ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MASIVET 50 mg film-coated tablets for dogs
MASIVET 150 mg film-coated tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Active substance:
Masitinib 50 mg (equivalent to masitinib mesylate 59.6 mg)
Masitinib 150 mg (equivalent to masitinib mesylate 178.9 mg)

Excipients.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Light-orange, round shape, film-coated tablet embossed with "50" or "150" on one side and the company logo on the other side.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

Treatment of non-resectable dog mast cell tumours (Grade 2 or 3) with confirmed mutated c-kit tyrosine kinase receptor.

4.3 Contraindications

Do not use in pregnant or lactating bitches (see section 4.7).
Do not use in dogs less than 6 months of age or less than 4 kg body weight.
Do not use in dogs suffering from liver impairment, defined as AST or ALT > 3 x Upper Limit of Normal (ULN). Do not use in dogs suffering from renal function impairment, defined as Urinary Protein Creatinine (UPC) ratio > 2 or albumin < 1 x Lower Limit of Normal (LLN).
Do not use in dogs with anaemia (haemoglobin < 10 g/dl).
Do not use in dogs with neutropenia defined as absolute neutrophil count < 2,000 /mm^3.
Do not use in case of hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings

For any mast cell tumour treatable by surgery, surgery should be the first choice of treatment.
Masitinib treatment should only be used in dogs with non-resectable mast cell tumours and which express the mutated c-kit tyrosine kinase receptor. The presence of a mutated tyrosine kinase c-kit receptor must be confirmed prior to treatment (see also section 5.1).

4.5 Special precautions for use

Special precautions for use in animals

Dogs should be carefully monitored and treatment might need to be adjusted or discontinued, if necessary.

Monitoring of renal function
Renal function should be adequately monitored every month using dipstick urine testing.
In case of positive semiquantitative dipstick results (protein ≥ 30 mg/dl), urinalysis should be performed to determine urinary protein creatinine (UPC) ratio, and a blood sample to measure creatinine, albumin and BUN.
If UPC ratio > 2, or creatinine > 1.5 upper limit of normal (ULN), or albumin < 0.75 lower limit of normal (LLN) or blood urea nitrogen (BUN) > 1.5 ULN, discontinue treatment.

Monitoring of Protein loss syndrome
Perform every month a dipstick urine test. In case of positive semi-quantitative dipstick results (protein ≥ 30 mg/dl), perform urinalysis to determine urinary protein creatinine (UPC) ratio.
Perform every month a blood measurement of albumin.

- In case of UPC ratio > 2 or albumin < 0.75 lower limit of normal (LLN), treatment should be interrupted until albumin and UPC values have returned to limit value (UPC ratio < 2 and albumin > 0.75 LLN), treatment can then be continued at the same dose.
- If of one of these events (UPC ratio > 2 or albumin < 0.75 LLN) occurs for a second time, treatment should be permanently discontinued.

Anaemia and/or haemolysis
Dogs should be carefully monitored for signs of (haemolytic) anaemia. In case of clinical signs of anaemia or haemolysis, haemoglobin, free bilirubin and haptoglobin should be measured and blood cell counts (including reticulocyte) should be performed.
Treatment should be discontinued in case of:

- Haemolytic anaemia, i.e. haemoglobin < 10 g/dl and haemolysis, i.e. free bilirubin > 1.5 ULN and haptoglobin < 0.1 g/dl,
- Anaemia due to lack of regeneration, i.e. haemoglobin< 10 g/dl and reticulocytes < 80,000/mm^3.

Hepatic toxicity (ALT or AST elevation), neutropenia
In case of an increase of ALT or AST > 3 ULN, decrease of neutrophil count < 2,000/mm^3 or any other severe adverse events, treatment should be modified as follows:
At the first occurrence, treatment should be interrupted until resolution, and then resumed at the same dose level;
At the second occurrence of the same event, treatment should be interrupted until resolution; treatment should then be continued with a reduced dose of 9 mg/kg bodyweight/day;
At the third occurrence of the same event, treatment should be interrupted until resolution; treatment should then be continued with a dose further reduced to 6 mg/kg/day;
Treatment should be discontinued, if severe adverse reactions are still encountered at the 6 mg/kg/day dose.

