using the dose regime of 100 000 IU/kg body weight once or twice in 48 hours interval, have been presented. In these studies the efficacy of spiramycin had been compared to negative controls or to other antibiotics approved for these indications (oxytetracycline and tylosin). Spiramicin proved to be more efficacious and with a lower relapse rate compared to the positive controls.

Lactating cows

Treatment of acute clinical mastitis in lactating cows caused by Staphylococcus aureus strains sensitive to spiramycin at a dose regime of 30 000 IU/kg body weight twice at 24 hours of interval.

The indication was substantiated by *in vitro* susceptibility data for *Staphylococcus aureus strains* and by PK data of spiramycin in the target species, on the basis of which a detailed PK/PD assessment has been performed. In addition, clinical efficacy data have been presented to support the aforementioned indication.

Data from clinical surveillance monitoring programs (VetPath I: 1997-2004, VetPath III: 2007-2012) show that a considerable proportion of bovine mastitis strains of *S. aureus* were susceptible to

spiramycin *in vitro,* with MIC_{50} and MIC_{90} of 4 µg/ml and 8 µg/ml, respectively. A limited resistant populaton was observed above 64 µg/ml. The MIC distribution pattern has not changed notably during recent years.

The pharmacokinetic properties of spiramycin at the dose of 30 000 IU/kg body weight have been examined in one study. The pharmacokinetic characteristics derived from this study demonstrate that in plasma relatively low spiramycin levels (Cmax: 1.44 IU/ml corresponding to 0.45 µg/ml) were reached with the treatment regime, whereas considerably higher spiramycin levels were reached in milk (50-fold of the plasma levels).

By using the pharmacodynamic and pharmacokinetic data mentioned above, a detailed PK/PD-assessment was performed, which was based on two parameters: the T>MIC, which is recommended for time-dependent antibiotics like the macrolides, and the AUC/MIC, which is recommended for specific macrolides like azithromycin.

The clinical data on bovine mastitis consisted primarily of an experimental *S. aureus* mastitis study using a challenge strain with a spiramycin MIC of 4 µg/ml. Despite of several limitations, in particular the small number of animals and the short (14 days) observation period, the study was found appropriate to justify the indication 'acute *S. aureus* mastitis', since results in the primary end point (bacteriological cure was reached in 7 out of 8 test cows, but in none of the 9 control cows) and some of the secondary endpoints (particularly the somatic cell count) were convincing. The data were, however, not appropriate to support subclinical or chronic mastitis or mastitis caused by other bacteria like *S. uberis*.

Other indications in cattle and all indications in pigs

Insufficient data or no data at all are available for all other indications and dosage regimens in cattle (i.e. metritis, enteric infections, omphalitis, omphalophlebitis, arthritis, interdigital abscesses) and all indications in pigs.

Antimicrobial resistance

Regarding bovine respiratory pathogens like *Pasteurella multocida* and *Mannheimia haemolytica*, *in vitro* MIC-values of spiramycin are generally high, but their mono-modal distribution pattern does not indicate a relevant resistant fraction. The comparison of earlier with more recently determined MIC-data is, more over, complicated by the different laboratory methods used, and the fact that no break points validated for veterinary medicine exist. Therefore, the risk of resistance development among these bacteria can presently not be fully evaluated.

Regarding bovine mastitis pathogens such as *S. aureus* and *S. uberis*, there exists already a resistant proportion of strains, as evident from recent surveillance programs. While for *S. aureus* this fraction amounted to less than 10% of the strains examined, the tri-modal MIC-distribution pattern obtained for *S. uberis* indicated that in addition to the susceptible fraction 10% of the strains examined had intermediate susceptibility and 20% were resistant.

Withdrawal periods

Suanovil 20

Further to the efficacy assessment the recommended dose for respiratory infections in cattle is 100 000 IU/kg body weight, intramuscularly twice at 48 hours of interval.

