MASIVET®

For the treatment of inoperable mast cell tumours (Grade 2 or 3)*

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

Masivet®

MAST CELL TUMOURS

Mast cell tumours (MCTs) are the most common cutaneous malignancies in dogs, accounting for 16 to 21% of all skin tumours. [1]

- Known as the "great pretender", MCTs demonstrate a wide range of behaviour, presentation and patterns of progression – all of which make these tumours a challengeto treat
- MCTs are classified by histological grade, with poorly differentiated high grade tumours being more aggressive resulting **in a poor prognosis** for the patient due to **systemic spread of the disease.**
- MCTs result from the uncontrolled proliferation and prolonged survival of neoplastic mast cells, caused by **dysregulated c-Kit activity.**

C-KIT IS A TYROSINE KINASE RECEPTOR AND STUDIES HAVE SHOWN THAT INHIBITION OF THIS ENZYME CAN INHIBIT THE GROWTH OF MCTs[1]

MASIVET® IS A TARGETED THERAPY WORKING SPECIFICALLY AND SELECTIVELY ON KEY ENZYME PATHWAYS THAT CAUSE GROWTH AND SPREAD OF MAST CELL TUMOURS

Unlike cytotoxic chemotherapeutic agents, Masivet® accurately targets the cause of the tumour by acting on dysregulated tyrosine kinase activity.[2]

- Masivet® (masitinib) acts systemically to block the c-Kit receptor, leading to apoptosis of neoplastic mast cells and inhibition of mast cell proliferation.
- Masitinib *in vitro* has been shown to also inhibit a small number of other selective targets including PDGFR, known to be involved in angiogenic and metastatic processes[2]

MASITINIB IS A HIGHLY SELECTIVE MOLECULE ACTING ONLY ON CERTAIN KINASE PATHWAYS.

Masitinib does not inhibit kinases that are known to be linked to toxic effects and therefore the potential for unwanted secondary effects will be limited. [2]

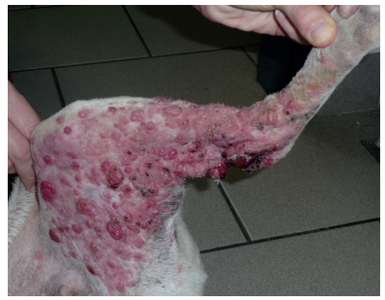
Masivet is given orally and acts systemically causing apoptosis of malignant mast cells, thereby shrinking the mast cell tumour and slowing tumour progression.[3,4, 9]

CLINICAL STUDIES HAVE SHOWN MASIVET® TO BE HIGHLY EFFECTIVE IN THE TREATMENT OF MAST CELL TUMOURS

A major placebo-controlled study has investigated the efficacy and safety of Masivet® in 202 dogs with inoperable grade 2 and grade 3 MCTs[4]

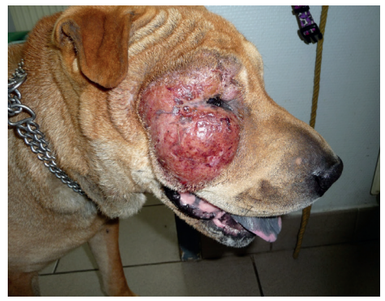
The pivotal regulatory study, published in J Vet Intern Med in 2008 by Hahn K A et al[4] was a multi-centre, randomized, placebo-controlled, double-blind study of oral Masivet® in 202 dogs with inoperable grade 2 or grade 3 cutaneous MCTs. Response to treatment was evaluated according to the WHO Guidelines for tumour response. Analyses were also conducted to evaluate the clinical response of tumours with mutated vs. non-mutated c-Kit receptor.

- Dogs were randomized to receive either Masivet® or placebo (4:1 ratio) for an initial 6 months.
- All dogs with a demonstrable biological response at the end of the 6 months period continued to receive treatment for up to 2 years.
- A total of 161 dogs received Masivet® (12.5mg/kg/day) and 41 dogs received placebo.

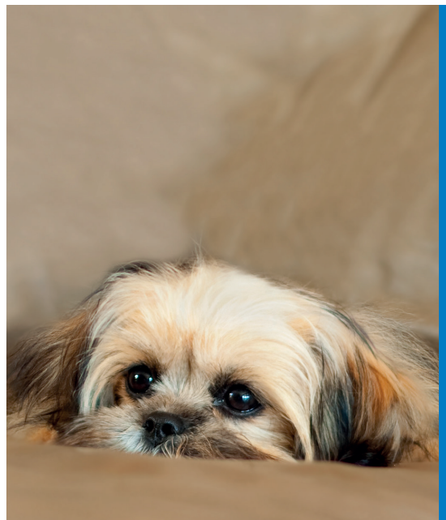


Four clinical investigations have also been conducted by oncology referral clinics in the United Kingdom, the Netherlands, the USA and France.[5,6,7,8]

- These investigations included more than 200 dogs with high grade, inoperable MCTs; 96 dogs had confirmed metastases and at least 73 dogs had grade 3 disease at the time of Masivet® initiation.
- Treatment protocols used Masivet® in both the first and second line of treatment.
- Masivet® was given as monotherapy or in combination with steroid treatment. A small number of dogs also received Masivet® in combination with chemotherapy. [5,6]



Results from 3 of these investigations are shown on page 5.