Other precautions
Treatment should be permanently discontinued in case of renal toxicity, immune-mediated haemolytic anaemia (IMHA) and/or anaemia due to lack of regeneration, and if severe neutropenia, and/or severe diarrhoea and/or severe vomiting persist after dose reduction.

Dogs should not be used for breeding while under treatment.

Summary of thresholds for laboratory evaluations resulting in contra-indication or treatment modification (interruption, dose reduction or discontinuation)

Management of Hepatic Toxicity (ALT or AST)			
Contra-indication	**Interruption**	**Dose reduction**	**Discontinuation**
> 3 ULN	> 3ULN (1^{st} time)	> 3 ULN (2^{nd}/3^{rd} time)	> 3ULN (4^{th} time)
Management of Neutropenia (neutrophil counts)			
Contra-indication	**Interruption**	**Dose reduction**	**Discontinuation**
< 2,000/mm^3	< 2,000/mm^3 (1^{st} time)	< 2,000/mm^3 (2^{nd}/3^{rd} time)	< 2,000/mm^3 (4^{th} time)
Management of Protein-Loss Syndrome (Albuminemia and/or UPC)			
Contra-indication	**Interruption**	**Dose reduction**	**Discontinuation**
Albumin < 1 LLN or UPC > 2	Albumin < 0.75 LLN or UPC >2 (1^{st} time)	Not applicable	Albumin < 0.75 LLN or UPC > 2 (2^{nd} time)
Management of Haemolytic and aregenerative Anaemia (haemoglobin, bilirubin, haptoglobin, reticulocytes)			
Contra-indication	**Interruption**	**Dose reduction**	**Discontinuation**
Haemoglobin < 10 g/dL	Not applicable	Not applicable	Haemoglobin < 10 g/dl and either free bilirubin > 1.5 ULN and haptoglobin < 0.1 g/dl or reticulocytes < 80,000/mm^3

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

Repeated dermal contact with masitinib may impair female fertility and foetal development.
The active substance of Masivet can cause skin sensitisation.

- Avoid skin contact with faeces, urine, and vomit of treated dogs.
- Wear protective gloves while disposing of vomit, urine or faeces of treated dogs.
- If broken tablets, vomit, urine or faeces of treated dogs come into contact with the skin, rinse immediately with plenty of water.

The active substance of Masivet can cause severe eye-irritation and serious damage to the eyes.

- Avoid contact with the eyes.
- Take care not to touch the eyes before gloves have been removed and disposed of and the hands have been thoroughly washed.
- If the product comes into contact with the eyes, rinse immediately with plenty of water.

People with known hypersensitivity to masitinib should not handle the product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Do not eat, drink, or smoke when treating the dog.
Children should not have close contact to treated dogs, treated dog faeces or vomit.

4.6 Adverse reactions (frequency and seriousness)

Very common

- Mild to moderate gastrointestinal reactions (diarrhoea and vomiting) with a mean duration of approximately 21 and 9 days, respectively.
- Mild to moderate alopecia with a mean duration of approximately 26 days.

Common

- Severe renal toxicity may occur in dogs suffering from renal disorders at the start of treatment (including high blood creatinine level or proteinuria).
- Moderate to severe anaemia (aplastic/haemolytic) with a mean duration of approximately 7 days.
- Protein-loss syndrome (mainly due to a decrease in serum albumin).

- Mild or moderate neutropenia with a mean duration of approximately 24 days.
- Increase in aminotransferase (ALT or AST) with a mean duration of approximately 29 days.

Specific measures to be taken in case of the above reactions are described in section 4.5.

Other commonly observed adverse reactions were in most cases mild or moderate:
- Lethargy and asthenia with a mean duration of approximately 8 and 40 days, respectively.
- Decrease in appetite or anorexia with a mean duration of 45 days and 18 days, respectively.
- Cough (mean duration 23 days).
- Lymphadenopathy (mean duration 47 days).
- Oedema (mean duration of oedema was 7 days).
- Lipoma (mean duration 53 days).

