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Committee for Medicinal Products for Veterinary Use

CVMP type II variation assessment report for Activyl Tick Plus (EMEA/V/C/002234/II/0008)

International non-proprietary name: permethrin / indoxacarb

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Intervet International B.V. (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for Activyl Tick Plus.

1.1.1. Scope of the variation

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The variation is to add a new therapeutic indication for sand flies (*Phlebotomus perniciosus*)

Current	**Proposed**
Annex I - SPC - section 4.2 Indications for use, specifying the target species Treatment of flea infestations (*Ctenocephalides felis*); the product has persistent insecticidal efficacy for up to 4 weeks against *Ctenocephalides felis*. The product has persistent acaricidal efficacy for up to 5 weeks against *Ixodes ricinus* and up to 3 weeks against *Rhipicephalus sanguineus*. If ticks of these species are present when the product is applied, all the ticks may not be killed within the first 48 hours but they may be killed within a week. The veterinary medicinal product can be used as part of a treatment strategy for flea allergy dermatitis (FAD). Developing stages of fleas in the pet's immediate surroundings are killed following contact with Activyl Tick Plus treated pets.	Annex I - SPC - section 4.2 Indications for use, specifying the target species Treatment of flea infestations (*Ctenocephalides felis*); the product has persistent insecticidal efficacy for up to 4 weeks against *Ctenocephalides felis*. The product has persistent acaricidal efficacy for up to 5 weeks against *Ixodes ricinus* and up to 3 weeks against *Rhipicephalus sanguineus*. If ticks of these species are present when the product is applied, all the ticks may not be killed within the first 48 hours but they may be killed within a week. The veterinary medicinal product can be used as part of a treatment strategy for flea allergy dermatitis (FAD). Developing stages of fleas in the pet's immediate surroundings are killed following contact with Activyl Tick Plus treated pets. **One treatment provides repellent (anti-feeding) activity against sand flies (*Phlebotomus perniciosus*) for up to three weeks.**
Annex IIIB - Package Leaflet - section 4 Indication(s) Treatment of flea infestations (*Ctenocephalides felis*); the product has persistent insecticidal efficacy for up to 4 weeks against *Ctenocephalides felis*. The product has persistent acaricidal efficacy for up to 5 weeks against *Ixodes ricinus* and up to 3 weeks against *Rhipicephalus sanguineus*. If ticks of these species are present when the product is applied, all the ticks may not be killed within the first 48 hours	Annex IIIB - Package Leaflet - section 4 Indication(s) Treatment of flea infestations (*Ctenocephalides felis*); the product has persistent insecticidal efficacy for up to 4 weeks against *Ctenocephalides felis*. The product has persistent acaricidal efficacy for up to 5 weeks against *Ixodes ricinus* and up to 3 weeks against *Rhipicephalus sanguineus*. If ticks of these species are present when the product is applied, all the ticks may not be killed within the first 48 hours

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Part 4.A.1 Pharmacology + Part 4.B Clinical Trials	Part 4.A.1 Pharmacology + Part 4.B Clinical Trials Data added in support of the new indication, including two study reports and a number of scientific publications.

2. Scientific discussion

The applicant provided a well written expert's critical summary review of the preclinical and clinical documentation to support variation. The preclinical documentation comprised two studies, including a dose confirmation study. In response to the questions posed, the applicant also provided an additional dose confirmation study which investigated the repellent efficacy within 24 hours after treatment.

Preclinical studies

The first study (Williams, 2009) evaluated indoxacarb's ectoparasitic in vitro activity against adult fleas, juvenile ticks, blowflies and mosquitos. Indoxacarb was demonstrated to have insecticidal activity against adult fleas, blowfly and mosquito larvae. Indoxacarb's anti-flea activity was good at the highest test concentration (feeding activity: 100 ppm resulted in 90% mortality and contact activity: 1000 ppm resulted in 50% mortality) but had a lower potency than the reference standard fipronil under given test conditions.

The second study (Murphy, 2012) is a controlled and blinded GCP compliant study to confirm the repellent efficacy of indoxacarb/permethrin against a laboratory reared sand fly (*Phlebotomus perniciosus*) strain, when used in dogs (n=8) at the recommended dose, in comparison with a negative control (placebo) (n=8). Dogs in each group were exposed to approximately 75 female sand flies for about 1 hour at study days 2, 7, 14, 21 and 29 while sedated and clinical observations were recorded at intervals, for up to 6 hours post-treatment with Activyl Tick Plus. Efficacy was based on the arithmetic mean numbers of fed female sand flies (repellent efficacy) or live female sand flies (insecticidal efficacy) compared between both groups. For evaluation of both parameters Abbott formula was used. All tests were two-sided at the 5% level of significance. All statistical analyses were performed in SAS/STAT (version 9.2)

No treatment related adverse events were observed.