The recommended dose for acute clinical mastitis in lactating cows caused by *Staphylococcus aureus* strains susceptible to spiramycin is 30 000 IU/kg body weight, intramuscularly twice at 24 hours of interval.

Residue depletion studies performed at the dose of 100 000 IU/kg body weight, intramuscularly at 48 hours interval, were available in adult cattle. The establishment of withdrawal periods was based on the better conducted and most reliable study. Using the statistical analysis[1] the residues depletion at the injection sites suggested a withdrawal period of 52 days. However since the assessment identified some deficiencies such as no surrounding injection site samples in adult cattle, it was considred necessary to use the alternative approach[1] and add a 20% safety span. Thus a 62 days withdrawal period for meat and offal is recommended. The maximal volume to be injected is 20 ml per injection site as this was the maximal volume administered at the residue depletion study.

Based on a residue depletion study performed in accordance with the current guidance[2] for the determination of withdrawal periods for milk, a withdrawal period of 27 milkings (13.5 days) can be recommended for milk. This withdrawal period is valid for Suanovil 20 administered at the dose of 30 000 IU/per kg body weight, intramuscularly twice at 24 hours of interval.

As no residue depletion study was provided following administration of 100 000 IU/kg intramuscularly twice with 48 hours of interval, no withdrawal period for milk is recommended for this dosage regimen. Therefore Suanovil 20 should not be used for treatment of respiratory infections in animals producing milk for human consumption.

Spirovet

Further to the efficacy assessment the recommended dose for respiratory infections in cattle is 100 000 IU/kg body weight intramuscularly twice at 48 hours of interval.

The recommended dose for acute clinical mastitis in lactating cows caused by *Staphylococcus aureus* strains susceptible to spiramycin is 30 000 IU/kg body weight, intramuscularly twice at 24 hours of interval.

Spirovet has been shown to be bioequivalent to Suanovil 20 and consequently the time taken for residue levels in non-injection site muscle, liver, fat, kidney and milk can be assumed to be the same as for the two products. However, in line with CVMP guideline on the conduct of bioequivalence studies in veterinary medicinal products (EMA/CVMP/016/00)[3], product specific data are required to establish the residue depletion profile at the injection site.

One study was conducted at the recommended dose of 100 000 IU/kg body weight twice at 48 hours of interval, which showed that the injection site muscle residues were still above the maximum residue limit for muscle (200 µg/kg) at Day 49 post-treatment. Using the statistical analysis the calculated withdrawal period for cattle meat and offal is 75 days. This withdrawal period is valid after administration of 100 000 IU/kg body weight twice at 48 hours of interval. The maximal volume to be injected is 15 ml per injection site as this was the maximal volume administered at the residue depletion study.

No residue depletion data in milk was provided following the admistration of Spirovet at the dose of 30 000 IU/per kg body weight, intramuscularly twice at 24 hours of interval. However, as Spirovet is bioequivalent to Suanovil 20 the same withdrawal period of 27 milkings (13.5 days) can be recommended. This withdrawal period is valid for Spirovet administered at the dose of 30 000 IU/per kg body weight, intramuscularly twice at 24 hours of interval.

[1] CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004428.pdf
[2] CVMP note for guidance for the determination of withdrawal periods for milk (EMEA/CVMP/473/98) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004496.pdf
[3] CVMP guideline on the conduct of bioequivalence studies in veterinary medicinal products (EMA/CVMP/016/00) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105372.pdf

As no residue depletion study was provided following administration of 100 000 IU/kg intramuscularly twice with 48 hours of interval, no withdrawal period for milk is recommended for this dosage regimen. Therefore Spirovet should not be used for treatment of respiratory infections in animals producing milk for human consumption.

Captalin

The recommended dose for respiratory infections in cattle is 100 000 IU/kg body weight, intramuscularly twice at 48 hours of interval.