Definitions of tumour response in the Masivet® pivotal study (Hahn et al) [4]

COMPLETE RESPONSE (CR): DISAPPEARANCE OF MCT

0% of baseline tumour size

PARTIAL RESPONSE (PR):

Tumour shrinkage (at least 50%) with no new tumours or metastases

STABLE DISEASE (SD):

Tumour shrinkage (less than 50%) or stable disease with no new tumours or metastases

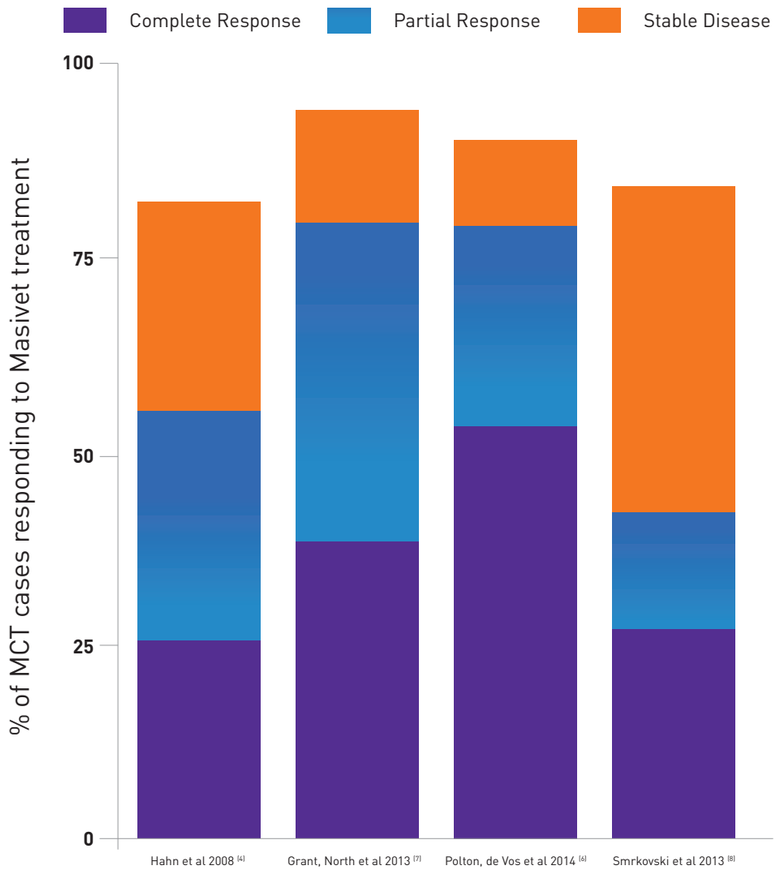
PROGRESSIVE DISEASE (PD):

All other cases

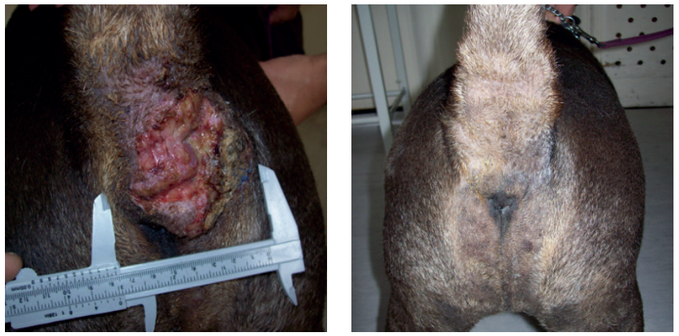
MASIVET® TREATMENT INDUCES TUMOUR SHRINKAGE AND STABILISATION IN DOGS WITH GRADE 2 OR GRADE 3 MCT DISEASE*

Clinical investigations have described a biological tumour response (MCTs have disappeared completely, regressed or stablised) in up to 90% of treated dogs[4,5,6,7,8]

- Response rates reported from 4 clinical investigations in grade 2 and grade 3 MCTs are summarised below:



A rapid and complete response in grade 3 non-resectable MCT



Before Masivet® therapy — After 53 days of Masivet® therapy

Courtesy of Malcolm Brearley, Univ Cambridge

- In the pivotal study, 50% of dogs receiving Masivet® demonstrated a complete response or significant partial response during the first 6 months of therapy (p = 0.02 vs. placebo).[4]

4. Hahn et al 2008: Pivotal study: randomized double-blind, involving 202 dogs. Masitinib was administered at a dose of 12.5 mg / kg to 161 dogs, others (41) received placebo. Complete Response (CR) 28.9%; Partial Response (PR) 23.7%,; Stable Disease (SD) 28.9%

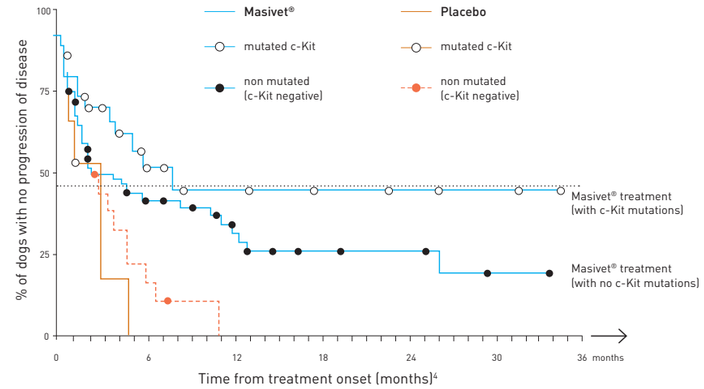
6. Polton et al: 147 dogs with inoperable MCT all with a high metastatic risk or metastases already present. Treatment included: masitinib alone, masitinib + prednisolone, Chemo + pred + Masitinib

7. Grant et al 2013: Retrospective study of 39 dogs treated with Masitinib. Clinical response in 82.1% of cases (CR 38.5%, PR 43.6%)

8 Smrkovski et al: 26 dogs in 2 groups treated 300 days on average. 1st group 1st line treatment 14 dogs, 2nd group 12 dogs masitinib as rescue treatment CR 27%, PR 15%, SD 42%. Median of survival 630 days versus 137 days.

MASIVET® ACTS SYSTEMICALLY AND SIGNIFICANTLY PROLONGS TIME TO TUMOUR PROGRESSION.[4,9]

- In a placebo-controlled clinical study, follow-up data for 36 months demonstrated that Masivet® treatment significantly prolonged Time to Tumour Progression (TPP).
- Masivet® acts systemically, and in the pivotal clinical study Masivet® treatment increased the probability of long-term survival with 39.8% of treated dogs alive at 2 years vs 15% of dogs which had received placebo (Fisher's p value 0.04) [4,9]



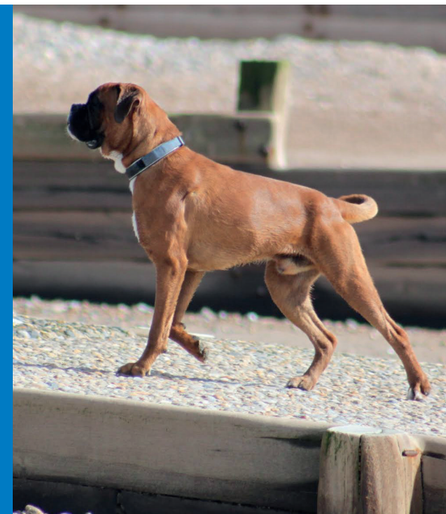
- Data from the pivotal study indicated that Masivet is most effective when used as a first line medical treatment (median TPP 178 days Masivet® vs 75 days Placebo; p = 0.001).[4,9]

Prolonged TPP has also been demonstrated in four clinical investigations[5,6,7,8]

- Progression free survival (PFS) in these studies ranged from 79 to 453 days in dogs treated with Masivet®.[6,7,8]
- The degree of MCT response significantly influenced overall time to disease progression and longer term survival; the greater the initial response the longer the overall survival time (p< 0.001). [5,6]
- In dogs that responded to Masivet®, median overall survival time has been reported up to 630 days.[8]

In the pivotal study Masivet® treatment significantly reduced the frequency of visceral and nodal metastases [3,9]

Emergence of metastases during the study	Treatment		Fisher's p-value
	Masivet® (N=161)	Placebo (N=41)	
Mets to lymph node or internal organs number (%) of dogs	6 (3.7%)	7 (17.1%)	0.006



MASIVET® IS WELL TOLERATED WHEN USED AT THE RECOMMENDED DOSES [3,4]

Dogs must be regularly monitored to allow early identification and management of any possible adverse effects.

Adverse effects can be managed and rapidly reversed using dose reductions or adjustments so that treatment of the MCT can be continued with minimal interruption. Monthly monitoring is recommended.

