

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spizobactin 750,000 IU / 125 mg chewable tablets for dogs
(AT, BE, BG, CY, CZ, DE, EL, ES, FR, HR, HU, IE, IT, LU, NL, PT, RO, SI, SK, UK)
Spizobactin vet 750,000 IU / 125 mg chewable tablets for dogs
(DK, FI, IS, NO, EE, LT, LV, PL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains:

Active substances:

Spiramycin	750,000 IU
Metronidazole	125 mg

Excipient(s):

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.

Light brown with brown spots, round and convex flavoured tablet with a cross-shaped break line on one side.

Tablets can be divided into 2 or 4 equal parts.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For the adjunct treatment of mechanical or surgical periodontal therapy in the treatment of multi-bacterial infections of periodontal and related (peri)oral conditions – e.g. gingivitis, stomatitis, glossitis, periodontitis, tonsillitis, dental fistula and other fistulas wounds in the oral cavity, cheilitis and sinusitis - in dogs caused by microorganisms susceptible to spiramycin / metronidazole, such as Gram-positive bacteria and anaerobes (see also section 4.4 and 4.5).

4.3 Contraindications

Do not use in case of hepatic disorders.

Do not use in case of hypersensitivity to spiramycin, metronidazole or to any of the excipients.

Do not use concomitantly with bactericidal antibiotics.

4.4 Special warnings

In many cases of endodontic/periodontal disease the primary treatment is non-medicinal and does not require antimicrobial medication.

Antimicrobial treatment of periodontal disease should be accompanied or preceded by endodontic therapy and/or professional dental cleaning especially if the disease is advanced. Dog owners are encouraged to routinely brush their dog's teeth to remove plaque to prevent or to control periodontal disease.

4.5 Special precautions for use

Special precautions for use in animals

The combination of spiramycin and metronidazole should not be used as first-line empirical treatment.

Whenever possible, metronidazole and spiramycin should only be used based on susceptibility testing. Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Treatment with this medicinal product must normally not exceed the specified treatment period (6 to 10 days). This time limit may only be exceeded in rare cases with particular strict indications.

Repetition of the treatment is also allowed only when having strict indications. Limiting the duration of treatment is necessary because damage to the germ cells cannot be excluded with the use of metronidazole, and because in long-term studies with high doses, an increase of certain tumours was seen in rodents.

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

Metronidazole has confirmed mutagenic and genotoxic properties in laboratory animals as well as in humans. Metronidazole is a confirmed carcinogen in laboratory animals and has possible carcinogenic effects in humans. However, there is inadequate evidence in humans for the carcinogenicity of metronidazole.

Spiramycin may in rare cases induce hypersensitivity reactions, e.g. contact dermatitis.

Direct contact with the skin or mucous membranes of the user should be avoided because of the risk of sensitization. Do not handle the product if you are known to be hypersensitive to the active substances or to any of the excipients.

Impervious gloves should be worn during administration of the product to avoid skin contact with the product.

To avoid accidental ingestion, particularly by a child, unused part-tablets should be returned to the open blister space and inserted back into the carton.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands thoroughly after handling the tablets.

4.6 Adverse reactions (frequency and seriousness)

Vomiting has rarely been observed in dogs.

In rare cases hypersensitivity can occur. In cases of hypersensitivity reactions, treatment should be stopped.

In very rare cases disorders of spermatogenesis may occur.

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

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

4.7 Use during pregnancy and lactation

Spiramycin has not been found to be teratogenic or embryo- or foetotoxic. Studies in laboratory animals have shown inconsistent results with regard to teratogenic/embryotoxic effects of metronidazole. Therefore, use of this product during pregnancy is not recommended. Metronidazole and spiramycin are excreted in milk and use during lactation is therefore not recommended.

4.8 Interaction with other medicinal products and other forms of interaction

Macrolides, such as e.g. spiramycin act antagonistic to penicillins and cephalosporins.

The product should not be used concurrently with other antibiotics of the macrolide group. Metronidazole may have an inhibitory effect on the degradation of other drugs in the liver, such as phenytoin, cyclosporine and warfarin. Phenobarbital may increase hepatic metabolism of metronidazole resulting in decreased serum concentration of metronidazole.

4.9 Amounts to be administered and administration route

For oral administration.

75 000 IU spiramycin + 12.5 mg metronidazole per kg body weight, in more severe cases 100 000 IU spiramycin + 16.7 mg metronidazole per kg body weight, administered daily for 6 - 10 days depending on the severity of the disease.

In severe cases one can start with the higher dose and go back in the course of treatment on to the lower dose.

The daily dose may be given once daily or divided equally for twice daily administration.