One study conducted at the recommended dose showed that the injection site muscle residues were below the maximum residue limit (200 µg/kg) at Day 52. Since the study has shortcomings (no data for tissues other than injection site and in some samples residues in the surrounding injection site were higher than in the core), it was considered necessary to use the alternative approach and add a 30% safety span which resulted in a withdrawal period of 68 days for cattle meat and offal. The maximal volume to be injected is 15 ml per injection site as this was the maximal volume administered at the residue depletion study.

No residue depletion study in milk was provided, hence no withdrawal period for milk is recommended. Therefore Captalin should not be used in animals producing milk for human consumption.

3. Benefit-risk assessment

Overall, the benefit-risk balance of all concerned products is considered positive provided their use will be limited to the treatment of bovine respiratory infections caused by susceptible strains of *Pasteurella multocida* and *Mannheimia haemolytica* at a dose of 100 000 IU/kg administered intramuscularly twice at 48 hours of interval.

The benefit-risk balance of Suanovil 20 and Spirovet is considered positive provided that their use in the treatment of mastitis will be limited to treatment of acute bovine *S. aureus*-mastitis caused by susceptible strains at a dose of 30 000 IU/kg administered intramuscularly twice at 24 hours of interval.

No sufficient data or no data at all are available for all other indications and dosage regimens in cattle (i.e. metritis, enteric infections, omphalitis, omphalophlebitis, arthritis, interdigital abscesses) and all indications in pigs. Therefore, the benefit-risk balance is considered negative for these indications in cattle and all indications in pigs. Consequently these indications/dosage regimens in cattle and target species pigs should be deleted from the product information.

The withdrawal periods for cattle meat and milk should be amended as proposed to provide assurance for consumer safety.

Quality, target animal safety, user safety and environmental risk were not assessed in this referral procedure.

The overall benefit-risk balance of the products under this procedure was deemed positive subject to the recommended changes in the product information (see Annex III).

Grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Whereas:

- on the basis of the available data, the CVMP considered that indications as provided in Annex III were justified;
- on the on basis of the available data, the CVMP considered that all other indications and dosage regimens in cattle and all indications in pigs should be deleted from the product information;
- on the basis of the available residue depletion data in cattle, the CVMP considered that withdrawal periods should be amended to provide assurance for consumer safety;
- the CVMP considered that the overall benefit-risk balance is positive for the veterinary medicinal products (see annex I), subject to amendments in the product information;

the CVMP recommended variations of the marketing authorisations for Suanovil 20 and associated names, Captalin and associated names, and generic products thereof, in order to amend the summaries of product characteristics, labelling and package leaflets as set out in Annex III.

Annex III

Amendments in the relevant sections of the summaries of product characteristics, labelling and package leaflets

A. For Suanovil 20 and its associated names listed in Annex I containing 600 000 IU spiramycin per ml

Delete, target species pigs and any information related to these species from the product information.

Summary of product characteristics

4.1 Target species

Cattle.

4.2 Indications for use, specifying the target species

Treatment of respiratory infections caused by *Pasteurella multocida* and *Mannheimia haemolytica*.
Treatment of acute clinical mastitis in lactating cows caused by *Staphylococcus aureus* strains sensitive to spiramycin.

4.5 Special precautions for use

Special precautions for use in animals

Do not administer more than 20 ml per injection site.
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. Use of the product deviating from the instructions given in the product information may increase the prevalence of bacteria resistant to spiramycin. Official, national and regional antimicrobial policies should be taken into account when the product is used.
Mastitis caused by *S. aureus* should be treated once clinical signs are observed.
Only acute cases of mastitis caused by *S. aureus* with clinical signs observed for less than 24 h should be treated.