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)

4.7 Use during pregnancy, lactation or lay

Do not use in pregnant or lactating bitches. Laboratory studies in rats have shown evidence of impaired female fertility at dose of 100 mg/kg/day, embryotoxicity and developmental toxicity at dose above 30 mg/kg/day. Studies in rabbits did however not reveal embryotoxicity or developmental toxicity.

4.8 Interaction with other medicinal products and other forms of interaction

In vitro tests with human microsomes demonstrate that concomitant treatment with substances which are metabolised by CYP450 isoforms may result in higher or lower plasma levels of either masitinib or those substances. No corresponding information is available for dogs. Hence, caution is advised with the concurrent use of masitinib and other substances.
Concurrent use of other substances with a high degree of protein binding may compete with masitinib binding and thus cause adverse effects.
The efficacy of Masivet might be reduced in dogs previously treated with chemotherapy and/or radiotherapy. No information relating to potential cross-resistance with other cytostatic products is available.

4.9 Amounts to be administered and administration route

For oral use.

The recommended dose is 12.5 mg/kg (with a dose range of 11–14 mg/kg) once daily as presented in the table below.

In dogs with a bodyweight of less than 15 kg accurate dosing is not always possible. These dogs may be treated with either 50, 100 or 150 mg, if it is feasible to achieve a target dose of 11–14 mg/kg bw.

The tablets must be administered as a whole and should not be divided, broken or ground. If a broken tablet is rejected by the dog after chewing, it should be disposed of.
Tablets should always be administered in the same manner, with food.

12.5 mg/kg bw		Number of tablets per day			Dose mg/kg	
Dog body-weight in kg		50 mg		150 mg	lower weight	upper weight
≥ 15	18	1	plus	1	13.7	11.1
> 18	22	2	plus	1	13.9	11.4
> 22	26			2	13.6	11.5
> 26	30	1	plus	2	13.5	11.7
> 30	34	2	plus	2	13.3	11.8
> 34	38			3	13.2	11.8
> 38	42	1	plus	3	13.2	11.9
> 42	46	2	plus	3	13.1	12.0
> 46	50			4	13.0	12.0
> 50	54	1	plus	4	13.0	12.0
> 54	58	2	plus	4	13.0	12.1
> 58	62			5	12.9	12.1
> 62	66	1	plus	5	12.9	12.1
> 66	70	2	plus	5	12.9	12.1
> 70	74			6	12.9	12.2
> 74	78	1	plus	6	12.8	12.2
> 78		2	plus	6	12.8	

If the tablet is regurgitated or vomited within 10 minutes following administration, treatment should be repeated. If the tablet is regurgitated or vomited later than 10 minutes following administration, treatment should not be repeated.

The treatment should be reviewed after 4 to 6 weeks in order to assess the initial response. Duration of treatment depends on the response to treatment. Treatment should be maintained in the case of stable disease, i.e. static, partial or complete tumour response, provided that the product is sufficiently well tolerated. In case of tumour progression, treatment is unlikely to be successful and the treatment should be reviewed.

Dose reduction, treatment interruption and treatment discontinuation:

Dogs should be monitored carefully and professional judgement should be used to determine the need for dose reduction in the event of possible significant adverse reactions (see section 4.5). Doses can be reduced to 9 mg/kg bodyweight (range 7.5–10.5 mg/kg) or 6 mg/kg bw (range 4.5–7.5 mg/kg) according to the tables below.
During clinical studies, the daily dose was decreased due to adverse events in approximately 16 % of treated dogs and mainly due to an increase in transaminases.

9 mg per kg bodyweight once daily as presented in the table below.

Dog body-weight in kg		Number of tablets per day 50 mg		150 mg	Dose mg/kg lower weight	upper weight
≥ 15.0	19.4			1	10.0	7.7
> 19.4	25.0	1	plus	1	10.3	8.0
> 25.0	30.6	2	plus	1	10.0	8.2
> 30.6	36.1			2	9.8	8.3
> 36.1	41.7	1	plus	2	9.7	8.4
> 41.7	47.2	2	plus	2	9.6	8.5
> 47.2	52.8			3	9.5	8.5
> 52.8	58.3	1	plus	3	9.5	8.6
> 58.3	63.9	2	plus	3	9.4	8.6
> 63.9	69.4			4	9.4	8.6
> 69.4	75.0	1	plus	4	9.4	8.7
> 75.0	80.6	2	plus	4	9.3	8.7

6 mg per kg bodyweight once daily as presented in the table below.

