ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Yarvitan 5 mg/ml oral solution for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Mitratapide 5 mg/ml

Excipient(s):

Butylated hydroxyanisole (E 320) 2 mg/ml

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution.
A colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

As an aid in the management of overweight and obesity in adult dogs. To be used as part of an overall weight management programme which also includes appropriate dietary changes. Introducing appropriate lifestyle changes (e.g. increased exercise), in conjunction with this weight management programme, may provide additional benefits.

4.3 Contraindications

Do not use in dogs with impaired liver function.
Do not use in case of hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs during pregnancy and lactation.
Do not use in dogs less than 18 months of age.
Do not use in dogs in which overweight or obesity is caused by a concomitant systemic disease such as hypothyroidism or hyperadrenocorticism.

4.4 Special warnings

None.

4.5 Special precautions for use

Special precautions for use in animals

The use in dogs for breeding purposes has not been evaluated.

If vomiting, significantly reduced appetite or diarrhoea repeatedly occurs, treatment should be interrupted and the advice of a veterinarian should be sought. Where treatment is interrupted due to vomiting, it is recommended that when treatment is resumed, the product should be administered after a meal. In addition, treatment should be interrupted and the advice of a veterinarian should be sought where the observed body weight loss is severe and rapid.

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

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

If accidental eye contact occurs, flush immediately with copious amounts of water.

4.6 Adverse reactions (frequency and seriousness)

A decreased appetite may occur during treatment. This is related to the mode of action of the product and should not be considered as an adverse reaction unless it becomes very significant.

Vomiting, diarrhoea or softened stools may occur during treatment. In most cases, these effects are mild and transient. In case an adverse reaction repeatedly occurs or in case the dog stops eating for two consecutive days, treatment should be interrupted and the advice of a veterinarian should be sought. In laboratory studies, decreases in serum albumin, globulin, total protein, calcium and alkaline phosphatase and increases in ALT and AST were detected following administration of the product at the recommended treatment dose. In addition, hyperkalaemia was occasionally observed. Generally, the severity of these effects increased with increasing dose. Typically, these findings normalised, or appeared to be reversing, within two weeks following the end of treatment.

The following adverse reactions were observed during the clinical trials (pooled data*):

Clinical observation	Mitratapide	Placebo
vomiting : occasional (≤ 3x)	20.0%	5.6 %
vomiting : repeated (> 3 x)	10.0 %	2.2 %
diarrhoea / soft stools	10.0%	4.4 %
anorexia / decreased appetite	17.8%	10.0 %
lethargy / weakness	5.2%	2.2 %

* data from 360 dogs over the whole treatment period.

4.7 Use during pregnancy, lactation or lay

Do not use in dogs during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

No drug interactions were observed in studies where Yarvitan was administered concomitantly with NSAIDs (carprofen, meloxicam) or ACE inhibitors (enalapril, benazepril). Interactions with other drug types were not specifically investigated. The absorption of lipid soluble drugs used concomitantly with mitratapide has not been investigated. Therefore, for dogs receiving treatments in addition to the product, drug interactions should be monitored closely.

4.9 Amounts to be administered and administration route

Administer orally once daily at 0.63 mg mitratapide/kg bodyweight (1 ml of the product per 8 kg) given for 2 periods of 21 days with 14 days without treatment in between. In order to allow proper dosing, the dog should be weighed on day 1 and on day 35 (i.e. at the start of each treatment period). Treatment should be given with food. Use the dosing pipette as provided with the product.

During the first 21 days of treatment, the quantity of food the animal receives may remain unchanged. Thereafter, feeding should be in accordance with energy requirements for maintenance (to be calculated by the veterinarian). This can be achieved either with a regular pet food or with a low calorie (diet) pet food.

In clinical trials, treated animals rapidly regained weight following cessation of treatment when diet was not restricted. In order to avoid this rebound weight gain, it is necessary to continue the feeding for maintenance regimen after the end of treatment with the product.

Mitratapide therapy should be restricted to one treatment course for an individual dog.