4.9 Amounts to be administered and administration route

Intramuscular use.
Body weight should be determined as accurately as possible to avoid underdosing.
Mastitis: 30 000 IU of spiramycin per kg body weight (i.e. 5 ml of product per 100 kg body weight) twice at 24 h of interval.
Respiratory infections: 100 000 IU of spiramycin per kg body weight (i.e. 5 ml of product per 30 kg body weight) twice at 48 h of interval.
Do not administer more than 20 ml per injection site. If this means that the dose must be divided into two injections, then injections should be administered on opposite sides of the neck. If more than two injections are needed, a distance of at least 15 cm should be maintained between injections given on the same side of the neck.
For the second dose (after 24 h or 48 h) the same practice should be followed, ensuring that a distance of at least 15 cm is maintained between all injections administered as part of the treatment. This procedure is necessary so that individual injection sites are kept apart. Failure to follow these instructions may result in residues above the established maximum residue limit of 200 µg/kg for muscle.

4.11. Withdrawal period(s)

Mastitis:
Meat and offal: 62 days.
Milk: 13.5 days.

Respiratory infections:
Meat and offal: 62 days.
Milk: In case of treatment at the dose required for respiratory diseases the product is not authorised for use in animals producing milk for human consumption.

5.1 Pharmacodynamic properties

Spiramycin acts on bacterial protein synthesis by binding to the 50S ribosomal subunits, inhibiting the translocation step. Spiramycin is able to reach so high tissue concentrations that it succeeds in penetrating into the cells to bind the 50S ribosomal subunits.
Spiramycin is an antimicrobial exerting bacteriostatic action against Mycoplasma, Gram-negative and Gram-positive bacteria.
Spiramycin is active against *Staphylococcus aureus, Mannheimia haemolytica* and *Pasteurella multocida.*
The following Minimum Inhibitory Concentrations (MIC) have been determined for spiramycin in European isolates collected from diseased animals between 2007 to 2012:

Bacteria species	**Origin**	**Number of strains**	**MIC of spiramycin (µg/mL)**		
			Range	**MIC_{50}**	**MIC_{90}**
Pasteurella multocida	Cattle	129	1 - ≥512	16	32
Mannheimia haemolytica	Cattle	149	4 -512	64	128
Staphylococcus aureus	Cattle	211	1 - ≥64	4	8

5.2 Pharmacokinetic particulars

Following intramuscular injection, spiramycin is rapidly absorbed and maximal plasma concentrations are reached within 3 hours. Spiramycin is a weak base, not ionized and liposoluble which crosses easily cellular membranes by passive diffusion. Spiramycin is weakly bound to plasma proteins. Its tissue distribution is extensive, with high concentration particularly in bronchial secretions, lung parenchyma, alveolar macrophages, udders and milk.
Spiramycin is metabolised in the liver; its primary metabolite, neospiramycin, possesses antimicrobial activity.
Spiramycin is eliminated primarily by biliary excretion.

Labelling:

5. TARGET SPECIES

Cattle.

8. WITHDRAWAL PERIOD

Mastitis:
Meat and offal: 62 days.
Milk: 13.5 days.

Respiratory infections:
Meat and offal: 62 days.
Milk: In case of treatment at the dose required for respiratory diseases the product is not authorised for use in animals producing milk for human consumption.

Package leaflet:

4. INDICATIONS

Treatment of respiratory infections caused by *Pasteurella multocida* and *Mannheimia haemolytica*.
Treatment of acute clinical mastitis in lactating cows caused by *Staphylococcus aureus* strains sensitive to spiramycin.

7. TARGET SPECIES

Cattle.

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

Intramuscular use.
Body weight should be determined as accurately as possible to avoid underdosing.
Mastitis: 30 000 IU of spiramycin per kg body weight (i.e. 5 ml of product per 100 kg body weight) twice at 24 h of interval.
Respiratory infections: 100 000 IU of spiramycin per kg body weight (i.e. 5 ml of product per 30 kg body weight) twice at 48 h of interval.
Do not administer more than 20 ml per injection site. If this means that the dose must be divided into two injections, then injections should be administered on opposite sides of the neck. If more than two injections are needed, a distance of at least 15 cm should be maintained between injections given on the same side of the neck.
For the second dose (after 24 h or 48 h) the same practice should be followed, ensuring that a distance of at least 15 cm is maintained between all injections administered as part of the treatment. This procedure is necessary so that individual injection sites are kept apart. Failure to follow these instructions may result in residues above the established maximum residue limit of 200 µg/kg for muscle.