The treatment should always be continued for 1-2 days after resolution of symptoms in order to prevent relapses. The tablets are to be administered either deep in the mouth (on the base of the tongue) or given with a small amount of food containing the tablet, to ensure all the tablet is consumed.

To ensure administration of the correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing. The following table is intended as a guide to dispensing the product at approximately the standard dose rate of 75 000 IU spiramycin + 12.5 mg metronidazole per kg body weight.

Bodyweight	Spizobactin 750,000 IU / 125 mg for dogs	Spizobactin 1,500,000 IU / 250 mg for dogs	Spizobactin 3,000,000 IU / 500 mg for dogs
2.5 kg	□		
5.0 kg	□	□	
7.5 kg	□		
10 kg	□	□	□
12.5 kg	□		
15 kg	□	□	
17.5 kg	□		
20 kg	□	□	
25 kg		□	
30 kg		□	
35 kg		□	
40 kg		□	□
50 kg		□	□
60 kg		□	□
70 kg		□	□
80 kg		□	□

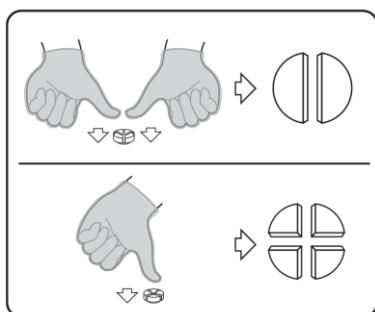
□ = 1/4 Tablet

□ = 1/2 Tablet

□ = 3/4 Tablet

□ = 1 Tablet

Tablets can be divided into 2 or 4 equal parts to ensure accurate dosing. Place the tablet on a flat surface, with its scored side facing up and the convex (rounded) side facing the surface.



Halves: press down with your thumbs on both sides of the tablet.

Quarters: press down with your thumb in the middle of the tablet

4.10 Overdose (symptoms, emergency procedures, antidotes)

Adverse events are more likely to occur at doses and treatment durations in excess of the recommended treatment regimen. If neurological signs occur, treatment should be discontinued and the patient should be treated symptomatically.

4.11 Withdrawal period

Not applicable

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use

ATCvet code: QJ01RA04, spiramycin and metronidazole

5.1 Pharmacodynamic properties

Spiramycin is an antibiotic of the macrolide group. It acts markedly bacteriostatic by inhibition of protein synthesis (interfering with the translation reaction on the ribosome). Its spectrum of activity includes mainly Gram-positive bacteria. Three different mechanisms account for most bacterial resistance to the action of macrolides: (1) rRNA methylation; (2) active efflux; and (3) enzymatic inactivation. The first two mechanisms are the most frequent ones and genes coding for these mechanisms are often located on mobile elements. rRNA methylation, encoded by erythromycin-resistant methylase (erm) genes, results in cross-resistance to the macrolides, lincosamides, and streptogramin B (MLSB resistance).

Metronidazole is an imidazole derivative and acts against representatives of protozoa (flagellates and amoeba) and against Gram-positive and Gram-negative anaerobes.

The combination spiramycin and metronidazole broadens the spectrum due to the complementary antibacterial pattern of the two drugs. Synergistic effects have been demonstrated in some pathogens in *in vitro* studies and in experimental infections of laboratory animals.

5.2 Pharmacokinetic particulars

After oral administration, peak plasma levels of spiramycin-I (main component of spiramycin) of 4.4 µg/ml are obtained within 1.3 hours. Spiramycin rapidly reaches high tissue levels that are 10-15 times higher than in plasma. The concentrations in the mucous membranes and saliva are particularly high. After a single oral dose of spiramycin concentrations remain present for about 30-40 hours. Spiramycin is eliminated in the dog via the bile. The terminal half-life is about 8.6 hours.

After oral administration, peak plasma levels of metronidazole of 18 µg/ml are obtained within 1.4 hours. After oral ingestion metronidazole diffuses rapidly and completely in all body tissues. After 24

hours blood levels $> 0.5 \mu\text{g/ml}$ are still detectable in most dogs. Excretion is via the urine. The terminal half-life is about 5.3 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch, pregelatinised
Cellulose, microcrystalline
Lactose monohydrate
Hydroxypropylcellulose
Yeast (dried)
Chicken flavour
Silica, colloidal anhydrous
Magnesium stearate

6.2 Major incompatibilities

Not applicable

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 18 months
Shelf life of divided tablets after first opening the immediate packaging: 3 days.

6.4. Special precautions for storage

Do not store above 30°C.

6.5 Nature and composition of immediate packaging

Aluminium - PVC/PE/PVDC blister
Cardboard box of 1, 2 or 3 blisters of 10 tablets
Cardboard box containing 10 separate cardboard boxes, each containing 1 blister of 10 tablets.
Not all pack sizes may be marketed.