Repellent efficacy was 98% on Days 2 and 7 and 93%, 86% and 83% on Days 14, 21 and 29, respectively. The secondary efficacy parameter investigated insecticidal effect. However, an acceptable level of efficacy was not demonstrated at any time point (insecticidal efficacy peaked at 31% (Day 2), falling to 4% on Day 29). No insecticidal claim is proposed. At each time point the mean number of fed female sand flies was significantly lower in the treated group compared to the control group ($p<0.0001$). The total number of engorged sand flies at each time point ranged between 307 and 430 in the placebo group. In the treated group, the smallest number of engorged sand flies

(6) was recorded on Day 2 and the highest (61) on Day 21. The number of live sand flies was significantly higher in the placebo group compared to the treatment group on day 2 (p=0.0002) and day 7 (p=0.0011). The applicant concluded that the results of this study demonstrate that Activyl Tick Plus, when used in dogs at the recommended dose, has an excellent repellent efficacy (>80%) against sand flies (*Phlebotomus perniciosus*), from 2 to 29 days post treatment. However, efficacy of >90% was only demonstrated for 2 weeks. In addition, some insecticidal activity was observed on Study Days 2 and 7. Activyl Tick Plus was well tolerated in this study.

In response to the questions posed, the applicant provided an additional well conducted GCP study (Doyle, 2016) with the objective of confirming the repellent efficacy of Activyl Tick Plus against sand flies (*Phlebotomus perniciosus*), when used in dogs at the recommended dose. The study included 16 Beagle dogs (8 male and 8 female), randomly allocated to two groups of 8 dogs. On study day 0, the first group was treated with Activyl Tick Plus at the recommended dose, while the second group was un-treated. The efficacy of Activyl Tick Plus was determined by exposing each dog on study days 1, 7, 14, 21 and 28 to approximately 85 female and 10-20 male sand flies (Phlebotomus perniciosus) for approximately one hour. After exposure, the flies were collected and counted. The repellent efficacy (primary efficacy criterion) was based on a comparison of the feeding rate of sand flies between the two groups. The repellent efficacy was evaluated using Abbott's formula.

The repellent efficacy of Activyl Tick Plus (based on the arithmetic mean numbers of fed female sand flies) was approximately 96%, 97%, 92%, 92% and 81% on study days 1, 7, 14, 21 and 28 respectively. At each time point, the mean number of fed female sand flies in the Activyl Tick Plus treated group was significantly lower than in the untreated group (P<0.0001).

It was concluded that the study demonstrated a repellent efficacy of more than 80% against sand flies for 4 weeks. However, efficacy of >90% was only demonstrated for 3 weeks. As the applicant pointed out repellent efficacy (>95%) was observed on day 1, the dogs were exposed to sand flies just after clinical inspection at 24±2h.

In the first study, ingestion of indoxacarb resulted in better insecticidal efficacy than contact. The insecticidal efficacy of indoxacarb was not tested against *Phlebotomus perniciosus*. The outcomes measured were '% mortality' and/or '% inhibition' (defined as comprising killing and damaging effects). Further, indoxacarb is a pro-drug requiring bioactivation by enzymes in susceptible insects (primarily following ingestion, but also following absorption) in order to exert pharmacological action. It is therefore assumed that permethrin will be the only component of this fixed combination product that has the potential for repellent (anti-feeding) activity (as per the proposed new indication).

Consequently, the outcomes reported in this study summary are considered to have little relevance for the proposed indication 'repellent (anti-feeding)'.