Dog body-weight in kg		Number of tablets per day 50 mg		150 mg	Dose mg/kg lower weight	upper weight
≥ 15.0	20.8	2			6.6	4.8
> 20.8	29.2			1	7.2	5.1
> 29.2	37.5	1	plus	1	6.9	5.3
> 37.5	45.8	2	plus	1	6.7	5.5
> 45.8	54.2			2	6.5	5.5
> 54.2	62.5	1	plus	2	6.5	5.6
> 62.5	70.8	2	plus	2	6.4	5.6
> 70.8	79.2			3	6.4	5.7
> 79.2		1	plus	3	6.3	

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

The recommended daily dose of 12.5 mg/kg body weight corresponds to the Maximum Tolerated Dose (MTD) that was derived from repeat dose toxicity studies in healthy Beagle dogs.

Overdosing signs were observed in toxicity studies conducted in healthy dogs, treated for 39 weeks at doses of around 2 times the recommended dose (25 mg masitinib), treated for 13 weeks and 4 weeks at doses of around 3 times the recommended dose (41.7 mg masitinib), and treated for 4 weeks at doses of around 10 times the recommended dose (125 mg masitinib). The main target organs of toxicity in dogs are the gastrointestinal tract, the haematopoetic system, the kidney and the liver.

In case of adverse events following overdose, treatment should be discontinued until resolution, and then resumed at the recommended therapeutic dose level.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: protein-tyrosine kinase inhibitor.
ATCvet code: QL01XE90.

5.1 Pharmacodynamic properties

Masitinib is a protein-tyrosine kinase inhibitor which, *in vitro*, potently and selectively inhibits the mutated form, in the juxtamembrane (JM) region, of the c-kit receptor. It also inhibits the Platelet Derived Growth Factor (PDGF) receptor and the Fibroblast Growth Factor Receptor (FGFR3).

In the pivotal clinical field study, dogs of various breeds, ranging in age from two to seventeen years, were randomly treated with Masivet at a dose of 12.5 mg/kg or with a placebo. In dogs with non-resectable mast cell tumours, Grade 2 or 3, expressing a mutated tyrosine kinase c-kit receptor, treatment with Masivet showed a significantly longer Time-to-Tumour Progression (TTP) with a median of 241 days as compared to 83 days for placebo. Response to treatment with masitinib was expressed as stable disease; i.e. static, partial or complete response.

Masitinib treatment should only be used in dogs with non-resectable mast cell tumours, which express the mutated c-kit tyrosine kinase receptor. The presence of a mutated tyrosine kinase c-kit receptor must be confirmed prior to treatment.

5.2 Pharmacokinetic particulars

Following oral administration in dogs at a dose of 11.2 mg (±0.5 mg) per kg of bodyweight, masitinib is rapidly absorbed and the time to maximal concentration (T_{max}) is approximately 2 hours. The elimination half-life (t½) is approximately 3–6 hours. Masitinib is approximately 93 % bound to plasma proteins.

Masitinib is metabolised predominantly by N-dealkylation. Excretion takes place in the bile.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Povidone K30
Pig liver powder
Crospovidone
Magnesium stearate

Tablet coating:
Macrogol 3350
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Sunset yellow (E110) aluminium lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 4 years.

6.4. Special precautions for storage

Keep the bottle tightly closed.

6.5 Nature and composition of immediate packaging

White HDPE bottle closed with a thermosealable film and covered by a child-resistant closure cap.
30 ml bottle containing 30 Masivet 50 mg film-coated tablets.
40 ml bottle containing 30 Masivet 50 mg film-coated tablets.
60 ml bottle containing 30 Masivet 150 mg film-coated tablets.