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

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

7. MARKETING AUTHORISATION HOLDER

Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}

10 DATE OF REVISION OF THE TEXT

{DD/MM/YYYY}

PROHIBITION OF SALE, SUPPLY AND/OR USE

National issue

ANNEX B
LABELLING AND PACKAGE LEAFLET

I. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE**Cardboard box single packs and multipacks****1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Spizobactin 750,000 IU / 125 mg chewable tablets for dogs
Spiramycin / Metronidazole

**2. STATEMENT OF ACTIVE SUBSTANCES**

One tablet contains:

Spiramycin 750,000 IU
Metronidazole 125 mg

3. PHARMACEUTICAL FORM

Chewable tablets

4. PACKAGE SIZE

10 tablets

20 tablets

30 tablets

10 x 10 tablets

5. TARGET SPECIES

Dogs

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

For oral use

Read the package leaflet before use.

8. WITHDRAWAL PERIODS**9. SPECIAL WARNINGS, IF NECESSARY**

User warning: Metronidazole may cause severe adverse reactions. **IMPERVIOUS GLOVES SHOULD BE WORN.** See package leaflet for full user warnings.

10. EXPIRY DATE

EXP:

Shelf life of divided tablets: 3 days.

11. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL 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

Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Aluminium-PVC/PE/PVDC **blisters**

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spizobactin 750,000 IU / 125 mg tablets
Spiramycin / Metronidazole



2. NAME OF THE MARKETING AUTHORISATION HOLDER

Le Vet. Beheer B.V.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

II. PACKAGE LEAFLET

PACKAGE LEAFLET

Spizobactin chewable tablets for dogs

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

Marketing authorisation holder:

Name: Le Vet Beheer B.V.
Address: Wilgenweg 7
3421 TV Oudewater
The Netherlands

Manufacturer responsible for batch release:

Name: LelyPharma B.V.
Address: Zuiveringweg 42
8243 PZ Lelystad
The Netherlands

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Spizobactin 750,000 IU / 125 mg chewable tablets for dogs

3. STATEMENT OF THE ACTIVE SUBSTANCES AND OTHER INGREDIENTS

1 tablet Spizobactin 750,000 IU / 125 mg contains:

Active substances:

Spiramycin	750,000 IU
Metronidazole	125 mg

Light brown with brown spots, round and convex flavored chewable tablet with a cross-shaped break line on one side.

Tablets can be divided into 2 or 4 equal parts.

4. INDICATIONS

For the adjunct treatment of mechanical or surgical periodontal therapy in the treatment of multi-bacterial infections of periodontal and related (peri)oral conditions e.g.

Stomatitis (inflammation of the oral mucosa),

Gingivitis (inflammation of the gingiva),

Glossitis (inflammation of the tongue),

Periodontitis (periodontal inflammation)

Tonsillitis (inflammation of the tonsils),

Dental fistula and other fistulas wounds in the oral cavity,

Cheilitis (inflammation of the mucosa of the lips),

and sinusitis (inflammation of the sinuses) -

in dogs caused by microorganisms susceptible to spiramycin / metronidazole, such as Gram-positive bacteria and anaerobes. See also section 12 (special warnings).

5. CONTRAINDICATIONS

Do not use in case of hepatic disorders.

Do not use in case of hypersensitivity to spiramycin, metronidazole or to any of the excipients.

Do not use concomitantly with bactericidal antibiotics

6. ADVERSE REACTIONS

Vomiting has rarely been observed in dogs.

In rare cases hypersensitivity can occur. In cases of hypersensitivity reactions the treatment should be stopped.

In very rare cases disorders of spermatogenesis may occur.

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

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

If you notice any 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



Dogs

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

For oral administration.

75 000 IU spiramycin + 12.5 mg metronidazole per kg body weight, in more severe cases 100 000 IU spiramycin + 16.7 mg metronidazole per kg body weight, administered daily for 6 - 10 days depending on the severity of the disease. In severe cases one can start with the higher dose and go back in the course of treatment on to the lower dose.

The daily dose may be given once daily or divided equally for twice daily administration.

The treatment should always be continued for 1-2 days after resolution of symptoms in order to prevent relapses.

To ensure administration of the correct dosage bodyweight should be determined as accurately as possible to avoid underdosing. The following table is intended as a guide to dispensing the product at approximately the standard dose rate of 75 000 IU spiramycin + 12.5 mg metronidazole per kg body weight.

