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Veterinary Medicines and Product Data Management

Refusal EPAR for Masivet

Type II variation (EMEA/V/C/128/II/004)

Scope of variation: Extension of indication (mast cell tumours)

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1. Background information on the variation

In November 2008, the European Commission granted a marketing authorisation for Masivet film-coated tablets for dogs for the “Treatment of non-resectable mast cell tumours (Grade 2 or 3) with confirmed mutated c-kit tyrosine kinase receptor”.

In November 2009, the Marketing Authorisation Holder, AB Science S.A., submitted to the EMEA an application for a Type II for Masivet to extend the current indication to allow “treatment of non-resectable dog mast cell tumours (Grade 2 or 3)”, i.e. independent of the tyrosine kinase receptor. On 14 April 2010, the CVMP recommended the refusal of the variation application for Masivet

Following the receipt of the negative opinion by the CVMP, the MAH requested a re-examination of the CVMP opinion. An ad-hoc scientific advisory group (SAG) was involved in this re-examination consisting of experts in veterinary oncology and statistics. The MAH attended the ad-hoc SAG meeting on 17 June 2010 for an oral explanation.

During the meeting on 13 – 15 July 2010, the CVMP issued a final Opinion recommending the refusal of the variation for Masivet. On 26 August 2010, the Commission adopted a Commission Decision refusing the proposed amendment of the marketing authorisation for Masivet.

Scope of the proposed variation

Current indication	Proposed indication
SPC Section 4.2 (Indication for use, specifying the target species)	**SPC Section 4.2 (Indication 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.	Treatment of non-resectable dog mast cell tumours (Grade 2 or 3).

2. Scientific discussion

Study design

The pivotal clinical study (on which the initial authorisation was based on) included a total of 202 dogs with mast cell tumours (Grade 2 or 3), which were treated in a blinded study for 6 months with either Masivet or a placebo. Following this phase ("Phase 1"; Feb 2005 – Oct 2006) and provided there was no tumour progression, most of the surviving dogs continued with treatment in a second study phase ("compassionate program"; Phase 2; Aug 2005 – May 2009), which followed a similar protocol to the initial study phase but with longer periods between observation points (after unblinding). Unblinding occurred in October 2006, once the last dog had left the initial study phase, i.e. all the surviving dogs were treated for 6 months, and most of the surviving dogs had already entered the second study phase and many already been treated for at least 12 months.

Dogs were assessed in 4- (before unblinding) or 12-weekly (after unblinding) intervals at the study centre until the end of treatment period (clinical examination, blood sampling, urinalysis, c-Kit mutation assessment (in case of progression), and, if necessary, dose adjustment in case of severe adverse events).

For the current application, the applicant provided 12 and 24 months survival data for all dogs initially included in the study, and follow-up data for those treated dogs that remained included in the compassionate programme (second study phase).

Efficacy assessment was based on the primary efficacy endpoints (time-to-tumour progression for individual animals remaining during the follow-up period, presented as Kaplan Meier curves for non-progression probability) and the secondary efficacy endpoint (survival rate at 12 and 24 months).

Target animal tolerance was evaluated by the frequency of adverse events (at 12 months and more than 12 months).

Study results

Time to tumour progression (TTP)

Average TTP data were already presented in the initial application. The follow-up data for the individual dogs that remained in the study showed a plateau for both subgroups, mutated and wild-type c-kit tumours, indicating that dogs showing no tumour progression within the first 12 months of treatment continue to have a stable disease.

Although Kaplan-Meier presentations indicate that for some wild-type c-kit carriers disease is stable for a prolonged time, the proportion of animals for which disease is kept stable is considerably higher for dogs carrying mutated c-kit than for wild-type c-kit tumour carriers. In view of lack of data in the subgroups and taking into account other available treatments, the CVMP considered that the low non progression probability (NPP) of wild-type c-kit carriers would not be acceptable.

The CVMP, therefore, remained of the opinion that the results in regard to this parameter confirm the results of the initial study; i.e. a significant improvement only in dogs expressing the mutated c-kit tumour.

Survival rate

Regarding the secondary endpoint (survival rate), the new data indicate that in dogs that remained in the study (phase 2), 12 months after study start survival rate among mutated c-kit carriers is significantly better for Masivet treated animals as compared to placebo animals. However, among wild-type carriers no significant effect is noted at any time point.

In regard to survival data for all dogs initially included in the study, a significant improvement at 12 and 24 months was noted for the full non-resectable population (as compared to placebo dogs) whereas for the dogs with wild type c-kit no effect on survival was demonstrated. Thus, CVMP considered these data insufficient to support efficacy for wild type c-kit carriers.