In relation to the second study (Murphy, 2012), indoxacarb is known for its insecticidal effect on adult fleas, juvenile ticks, blowflies and mosquitos (study by Williams, 2009) particularly after ingestion by the ectoparasite. However, this effect was not observed in sand flies, especially at days 21 and 29, i.e. there was no observed mortality in non-repelled (engorged) sand flies. The difference in the number of total engorged sand flies was evident between treatment group and control group (p<0.0001) although the number of engorged sand flies increased during time in the treatment group. Repellent efficacy was higher than 80% at all time points. However, according to the Guideline 'Demonstration of efficacy of ectoparasiticides' (7AE17a), overall efficacy of ectoparasiticides against diptera should be 80-100% (preferably more than 90%) using at least two controlled tests, whereas only one efficacy study has been carried out. The same guideline suggests that the mean may be the arithmetic mean, the geometric mean or other suitably transformed mean that has been justified. In this study, arithmetic means were used and this is considered acceptable. It should be noted that repellent

efficacy was lower than 90% on day 21 and day 29. At each time point the mean number of fed sand flies in the treatment group was significantly lower than in the placebo group ($p<0.0001$). No insecticidal efficacy of indoxacarb/permethrin was observed on day 21 and day 29 in non-repelled, fed sand flies and it was very low at day 2 to 14. This indicates that indoxacarb does not have an insecticidal effect on sand flies after ingestion.

The origin of sand flies used can be accepted as being sufficiently representative. The bodyweight of the majority of study animals (all >8.7 kg on study day -1) was towards the higher end of the dose weight range (5.1-10 kg) and will therefore have received doses towards the lower end of the exposure range. This is considered appropriate and may be seen as representing a more conservative assessment of efficacy.

The primary efficacy parameter investigated was repellent effect, based upon a comparison of the numbers of fed female sand flies between groups. Results suggest a repellent (anti-feeding) efficacy of >80% for 29 days. However, efficacy of >90% was only demonstrated for 14 days.

The secondary efficacy parameter investigated insecticidal effect. However, an acceptable level of efficacy was not demonstrated at any time point. No insecticidal claim is proposed.

As treatment was performed on Day 0 and the first exposure to sand flies on Day 2, repellent effect within 24 hours following treatment application was not investigated. Generally the repellency demonstration should be performed within the 24 hour period of time after administration of the product. In conclusion, the results of this study are considered to support the proposed claim for repellent (anti-feeding) activity against sand flies (*Phlebotomus perniciosus*) for up to three weeks (albeit that percentage efficacy was 86% (marginally less than 90%) at day 21).

The GCP study (Doyle, 2016) demonstrated a repellent efficacy of more than 80% against sand flies for 4 weeks. However, efficacy of >90% was only demonstrated for 3 weeks. As the applicant pointed out repellent efficacy (>95%) was observed on day 1, the dogs were exposed to sand flies just after clinical inspection at 24±2h.

As results from the second dose confirmatory study (Doyle, 2016) demonstrated 92% efficacy (based upon arithmetic means) for a period of 21 days post-product application, based on the totality of data provided, a duration of repellent (anti-feeding) efficacy of 3 weeks is accepted.

Regarding the dose justification of product for the new claimed indication, the dose selected for the new indication was the current recommended dose of Activyl Tick Plus for the flea and tick indications in both dose confirmation studies. No new dose determination study was performed and no justification was provided. The current recommended dose of Activyl Tick Plus ranges from 15 to 30 mg/kg indoxacarb and 48 to 96 mg/kg permethrin. The recommended minimum dose of permethrin is therefore 48 mg/kg and is in line with the dose rate approved for other products containing permethrin and which have a claim of repellent activity against sand flies (*Phlebotomus perniciosus*).

Clinical study

A partly blinded, negative controlled GCP compliant field study (Frenais, 2012) to evaluate the efficacy and safety of a topical formulation of indoxacarb/permethrin (Activyl Tick Plus) on the prevention of the transmission of canine leishmaniosis (CanL) by sand flies in an endemic area was provided. Healthy, CanL negative dogs (n=139) from a kennel in a non-endemic area of France were used. The dogs were moved to two kennels in CanL-endemic areas (in Spain) with a high prevalence (up to 25%). They were exposed for 4 months. In that period, dogs in group A (n=67) were treated every 4 weeks with Activyl Tick Plus for up to 12 weeks. The negative control animals (group B, n=72) were not treated. Animals were clinically examined for the presence of clinical signs at time points Day 0, Week 4, Week 8, Week 12 and Week 16. Thereafter the dogs were moved back to the kennel of origin

(non-endemic area) where they underwent serological and parasitological examination for CanL at 32 and 48 weeks after withdrawal from the CanL-endemic area. 'Treatment failures' were dogs that became serologically or parasitologically positive to CanL

No treatment related adverse reactions were observed and there were no clinical signs of *Leishmania* infection. The percentages of 'treatment failures' in the treated and untreated groups were 34% and 50%, respectively. However, although the proportion of dogs exposed to *Leishmania* as a result of sand fly biting was numerically lower in the group of dogs treated with Activyl Tick Plus, the applicant concluded that the number of animals included in the study was insufficient to provide statistical evidence of a difference between the two groups which could be attributed to treatment.