10. WITHDRAWAL PERIOD

Mastitis:
Meat and offal: 62 days.
Milk: 13.5 days.

Respiratory infections:
Meat and offal: 62 days.
Milk: In case of treatment at the dose required for respiratory diseases the product is not authorised for use in animals producing milk for human consumption.

12. SPECIAL WARNINGS

Special precautions for use in animals:
Do not administer more than 20 ml per injection site.
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. Use of the product deviating from the instructions given in the product information may increase the prevalence of bacteria resistant to spiramycin. Official, national and regional antimicrobial policies should be taken into account when the product is used.
Mastitis caused by *S. aureus* should be treated once clinical signs are observed.
Only acute cases of mastitis caused by *S. aureus* with clinical signs observed for less than 24 h should be treated.

B. For Spirovet and its associated names listed in Annex I containing 600 000 IU spiramycin per ml

Delete, target species pigs and any information related to these species from the product information.

Summary of product characteristics

4.1 Target species

Cattle.

4.2 Indications for use, specifying the target species

Treatment of respiratory infections caused by *Pasteurella multocida* and *Mannheimia haemolytica*.
Treatment of acute clinical mastitis in lactating cows caused by *Staphylococcus aureus* strains sensitive to spiramycin.

4.5 Special precautions for use

Special precautions for use in animals

Do not administer more than 15 ml per injection site.
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. Use of the product deviating from the instructions given in the product information may increase the prevalence of bacteria resistant to spiramycin. Official, national and regional antimicrobial policies should be taken into account when the product is used.
Mastitis caused by *S. aureus* should be treated once clinical signs are observed.
Only acute cases of mastitis caused by *S. aureus* with clinical signs observed for less than 24 h should be treated.

4.9 Amounts to be administered and administration route

Intramuscular use.
Body weight should be determined as accurately as possible to avoid underdosing.
Mastitis: 30 000 IU of spiramycin per kg body weight (i.e. 5 ml of product per 100 kg body weight) twice at 24 h of interval.
Respiratory infections: 100 000 IU of spiramycin per kg body weight (i.e. 5 ml of product per 30 kg body weight) twice at 48 h of interval.
Do not administer more than 15 ml per injection site.
If this means that the dose must be divided into two injections, then injections should be administered on opposite sides of the neck. If more than two injections are needed, a distance of at least 15 cm should be maintained between injections given on the same side of the neck.
For the second dose (after 24 h or 48 h) the same practice should be followed, ensuring that a distance of at least 15 cm is maintained between all injections administered as part of the treatment. This procedure is necessary so that individual injection sites are kept apart. Failure to follow these instructions may result in residues above the established maximum residue limit of 200 µg/kg for muscle.

4.11. Withdrawal period(s)

Mastitis:
Meat and offal: 75 days.
Milk: 13.5 days.

Respiratory infections:
Meat and offal: 75 days.
Milk: In case of treatment at the dose required for respiratory diseases the product is not authorised for use in animals producing milk for human consumption.

5.1 Pharmacodynamic properties

Spiramycin acts on bacterial protein synthesis by binding to the 50S ribosomal subunits, inhibiting the translocation step. Spiramycin is able to reach so high tissular concentrations that it succeeds in penetrating into the cells to bind the 50S ribosomal subunits.
Spiramycin is an antibiotic exerting bacteriostatic action against Mycoplasma, Gram-negative and Gram-positive bacteria.
Spiramycin is active against *Staphylococcus aureus, Mannheimia haemolytica* and *Pasteurella multocida.*
The following Minimum Inhibitory Concentrations (MIC) have been determined for spiramycin in European isolates collected from diseased animals between 2007 to 2012:

Bacteria species	**Origin**	**Number of strains**	**MIC of spiramycin (µg/mL)**		
			Range	**MIC_{50}**	**MIC_{90}**
Pasteurella multocida	Cattle	129	1 - ≥512	16	32
Mannheimia haemolytica	Cattle	149	4 -512	64	128
Staphylococcus aureus	Cattle	211	1 - ≥64	4	8

5.2 Pharmacokinetic particulars

Following intramuscular injection, spiramycin is rapidly absorbed and maximal plasma concentrations are reached within 3 hours. Spiramycin is a weak base, not ionized and liposoluble which crosses easily cellular membranes by passive diffusion. Spiramycin is weakly bound to plasma proteins. Its tissue distribution is extensive, with high concentrations particularly in bronchial secretions, lung parenchyma, alveolar macrophages, udders and milk.
Spiramycin is metabolised in the liver; its primary metabolite, neospiramycin, possesses antimicrobial activity.
Spiramycin is eliminated primarily by biliary excretion.

Labelling:

5. TARGET SPECIES

Cattle.

8. WITHDRAWAL PERIOD

Mastitis:
Meat and offal: 75 days.
Milk: 13.5 days.

Respiratory infections:
Meat and offal: 75 days.
Milk: In case of treatment at the dose required for respiratory diseases the product is not authorised for use in animals producing milk for human consumption.

Package leaflet:

4. INDICATIONS

Treatment of respiratory infections caused by *Pasteurella multocida* and *Mannheimia haemolytica*.
Treatment of acute clinical mastitis in lactating cows caused by *Staphylococcus aureus* strains sensitive to spiramycin.

7. TARGET SPECIES

Cattle.

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

Intramuscular use.
Body weight should be determined as accurately as possible to avoid underdosing.
Mastitis: 30 000 IU of spiramycin per kg body weight (i.e. 5 ml of product per 100 kg body weight) twice at 24 h of interval.
Respiratory infections: 100 000 IU of spiramycin per kg body weight (i.e. 5 ml of product per 30 kg body weight) twice at 48 h of interval.
Do not administer more than 15 ml per injection site.
If this means that the dose must be divided into two injections, then injections should be administered on opposite sides of the neck. If more than two injections are needed, a distance of at least 15 cm should be maintained between injections given on the same side of the neck.
For the second dose (after 24 h or 48 h) the same practice should be followed, ensuring that a distance of at least 15 cm is maintained between all injections administered as part of the treatment. This procedure is necessary so that individual injection sites are kept apart. Failure to follow these instructions may result in residues above the established maximum residue limit of 200 µg/kg for muscle.

10. WITHDRAWAL PERIOD

Mastitis:
Meat and offal: 75 days.
Milk: 13.5 days.

Respiratory infections:
Meat and offal: 75 days.
Milk: In case of treatment at the dose required for respiratory diseases the product is not authorised for use in animals producing milk for human consumption.

12. SPECIAL WARNINGS

Special precautions for use in animals:
Do not administer more than 15 ml per injection site.
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. Use of the product deviating from the instructions given in the product information may increase the prevalence of bacteria resistant to spiramycin. Official, national and regional antimicrobial policies should be taken into account when the product is used.
Mastitis caused by *S. aureus* should be treated once clinical signs are observed.
Only acute cases of mastitis caused by *S. aureus* with clinical signs observed for less than 24 h should be treated.

C. For Captalin and its associated names listed in Annex I containing 1 000 000 IU spiramycin per ml

Summary of product characteristics

4.1 Target species

Cattle.

4.2 Indications for use, specifying the target species

Treatment of respiratory infections caused by *Pasteurella multocida* and *Mannheimia haemolytica*.

4.5 Special precautions for use

Special precautions for use in animals

Do not administer more than 15 ml per injection site.
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. Use of the product deviating from the instructions given in the product information may increase the prevalence of bacteria resistant to spiramycin. Official, national and regional antimicrobial policies should be taken into account when the product is used.