Tolerance

Most adverse events were of mild to moderate intensity. The CVMP considered that the adverse event data presented in the follow-up study are comparable to the safety pattern shown in the original application, and in line with events listed in the SPC and product literature. A somewhat lower incidence of adverse events was noted in the second study phase (as compared to the first phase of this study).

However, the CVMP attributed this lower incidence rate to a selection towards more tolerant animals during the course of the study (i.e. those animals showing severe reactions would have left the study at an earlier stage) and that the tolerance profile for Masivet could only be considered acceptable in dogs where a positive treatment effect could be expected, i.e. those with mutated c-kit.

3. Benefit-risk assessment

Benefit assessment

The follow-up data in regard to the primary parameter (TTP) confirm the results from the initial study phase, i.e. dogs expressing the mutated c-kit tumour, and without tumour progression within the first 12 months of treatment, continue to have a stable disease.

Although for some wild type c-kit carriers disease was also stable for a prolonged time, non-tumour progression-probability is much lower in this group (0.25) than in mutated c-kit carriers (0.5). Regarding the secondary endpoint (survival rate), the new data indicate that at 12 months after study start survival improvement was observed in the whole population. However, this improvement is statistically significant in the mutated c-Kit non-resectable population and not in the wild type non-resectable population.

The CVMP, therefore, concluded that the data confirmed efficacy of long term treatment only in a sub-group of dogs, i.e. dogs expressing the mutated c-kit tumour.

Risk assessment

Mainly mild to moderate adverse reactions, in line with reactions described in the product literature, were noted during the follow-up study. The CVMP considered that the adverse event data presented in the follow-up study are slightly milder than the safety pattern shown in the original application. This was attributed to a selection towards more tolerant animals during the course of the study.

However, since only dogs that benefited from the initial treatment were included in the follow-up study, a selection bias is very likely, which restricts the usefulness of these data. Also, comparison of

the tolerance profile in Masivet treated dogs versus placebo was no longer possible, as placebo dogs were removed from the study after unblinding.

The CVMP considered that the recommendations for the initial application would still apply, i.e. extent and frequency of adverse effects related to treatment with Masivet are only considered acceptable in dogs which can be expected to respond positive to treatment (i.e. partial/complete response or stable disease). The Committee, therefore, agreed that long-term treatment in dogs would not be acceptable for dogs unlikely to respond to treatment, i.e. the majority of dogs with wild-type c-kit tumours.

Evaluation of the benefit risk balance

Based on the above concerns and the lack of any new data relating to the TTP in the wild-type receptor sub-group, the CVMP concluded that the benefit-risk assessment for mastinib in dogs with non-resectable wild-type kit receptor mast cell tumours (grade 2 or 3) was negative. The Committee, therefore, remains of the opinion that the benefit-risk balance for Masivet is only positive in dogs with non-resectable mast cell tumours (grade 2 or 3) with confirmed mutated c-kit.

4. Overall conclusions

The CVMP considered that the results of the follow-up study confirm the differences in response rate in subgroups as previously noted, and concluded that Masivet treatment is only effective in dogs carrying the mutated c-kit.

Although efficacy of treatment was also seen in individual dogs in the wild type subgroup, this proportion was rather small, and treatment effects not significant. Taking into consideration that the majority of clinical cases of mast cell tumours is attributed to the wild type subgroup, the risk of (ineffective) treatment associated with adverse reactions in this subgroup is considered unacceptable.

The CVMP, therefore, remains of the opinion that the benefit-risk balance for Masivet is only positive in dogs with non-resectable mast cell tumours (grade 2 or 3) with confirmed mutated c-kit.

Grounds for refusal of the variation

Whereas

- Ground 1 for refusal (primary efficacy parameter)

The results in regard to the primary parameter ***Time to tumour progression (TTP)*** for the dogs that remained in the study during the second study phase (“compassionate program”) do not provide evidence for efficacy in carriers of wild-type c-kit. Thus benefit-risk balance is considered negative for this subgroup;

- Ground 2 for refusal (secondary efficacy parameter)

The results in regard to the secondary endpoint **(survival rate)** for the second study phase (“compassionate program”) do not provide evidence for clinically relevant effects for the wild-type c-kit carriers. Thus the benefit-risk balance is considered negative for this subgroup;

for the above stated reasons the variation application does not satisfy the criteria for authorisation and, therefore, CVMP recommends the refusal of the variation to the terms of the marketing authorisation for Masivet.