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

AB Science S.A.
3 avenue George V
75008 Paris
France
Tel.: +33 (0)1 47 20 00 14
Fax: +33 (0)1 47 20 24 11
MASIVET@ab-science.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/08/087/001
EU/2/08/087/002
EU/2/08/087/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17/11/2008

10. DATE OF REVISION OF THE TEXT

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

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Centre Spécialités Pharmaceutiques
Avenue du Midi
63800 Cournon d'Auvergne
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton Box Labelling

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MASIVET 50 mg film-coated tablets for dogs
Masitinib

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Masitinib 50 mg

3. PHARMACEUTICAL FORM

Film coated tablet

4. PACKAGE SIZE

30 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed.

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

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only - to be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AB Science
3 avenue George V
FR-75008
Paris
France

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/08/087/001
EU/2/08/087/003

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGE UNITS

Label

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MASIVET 50 mg film-coated tablets for dogs
Masitinib

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Masitinib 50 mg

3. CONTENTS

30 tablets

4. ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

5. WITHDRAWAL PERIOD

Not applicable

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton Box Labelling

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MASIVET 150 mg film-coated tablets for dogs
Masitinib

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Masitinib 150 mg

3. PHARMACEUTICAL FORM

Film coated tablet

4. PACKAGE SIZE

30 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed.

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

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only - to be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE REACH AND SIGHT OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AB Science
3 avenue George V
FR-75008 Paris
France

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/08/087/002

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGE UNITS

Label

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MASIVET 150 mg film-coated tablets for dogs
Masitinib

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Masitinib 150 mg

3. CONTENTS

30 tablets

4. ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

5. WITHDRAWAL PERIOD

Not applicable.

5. BATCH NUMBER

Lot {number}

6. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

MASIVET 50 mg film-coated tablets for dogs
MASIVET 150 mg film-coated 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:

AB Science S.A.
3 avenue George V
FR-75008 Paris
France

Manufacturer for batch release:

Centre Spécialités Pharmaceutiques
Avenue du Midi
63800 Cournon d'Auvergne
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

MASIVET 50 mg film-coated tablets for dogs
MASIVET 150 mg film-coated tablets for dogs

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

MASIVET is a light-orange, round, film-coated tablet.
Each tablet contains either 50 mg or 150 mg of masitinib, which is the active substance. Each tablet also contains Sunset yellow FCF (E 110) aluminium lake and Titanium dioxide (E171) as colourants. The tablets are market with "50" or "150" on one side, and with the company logo on the other side.

4. INDICATION(S)

Masivet is for the treatment of dogs with non-resectable mast cell tumours (Grade 2 or 3) with a confirmed mutated c-kit tyrosine kinase receptor.

5. CONTRAINDICATIONS

Your dog should not be given Masivet if it:

- is pregnant or nursing puppies,
- is less 6 months of age or weights less than 4 kg,
- is suffering from inadequate liver or renal function,
- has an anaemia or low neutrophil count,
- has an allergic reaction to masitinib, the active ingredient of Masivet or an excipient used in this medicine.

6. ADVERSE REACTIONS

Should I expect side effects for my dog during Masivet therapy?
Masivet like any other medicine may cause adverse reactions. Your veterinarian can best describe these for you.

Very common effects:
- Mild to moderate gastrointestinal reactions (diarrhoea and vomiting) with a mean duration of approximately 21 and 9 days, respectively.
- Mild to moderate hair loss with a mean duration of approximately 26 days.

Common effects:
Specific measures should be taken by your veterinarian in case of the following reactions (see section 15):
- Severe renal toxicity may occur in dogs suffering from renal disorders at the start of treatment (including high blood creatinine level or proteinuria).
- Moderate to severe anaemia (aplastic/haemolytic) with a mean duration of approximately 7 days.
- Protein-loss syndrome (mainly due to a decrease in serum albumin).
- Mild or moderate neutropenia with a mean duration of approximately 24 days.
- Increase in aminotransferase (ALT or AST) with a mean duration of approximately 29 days.

Other, commonly observed adverse reactions were in most cases mild or moderate:
- Lethargy and asthenia with a mean duration of approximately 8 and 40 days, respectively.
- Decrease in appetite or anorexia with a mean duration of 45 days and 18 days, respectively.
- Cough (mean duration 23 days).
- Lymphadenopathy (mean duration 47 days).
- Oedema (mean duration of oedema was 7 days).
- Lipoma (mean duration 53 days).