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

The following clinical signs were observed after 3 or 5 times overdosing in dogs: softened or liquid faeces, vomiting, salivation, anorexia, severe weight loss, emaciated appearance, dehydration and pale mucosae.

In case of accidental overdosing, symptomatic therapy should be administered. No specific antidote is available.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Peripherally acting antiobesity products, ATCvet Code: QA08AB90

5.1 Pharmacodynamic properties

Mitratapide is a potent inhibitor of the microsomal triglyceride transfer protein (MTP). Administration of mitratapide to dogs results in reduced uptake of dietary lipids, dose dependent decreases in serum cholesterol and triglyceride and an increased presence of triglyceride containing droplets in enterocytes. It is assumed that these effects are mediated by MTP inhibition at the level of the enterocyte. This results in blockage of the uptake of dietary lipids. Mitratapide also has a slight appetite decreasing effect, which is linked to its mode of action. Accumulation of triglycerides inside the enterocytes may be followed by decreased appetite. Mitratapide has no central effect.

In clinical trials, the following weight loss percentages were obtained:

Percentages of dogs per weight loss category for mitratapide versus placebo:

weight loss category	% of treated dogs*					
	EU field trial		US field trial		pooled data	
	placebo	mitratapide	placebo	mitratapide	placebo	mitratapide
≥ 10 %	6.8	25.2	9.5	22.5	8.1	23.8
≥ 7.5 %	11.4	41.7	11.9	47.3	11.6	44.5
≥ 5 %	22.7	63.8	31.0	65.1	26.7	64.4

*: in line with the recommended treatment schedule

5.2 Pharmacokinetic particulars

Laboratory animals and dogs rapidly absorb orally administered mitratapide. The most important metabolic transformation is sulphoxidation, which produces three active metabolites. Following oral administration, the bioavailability of mitratapide (parent compound and metabolites) is in the range from 55 to 69%, the volume of distribution is approximately 5 l/kg. Mitratapide and its metabolites bind very extensively (> 99 %) to plasma proteins and distribute to the tissues. After multiple dosing, the highest concentrations are present in the adrenal glands, liver, jejunum and kidney, but there is no exposure in the brain, excluding any central effect of the product. Excretion is rapid and mainly via the faeces.

In fed dogs, a single dose of 0.63 mg mitratapide/kg bodyweight results in maximum concentrations of the parent substance in plasma of on average 0.012 µg/ml attained 3.5 hours after dosing; the sulphoxide metabolites reach maximum concentration of on average 0.0136 µg/ml and 0.0168 µg/ml, respectively after 6.5 hours and 8.5 hours; the sulphone metabolite reaches 0.0092 µg/ml after 17.5 hours. At the end of a three week dosing period, mitratapide attains average steady-state concentrations of 0.0068 µg/ml, the sulphoxide metabolites 0.0089 µg/ml and 0.0167 µg/ml, respectively, the sulphone 0.0471 µg/ml. The terminal plasma half-life is 6.3 hours for mitratapide, 9.8 hours and 11.7 hours for the sulphoxides, respectively, and 44.7 hours for the sulphone metabolite. The pharmacokinetic parameters display variable dependency on dose and vary slightly between the first and the second three week treatment periods of a complete treatment schedule.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucralose
Butylated hydroxyanisole
Macrogol 400

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years
Shelf-life after first opening the immediate packaging: 3 months

6.4 Special precautions for storage

Do not refrigerate.This veterinary medicinal product does not require any special storage conditions.
After each dose, the pipette should be washed and dried and the bottle cap screwed back on tightly.

6.5 Nature and composition of immediate packaging

55, 120 or 210 ml amber glass bottle (type III) with a child resistant polypropylene closure and dosing pipette. The dosing pipette has a gradation in body weight:

- up to 36 kg for the 55 ml bottle
- up to 86 kg for the 120 ml bottle
- up to 48 kg for the 210 ml bottle

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

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/06/063/001-3

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/11/2006

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION REGARDING SUPPLY OR USE

C. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION WITH REGARD TO SAFE AND EFFECTIVE USE

D. STATEMENT OF THE MRLs

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION REGARDING SUPPLY OR USE

To be supplied only on veterinary prescription.