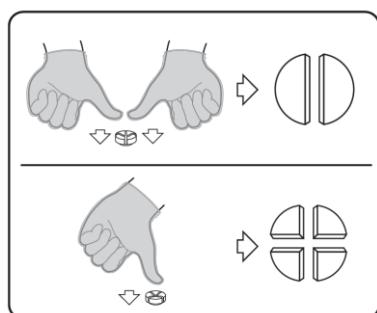
Bodyweight	Spizobactin 750,000 IU / 125 mg for dogs	Spizobactin 1,500,000 IU / 250 mg for dogs	Spizobactin-L 3,000,000 IU / 500 mg for dogs
2.5 kg	<input checked="" type="checkbox"/>		
5.0 kg	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
7.5 kg	<input checked="" type="checkbox"/>		
10 kg	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
12.5 kg	<input checked="" type="checkbox"/>		
15 kg	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
17.5 kg	<input checked="" type="checkbox"/>		
20 kg	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
25 kg	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
30 kg	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

35 kg			
40 kg			
50 kg			
60 kg			
70 kg			
80 kg			

= $\frac{1}{4}$ Tablet = $\frac{1}{2}$ Tablet = $\frac{3}{4}$ Tablet = 1 Tablet

9. ADVICE ON CORRECT ADMINISTRATION

The tablets are to be administered either deep in the mouth (on the base of the tongue) or given with a small amount of food containing the tablet, to ensure all the tablet is consumed. Tablets can be divided into 2 or 4 equal parts to ensure accurate dosing. Place the tablet on a flat surface, with its scored side facing up and the convex (rounded) side facing the surface.



Halves: press down with your thumbs on both sides of the tablet.

Quarters: press down with your thumb in the middle of the tablet

10. WITHDRAWAL PERIODS

Not applicable

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Shelf life of divided tablets after first opening the immediate packaging: 3 days.

Do not store above 30°C.

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

12. SPECIAL WARNINGS

In many cases of endodontic/periodontal disease the primary treatment is non-medicinal and does not require antimicrobial medication.

Antimicrobial treatment of periodontal disease should be accompanied or preceded by endodontic therapy and/or professional dental cleaning especially if the disease is advanced. Dog owners are encouraged to routinely brush their dog's teeth to remove plaque to prevent or to control periodontal disease

Special precautions for use in animals

The combination of spiramycin and metronidazole should not be used as first-line empirical treatment. Whenever possible, metronidazole and spiramycin should only be used based on susceptibility testing.

Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Treatment with this medicinal product must normally not exceed the specified treatment period (6 to 10 days). This time limit may only be exceeded in rare cases with particular strict indications.

Repetition of the treatment is also allowed only when having strict indications. Limiting the duration of treatment is necessary because damage to the germ cells cannot be excluded with the use of metronidazole, and because in long-term studies with high doses, an increase of certain tumours was seen in rodents.

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

Metronidazole has confirmed mutagenic and genotoxic properties in laboratory animals as well as in humans. Metronidazole is a confirmed carcinogen in laboratory animals and has possible carcinogenic effects in humans. However, there is inadequate evidence in humans for the carcinogenicity of metronidazole.

Spiramycin may in rare cases induce hypersensitivity reactions, e.g. contact dermatitis.

Direct contact with the skin or mucous membranes of the user should be avoided because of the risk of sensitization. Do not handle the product if you are known to be hypersensitive to the active substances or to any of the excipients. **IMPERVIOUS GLOVES SHOULD BE WORN** during administration of the product to avoid skin contact with the product.

To avoid accidental ingestion, particularly by a child, unused part-tablets should be returned to the open blister space and inserted back into the carton.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands thoroughly after handling the tablets.

Use during pregnancy and lactation

Spiramycin has not been found to be teratogenic or embryo- or foetotoxic. Studies in laboratory animals have shown inconsistent results with regard to teratogenic/embryotoxic effects of metronidazole. Therefore, use of this product during pregnancy is not recommended. Metronidazole and spiramycin are excreted in milk and use during lactation is therefore not recommended.

Interactions with other medicinal products and other forms of interaction

Macrolides, such as e.g. spiramycin act antagonistic to penicillins and cephalosporins.

The product should not be used concurrently with other antibiotics of the macrolide group.

Metronidazole may have an inhibitory effect on the degradation of other drugs in the liver, such as phenytoin, cyclosporine and warfarin.

Phenobarbital may increase hepatic metabolism of metronidazole resulting in decreased serum concentration of metronidazole.

Overdose (symptoms, emergency procedures, antidotes)

Adverse events are more likely to occur at doses and treatment durations in excess of the recommended treatment regimen. If neurological signs occur, treatment should be discontinued and the patient should be treated symptomatically.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCTS OR WASTE MATERIALS, IF ANY

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

Aluminium - PVC/PE/PVDC blister

Cardboard box of 1, 2 or 3 blisters of 10 tablets

Cardboard box containing 10 separate cardboard boxes, each containing 1 blister of 10 tablets.

Not all pack sizes may be marketed.

Divisible tablet