What should I do if side effects occur in my dog during Masivet treatment?
If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinarian. In case of adverse reactions, your veterinarian may decide to reduce the dose or to discontinue treatment.

7. TARGET SPECIES

Dogs.

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

Masivet is for oral use in dogs and should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount is right for your dog.

The recommended dose is 12.5 mg/kg (with a dose range of 11–14 mg/kg) once daily as presented in the table below. In dogs with a bodyweight of less than 15 kg, accurate dosing is not always possible. These dogs may be treated with either 50, 100 or 150 mg, if it is feasible to achieve a target dose of 11–14 mg/kg bw.

12.5 mg/kg bw		Number of tablets per day			Dose mg/kg	
Dog body-weight in kg		50 mg		150 mg	lower weight	upper weight
≥ 15	18	1	plus	1	13.7	11.1
> 18	22	2	plus	1	13.9	11.4
> 22	26			2	13.6	11.5
> 26	30	1	plus	2	13.5	11.7
> 30	34	2	plus	2	13.3	11.8
> 34	38			3	13.2	11.8
> 38	42	1	plus	3	13.2	11.9
> 42	46	2	plus	3	13.1	12.0
> 46	50			4	13.0	12.0
> 50	54	1	plus	4	13.0	12.0
> 54	58	2	plus	4	13.0	12.1
> 58	62			5	12.9	12.1
> 62	66	1	plus	5	12.9	12.1
> 66	70	2	plus	5	12.9	12.1
> 70	74			6	12.9	12.2
> 74	78	1	plus	6	12.8	12.2
> 78		2	plus	6	12.8	

If the tablet is regurgitated or vomited within 10 minutes following administration, treatment should be repeated. If the tablet is regurgitated or vomited later than 10 minutes following administration, treatment should not be repeated.

9. ADVICE ON CORRECT ADMINISTRATION

How should I administer Masivet to my dog, and for how long?

Tablets should always be administered in the same manner, with food. The tablets must be administered as a whole and should not be divided, broken or ground. If a broken tablet is rejected by the dog after chewing, it should be disposed of.
If a dose is missed, the next schedule dose should be given as prescribed. Do not increase or double the dose. If more than the prescribed amount of tablets were given, contact your veterinarian.
Duration of treatment will be dependent on the response observed. Treatment should be maintained in the case of stable disease, i.e. static, partial or complete tumour response, provided that the product is sufficiently well tolerated. In case of tumour progression, efficacy of treatment is unlikely to be successful and the treatment should be reviewed.
The treatment should be reviewed after 4 to 6 weeks in order to assess the initial response. Long term treatment should be under regular (at least monthly) veterinary control.

10. WITHDRAWAL PERIOD

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of reach and sight of children.
Keep the bottle tightly closed.
Do not use after the expiry date which is stated on the label after “EXP”.

12. SPECIAL WARNING(S)

12.1 Special precautions for use:

Special warnings:
For any mast cell tumor treatable by syrgery, surgery should be the first choice of treatment. Masitinib treatment should only be used in dogs with non-resectable mast cell tumours and which express the mutated c-kit tyrosine kinase receptor. The presence of a mutated tyrosine kinase c-kit receptor must be confirmed prior to treatment.

Special precautions for use in animals:

What are the special precautions for my dog?
Dogs should be carefully monitored by your veterinarian (at least every month) and treatment might need to be adjusted or discontinued, if necessary.
The treatment should be discontinued if any of these signs are observed: anaemia, severe neutropenia, severe renal toxicity, hepatic toxicity and/or severe diarrhoea or vomiting persistent after dose reduction.
Dogs should not be used for breeding while under treatment.
Do not use in pregnant or lactating bitches.

What are the special precautions to be taken by the person administering Masivet?
Repeated dermal contact with masitinib may impair female fertility and foetal development.
The active substance of Masivet can cause skin sensitisation.