C. CONDITIONS OR RESTRICTIONS OF THE MARKETING AUTHORISATION WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE PRODUCT

Not applicable.

D. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Yarvitan 5 mg/ml oral solution for dogs

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Mitratapide 5 mg/ml

3. PHARMACEUTICAL FORM

Oral solution.

4. PACKAGE SIZE

55 ml: ≤ 10 kg BW
120 ml: ≤ 22 kg BW
210 ml: ≤ 40 kg BW

5. TARGET SPECIES

Dogs

6. INDICATION(S)

As an aid in the management of overweight and obesity in adult dogs.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP:
Once opened, use within 3 months.

11. SPECIAL STORAGE CONDITIONS

Do not refrigerate.

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

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

Janssen Pharmaceutica N.V.
B-2340 Beerse, Belgium

16. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/001	55 ml
EU/0/00/000/002	120 ml
EU/0/00/000/003	210 ml

17. MANUFACTURER'S BATCH NUMBER

Lot

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL AMBER GLASS BOTTLE 55 ML

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Yarvitan 5 mg/ml oral solution for dogs

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Mitratapide 5 mg/ml

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

55 ml

4. ROUTE(S) OF ADMINISTRATION

Oral use.

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Lot:

7. EXPIRY DATE

EXP {month/year}
Once opened, use within 3 months.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

LABEL AMBER GLASS BOTTLE 120 and 210 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Yarvitan 5 mg/ml oral solution for dogs

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Mitratapide 5 mg/ml

3. PHARMACEUTICAL FORM

Oral solution

4. PACKAGE SIZE

120 ml
210 ml

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP:
Once opened, use within 3 months.

11. SPECIAL STORAGE CONDITIONS

Do not refrigerate

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

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"

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Pharmaceutica N.V.
B-2340 Beerse, Belgium

16. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/002 120 ml
EU/0/00/000/003 210 ml

17. MANUFACTURER'S BATCH NUMBER

Lot:

B. PACKAGE LEAFLET

PACKAGE LEAFLET
Yarvitan 5 mg/ml oral solution for dogs

Read all of this leaflet carefully before you start administering the medicine to your dog:
- *Keep this leaflet. You may need to read it again*
- *If you have further questions, please ask your veterinary surgeon or your pharmacist*
- *This medicine has been prescribed for your dog only and you should not pass it on to others.*

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

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340 Beerse
Belgium

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Yarvitan 5 mg/ml oral solution for dogs
Mitratapide

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

Mitratapide 5 mg/ml
Butylated hydroxyanisole (E 320)
Yarvitan is a colourless to slightly yellow solution.

4. INDICATION(S)

Yarvitan is indicated as an aid in the management of overweight and obesity in adult dogs. The treatment is part of an overall weight management programme which also includes a nutrition programme. Introducing appropriate lifestyle changes (e.g. increased exercise), in conjunction with this weight management programme, may provide additional benefits.

5. CONTRAINDICATIONS

Do not administer Yarvitan:
- if your dog has impaired liver function.
- if your dog is hypersensitive (allergic) to mitratapide or to any of the other ingredients.
- if your dog is pregnant or during lactation.
- in dogs less than 18 months of age.
- if overweight or obesity in your dog is caused by a concomitant systemic disease such as hypothyroidism (this is due to a malfunction of the thyroid gland) or hyperadrenocorticism.(this is due to a malfunction of the adrenal gland).