4.9 Amounts to be administered and administration route

Intramuscular use.
Body weight should be determined as accurately as possible to avoid underdosing.
100 000 IU of spiramycin per kg body weight (i.e. 1 ml of product per 10 kg body weight) twice at 48 h of interval.
Do not administer more than 15 ml per injection site. If this means that the dose must be divided into two injections, then injections should be administered on opposite sides of the neck. If more than two injections are needed, a distance of at least 15 cm should be maintained between injections given on the same side of the neck.
For the second dose (after 48 h) the same practice should be followed, ensuring that a distance of at least 15 cm is maintained between all injections administered as part of the treatment. This procedure is necessary so that individual injection sites are kept apart. Failure to follow these instructions may result in residues above the established maximum residue limit of 200 µg/kg for muscle.

4.11. Withdrawal period(s)

Meat and offal: 68 days.
Not authorised for use in animals producing milk for human consumption.

5.1 Pharmacodynamic properties

Spiramycin acts on bacterial protein synthesis by binding to the 50S ribosomal subunits, inhibiting the translocation step. Spiramycin is able to reach so high tissular concentrations that it succeeds in penetrating into the cells to bind the 50S ribosomal subunits.

Spiramycin is an antimicrobial exerting bacteriostatic action against Mycoplasma, Gram-negative and Gram-positive bacteria.
Spiramycin is active against *Mannheimia haemolytica* and *Pasteurella multocida,*
The following Minimum Inhibitory Concentrations (MIC) have been determined for spiramycin in European isolates collected from diseased animals between 2007 to 2012:

Bacteria species	**Origin**	**Number of strains**	**MIC of spiramycin (µg/mL)**		
			Range	**MIC_{50}**	**MIC_{90}**
Pasteurella multocida	Cattle	129	1 - ≥512	16	32
Mannheimia haemolytica	Cattle	149	4 -512	64	128

5.2 Pharmacokinetic particulars

Following intramuscular injection, spiramycin is rapidly absorbed and maximal plasma concentrations are reached within 3 hours. Spiramycin is a weak base, not ionized and liposoluble which crosses easily cellular membranes by passive diffusion. Spiramycin is weakly bound to plasma proteins. Its tissue distribution is extensive, with high concentrations particularly in bronchial secretions, lung parenchyma, alveolar macrophages, udders and milk.
Spiramycin is metabolised in the liver; its primary metabolite, neospiramycin, possesses antimicrobial activity.
Spiramycin is eliminated primarily by biliary excretion.

Labelling:

5. TARGET SPECIES

Cattle.

8. WITHDRAWAL PERIOD

Meat and offal: 68 days.
Not authorised for use in animals producing milk for human consumption.

Package leaflet:

4. INDICATIONS

Treatment of respiratory infections caused by *Pasteurella multocida* and *Mannheimia haemolytica*.

7. TARGET SPECIES

Cattle.

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

Intramuscular use.

Body weight should be determined as accurately as possible to avoid underdosing.
100 000 IU of spiramycin per kg body weight (i.e. 1 ml of product per 10 kg body weight) twice at 48 h of interval.
Do not administer more than 15 ml per injection site.
If this means that the dose must be divided into two injections, then injections should be administered on opposite sides of the neck. If more than two injections are needed, a distance of at least 15 cm should be maintained between injections given on the same side of the neck.
For the second dose (after 48 h) the same practice should be followed, ensuring that a distance of at least 15 cm is maintained between all injections administered as part of the treatment. This procedure is necessary so that individual injection sites are kept apart. Failure to follow these instructions may result in residues above the established maximum residue limit of 200 µg/kg for muscle.

10. WITHDRAWAL PERIOD

Meat and offal: 68 days.
Not authorised for use in animals producing milk for human consumption.

12. SPECIAL WARNINGS

Special precautions for use in animals:
Do not administer more than 15 ml per injection site.
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. Use of the product deviating from the instructions given in the product information may increase the prevalence of bacteria resistant to spiramycin. Official, national and regional antimicrobial policies should be taken into account when the product is used.