- Avoid skin contact with faeces, urine, and vomit of treated dogs.
- Wear protective gloves while disposing of vomit, urine or faeces of treated dogs.
- If broken tablets, vomit, urine or faeces of treated dogs come into contact with the skin, rinse immediately with plenty of water.

The active substance of Masivet can cause severe eye-irritation and serious damage to the eyes.

- Avoid contact with the eyes.
- Take care not to touch the eyes before gloves have been removed and disposed of and the hands have been thoroughly washed.
- If the product comes into contact with the eyes, rinse immediately with plenty of water.

People with known hypersensitivity to masitinib should not handle the product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Do not eat, drink, or smoke when treating the dog.
Children should not have close contact to treated dogs, treated dog faeces or vomit.

Can other medications be given while my dog is taking Masivet?

There are some medicines that you should not give to your dog during treatment because together, they might cause serious adverse effects.
Concurrent use of other substances with a high degree of protein binding may compete with masitinib binding and thus cause adverse effects.
Concurrent use of substances which are metabolised by CYP450 isoforms may result in higher or lower plasma levels of either masitinib or those substances.
Tell your veterinarian about all medicines, including over-the-counter products, that you intend to administer to your dog.
The efficacy of Masivet might be reduced in dogs previously treated with chemotherapy and/or radiotherapy. No information relating to potential cross-resistance with other cytostatic products is available.

Overdose:
The recommended daily dose of 12.5 mg/kg body weight corresponds to the Maximum Tolerated Dose (MTD).
The main target organs of toxicity in dogs are the gastrointestinal tract, the haematopoetic system, the kidney and the liver.
In case of adverse events following overdose, treatment should be discontinued until resolution, and then resumed at the recommended therapeutic dose level. Please contact your veterinarian.

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 veterinarian 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

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

15. OTHER INFORMATION

For animal treatment only.
The tablets are available in pack sizes of 30 tablets.

Masivet is a prescription medicine used to treat dog mast cell tumours. Mast cell tumours are cancerous proliferations of mast cells. It is a heterogeneous disease which can be relatively innocent or aggressively malignant. In certain circumstances, mast cell tumours can be life threatening for your dog. Masivet might extend the time before the tumours progress.

Special information for the veterinarian

Dogs should be monitored carefully and professional judgement should be used to determine the need for dose reduction in the event of possible significant adverse reactions.

Monitoring of renal function
Renal function should be adequately monitored every month using dipstick urine testing.
In case of positive semiquantitative dipstick results (protein ≥ 30 mg/dl), urinalysis should be performed to determine urinary protein creatinine (UPC) ratio, and a blood sample to measure creatinine, albumin and BUN.
If UPC ratio > 2, or creatinine > 1.5 upper limit of normal (ULN), or albumin < 0.75 lower limit of normal (LLN) or blood urea nitrogen (BUN) > 1.5 ULN, discontinue treatment.

Monitoring of Protein loss syndrome
Perform every month a dipstick urine test. In case of positive semi-quantitative dipstick results (protein ≥ 30 mg/dl), perform urinalysis to determine urinary protein creatinine (UPC) ratio.
Perform every month a blood measurement of albumin.

- In case of UPC ratio > 2 or albumin < 0.75 lower limit of normal (LLN), treatment should be interrupted until albumin and UPC values have returned to limit value (UPC ratio < 2 and albumin > 0.75 LLN), treatment can then be continued at the same dose.
- If of one of these events (UPC ratio > 2 or albumin < 0.75 LLN) occurs for a second time, treatment should be permanently discontinued.

Anaemia and/or haemolysis
Dogs should be carefully monitored for signs of (haemolytic) anaemia. In case of clinical signs of anaemia or haemolysis, haemoglobin, free bilirubin and haptoglobin should be measured and blood cell counts (including reticulocyte) should be performed.
Treatment should be discontinued in case of:

- Haemolytic anaemia, i.e. haemoglobin < 10 g/dl and haemolysis,
  i.e. free bilirubin > 1.5 ULN and haptoglobin < 0.1 g/dl,

- Anaemia due to lack of regeneration, i.e. haemoglobin< 10 g/dl and reticulocytes < 80,000/mm^3.