In the pivotal study the most commonly reported side effects included:

- Mild to moderate diarrhoea and vomiting (20% of dogs).
- Decreased appetite, peripheral oedema and alopecia (3 to 10% of dogs).
- Mild to moderate neutropenia, anaemia, haemolytic anaemia and increased ALT (2% to 3% of dogs).
- Hypoalbuminaemia.
  - A reversible protein losing effect has been reported in up to 4% of treated dogs
  - Monitoring of albumin levels every 2 weeks for the first 8 to 12 weeks of treatment, reducing to monthly monitoring thereafter, is recommended to detect any dogs sensitive to this effect.
- Some commonly reported adverse effects include clinical signs (e.g GI side effects and histamine-related effects) which may be partially tumour dependant and may need to be managed using symptomatic or prophylactic treatment.

Professional judgment should be used to determine the need for any dose adjustments. For further information consult the Summary of Product Characteristics (SPC)

HOW TO USE MASIVET®

Masivet is an oral therapy, convenient and easy to use for both Vets and owners.

- Masivet® tablets are supplied as round, film-coated orange tablets, available in 2 doses (150mg and 50mg) to be administered by the pet owner at home.
- The starting dose is 12.5mg/kg given once daily (dose range 11 - 14 mg/kg). Duration of treatment will depend on tumour response and should be maintained in the case of stable disease.
- Initial tumour response should be assessed during the first 4 to 6 weeks of therapy and long term treatment should be under monthly veterinary review.
- Dose adjustments or reduction in dose may be required to manage or reverse any adverse effects observed.
- Owners should be referred to the product packaging and leaflet for further information on side effects, handling precautions and method of administration.

MASIVET®
In Summary

- Masivet® is a highly effective and well tolerated, proven treatment.[4]
- Masivet® has been shown to induce tumour shrinkage and to prolong time to tumour progression in grade 2 and 3 mast cell tumours, [4,9]*
- Masivet® has a specific and selective mode of action, acting on the pathways responsible for the proliferation and spread of malignant cells.
- Masivet® can be used where surgery with full margins is not possible or where surgery alone will not be able to treat the tumour.
- Masivet® is an oral therapy, convenient and easy to use for both pet owners and vets.
- Starting dose is 12.5mg/kg once daily and the duration of treatment depends on the degree of tumour response.

*Masivet® has been shown to have the greatest effect in tumours with a mutated c-Kit receptor (TPP median 140 days vs 241 days, non-mutated vs. mutated respectively)[4,9]. It is licensed for treatment of dogs with non-resectable mast cell tumours (Grade 2 or 3) with a confirmed mutated c-Kit tyrosine kinase receptor.

Product Package Insert
Masivet® 50mg film-coated tablets for dogs
Masivet® 150mg 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, 75008 Paris, France
Manufacturer for batch release:
CSP 76-78 Avenue du Midi, BP77 63802 Cournon cedex, France

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 50mg 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.

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.

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

05/08/2009
Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.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.

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.

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/mm3.

Hepatic toxicity (ALT or AST elevation), neutropenia
In case of an increase of ALT or AST > 3 ULN, decrease of neutrophil count < 2000/mm3 or any other severe adverse events, treatment should be modified as follows:
At the first occurrence, treatment should be interrupted until resolution, 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)

Contra-indication	Treatment interruption	Dose reduction	Treatment discontinuation
Management of hepatic toxicity (ALT or AST)			
> 3 ULN	> 3ULN (1st time)	> 3 ULN (2nd/3rd time)	> 3ULN (4th time)
Management of neutropenia (Neutrophil counts)			
< 2000 /mm³	< 2000 /mm³ (1st time)	< 2000 /mm³ (2nd/3rd time)	< 2000 /mm³ (4th time)
Management of protein-loss syndrome (Albuminemia and/or UPC)			
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)			
Haemoglobin < 10g/dL	Not applicable	Not applicable	Haemoglobin < 10g/dL and either free bilirubin > 1.5 ULN and haptoglobin<0.1g/dl or reticulocytes < 80,000/mm³

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) according to the tables below.

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.

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.

10. WITHDRAWAL PERIOD

Not applicable

11. SPECIAL STORAGE PRECAUTIONS

Keep out of reach and sight of children.
Do not store above 25°C.
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:
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.

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.

9 mg/kg bw		Number of tablets per day			Dose mg/kg	
Dog body-weight in kg		50 mg		150 mg	lower weight	upper weight
≥ 15.0	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/kg bw		Number of tablets per day			Dose mg/kg	
Dog body-weight in kg		50 mg		150 mg	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	

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

Document Number:
2018-11-16/UK01.01

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