6. ADVERSE REACTIONS

Tell your veterinary surgeon if you notice any of the following:

- significant loss of appetite. Loss of appetite may occur during treatment. This is related to the mode of action of the product and should not be considered as a side effect, unless it becomes very significant (this is when your dog stops eating for two consecutive days).
- vomiting
- diarrhoea
- softened stools

In most of the cases, these side effects are mild and do not last very long. In case a side effect repeatedly occurs or in case the dog stops eating for two consecutive days, stop the administration of Yarvitan to your dog and seek the advice of your veterinary surgeon as soon as possible. In laboratory studies, decreases in serum albumin, globulin, total protein, calcium and alkaline phosphatase and increases in ALT and AST were detected following administration of the product at the recommended treatment dose. In addition, hyperkalaemia was occasionally observed. Generally, the severity of these effects increased with increasing dose. Typically, these findings normalised, or appeared to be reversing, within two weeks following the end of treatment.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

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

Always administer Yarvitan exactly as your veterinary surgeon has instructed you. You should check with your veterinary surgeon if you are unsure. The usual dose is once daily 0.63 mg mitratapide/kg bodyweight (1 ml of the product per 8 kg). The dosing pipettes provided with the product show graduations corresponding to the correct body weight of the dog.

Administer the product orally during 2 periods of 21 days with an interval of 14 days without treatment in between.

Day 1-21	Day 22-35	Day 36-56
treatment	no treatment	treatment
normal feeding	nutrition programme	nutrition programme

9. ADVICE ON CORRECT ADMINISTRATION

In order to allow proper dosing, the dog should be weighed on day 1 and day 35 (this is at the start of each treatment period).

Use the dosing pipette as provided with the product. Fill the syringe by pulling the plunger until it reaches the mark on the dosing pipette corresponding to the correct body weight of the dog.

Treatment should be given with food. Therefore, administer the product with the syringe onto a portion of the food. Once the dog has eaten the complete portion, give the remaining amount of food to the dog.

After each dose, the syringe should be removed from the bottle. The pipette should be washed and dried and the cap should be screwed back on tightly.

During the first 21 days of treatment, the quantity of food the animal receives may remain unchanged. Thereafter, your dog should follow a nutrition programme. Your veterinary surgeon will advise you on the type of food your dog will need. This can be achieved either with a regular pet food or with a low calorie (diet) pet food.

In order to avoid rebound weight gain, it is necessary to continue the feeding for maintenance regimen after the end of treatment with the product.

Mitratapide therapy should be restricted to one treatment course for an individual dog.

10. WITHDRAWAL PERIOD

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the reach and sight of children.
Do not refrigerate.
This veterinary medicinal product does not require any special storage conditions.
Do not use after the expiry date stated on the label and carton (EXP.).
Shelf-life after first opening the container: 3 months.

12. SPECIAL WARNING(S)

Special precautions for use in animals
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. The use in dogs for breeding purposes has not been evaluated.

Please inform your veterinary surgeon if your dog is taking or has recently taken any other medicines, even those not prescribed. No drug interactions were observed in studies where Yarvitan was administered concomitantly with NSAIDs (carprofen, meloxicam) or ACE inhibitors (enalapril, benazepril). The absorption of lipid soluble drugs used concomitantly with mitratapide has not been investigated. Your veterinary surgeon should monitor closely the intake of any other medicines in addition to the product.

In case vomiting, diarrhoea, softening stools repeatedly occurs or in case the dog stops eating for two consecutive days, stop the administration of Yarvitan to your dog and seek the advice of your veterinary surgeon as soon as possible. Where treatment is interrupted due to vomiting, it is recommended that when treatment is resumed, the product should be administered after a meal. In addition, treatment should be interrupted and the advice of a veterinarian should be sought where the observed body weight loss is severe and rapid.

In case of accidental overdosing, symptomatic therapy should be administered. No specific antidote is available.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
In case of accidental self-administration, seek medical advice immediately and show the package leaflet or the label to the physician.
If accidental eye contact occurs, flush immediately with copious amounts of water.

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

Medicines should not be disposed of via wastewater or household waste.

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

07/2007

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

15. OTHER INFORMATION

Pack sizes – amber glass bottles containing : 55ml: ≤ 10 kg bodyweight, 120ml: ≤ 22 kg bodyweight, 210ml: ≤ 40 kg bodyweight.
Not all pack sizes may be marketed.