Hepatic toxicity (ALT or AST elevation), neutropenia
In case of an increase of ALT or AST > 3 ULN, decrease of neutrophil count < 2,000/mm^3 or any other severe adverse events, treatment should be modified as follows:
At the first occurrence, treatment should be interrupted until resolution, and then resumed at the same dose level;
At the second occurrence of the same event, treatment should be interrupted until resolution; treatment should then be continued with a reduced dose of 9 mg/kg bodyweight/day;
At the third occurrence of the same event, treatment should be interrupted until resolution; treatment should then be continued with a dose further reduced to 6 mg/kg/day;
Treatment should be discontinued, if severe adverse reactions are still encountered at the 6 mg/kg/day dose.

Summary of thresholds for laboratory evaluations resulting in contra-indication or treatment modification (interruption, dose reduction or discontinuation)

Management of Hepatic Toxicity (ALT or AST)			
Contra-indication	**Interruption**	**Dose reduction**	**Discontinuation**
> 3 ULN	> 3ULN (1st time)	> 3 ULN (2nd/3rd time)	> 3ULN (4th time)
Management of Neutropenia (neutrophil counts)			
Contra-indication	**Interruption**	**Dose reduction**	**Discontinuation**
< 2,000/mm^3	< 2,000/mm^3 (1st time)	< 2,000/mm^3 (2nd/3rd time)	< 2,000/mm^3 (4th time)
Management of Protein-Loss Syndrome (Albuminemia and/or UPC)			
Contra-indication	**Interruption**	**Dose reduction**	**Discontinuation**
Albumin < 1 LLN or UPC > 2	Albumin < 0.75 LLN or UPC >2 (1st time)	Not applicable	Albumin < 0.75 LLN or UPC > 2 (2nd time)
Management of Haemolytic and aregenerative Anaemia (haemoglobin, bilirubin, haptoglobin, reticulocytes)			
Contra-indication	**Interruption**	**Dose reduction**	**Discontinuation**
Haemoglobin < 10 g/dL	Not applicable	Not applicable	Haemoglobin < 10 g/dl and either free bilirubin > 1.5 ULN and haptoglobin < 0.1 g/dl or reticulocytes < 80,000/mm^3

Dose adjustment

The recommended daily dose of 12.5 mg/kg body weight corresponds to the Maximum Tolerated Dose (MTD) that was derived from repeat dose toxicity studies in healthy Beagle dogs. In the case of adverse reactions, doses might be reduced to once daily doses of 9 mg/kg bodyweight (range 7.5–10.5 mg/kg) or 6 mg/kg bw (range 4.5–7.5 mg/kg) according to the tables below.

9 mg per kg bodyweight

Dog body-weight in kg		Number of tablets per day 50 mg		150 mg	Dose mg/kg lower weight	upper weight
≥ 15.0	19.4			1	10.0	7.7
> 19.4	25.0	1	plus	1	10.3	8.0
> 25.0	30.6	2	plus	1	10.0	8.2
> 30.6	36.1			2	9.8	8.3
> 36.1	41.7	1	plus	2	9.7	8.4
> 41.7	47.2	2	plus	2	9.6	8.5
> 47.2	52.8			3	9.5	8.5
> 52.8	58.3	1	plus	3	9.5	8.6
> 58.3	63.9	2	plus	3	9.4	8.6
> 63.9	69.4			4	9.4	8.6
> 69.4	75.0	1	plus	4	9.4	8.7
> 75.0	80.6	2	plus	4	9.3	8.7

6 mg per kg bodyweight

Dog body-weight in kg		Number of tablets per day 50 mg		150 mg	Dose mg/kg lower weight	upper weight
≥ 15.0	20.8	2			6.6	4.8
> 20.8	29.2			1	7.2	5.1
> 29.2	37.5	1	plus	1	6.9	5.3
> 37.5	45.8	2	plus	1	6.7	5.5
> 45.8	54.2			2	6.5	5.5
> 54.2	62.5	1	plus	2	6.5	5.6
> 62.5	70.8	2	plus	2	6.4	5.6
> 70.8	79.2			3	6.4	5.7
> 79.2		1	plus	3	6.3	