This was a well conducted study. The use of a surrogate parameter to indirectly measure feeding activity of sand flies is considered appropriate. The primary efficacy parameter was the proportion of dogs that become serologically or parasitologically positive to CanL (i.e., exposed to biting sand flies). It should be noted that a significant number of dogs seroconverted in both control and test groups, compared with data on seroconversion rates in the published literature. This suggests a relatively high incidence of *Leishmania* transmission by sand flies in both kennels. The results of this study failed to demonstrate a statistically significant difference in the proportion of infected dogs between the treated and untreated groups. The applicant suggests that this was most likely due to an inadequate study sample size ($1-\beta = 0.45$). The results of the field study did not demonstrate a significant reduction of CanL transmission by sand flies during a four month treatment period with Activyl Tick Plus applied every four weeks. It is concluded that efficacy of the product under field conditions that might support a claim for reduction of transmission of canine leishmaniasis has been inadequately supported by this study.

Submitted literature

The applicant submitted one published literature reference on the pharmacodynamic action of indoxacarb, three on the emergence, distribution and prevalence of CanL in Europe, and eight references on controlled laboratory studies on repellent and/or insecticidal efficacy of deltamethrin impregnated collars and permethrin spot-ons on sand flies. Six published controlled field studies which used either deltamethrin impregnated collars, permethrin spot-on or a combination of imidacloprid and permethrin spot-on combination were used, were also provided.

Given the results from the pivotal field trial (Frenáis, 2012), the applicant has referred to published literature in order to support the proposed indication for a repellent (anti-feeding) effect against sand flies.

In relation to the repellent and/or insecticidal efficacy, one laboratory study (Killick-Kendrick et al, 1997) tested a deltamethrin collar on one laboratory strain of *P. perniciosus,* and the high mortality rate recorded might indicate a high sensitivity of this strain to deltamethrin. Another study in which the repellent effect and killing effect of the spot on was tested on a Portuguese strain of sand flies reared in the laboratory (Lienard et al, 2013), the anti-feeding effect was >95% in the first two weeks after treatment and an immediate repellent effect was observed . Treatment dosages ranged from 68.27-192.65 mg/kg permethrin. Another study (Miro et al, 2007) in which the repellent and insecticidal efficacy of imidacloprid 10%/permethrin 50% spot-on was evaluated against laboratory-reared sand flies (*P. perniciosus*) using the Abbotts formula, the repellent efficacy was >90% on days 1 to 21, but decreased to 74% on day 29. The authors concluded that a three weekly application of the VMP would be a good tool to reduce sand fly bites during transmission season of leishmaniasis. In another similar study (Molina et al, 2012) using 65% permethrin spot-on against *Phelobotomus perniciosus*, anti-feeding efficacy was > 90% on day 1 and day 8 and 86.8% on day 15. Thereafter efficacy was < 70%. Insecticidal efficacy was > 95% on day 1 but decreased rapidly to 43% on day 15

and to 2.5% on day 43. It is noted that, in this study, each treated dog received approximately the same dose of permethrin as recommended for Activyl Tick Plus, and the authors recommended use of this product every 2-3 weeks during sand fly season.

The submitted literature is considered to have demonstrated that deltamethrin impregnated collars and permethrin spot-on have an anti-feeding effect on sand flies. However, although a correlation between repellent or anti-feeding efficacy and reduction of *Leishmania* infection is obvious not all factors involved are known. Nevertheless, it can be accepted that according to published literature, there is established use of permethrin (and other active substances) for their repellent effect against sand flies.

A field seroprevalence rate of 3.9-5.8% was reported from an Italian study (Ferroglio et al, 2005).

In three of the published field studies provided, only deltamethrin impregnated collars were tested. In one study (Foglia et al, 2006), 120 seronegative kennelled dogs were included in a highly endemic area of leishmaniasis. Fifty per cent were collared and serology was performed twice a year for seroconversion. It was noted that, although the collar lead to significantly fewer seroconversions in the treated groups compared to the untreated controls, 27% (12/44) seroconverted in the collared group over two seasons.

Two of the published field studies each tested a combination of 10% imidacloprid/50% permethrin for the prevention of leishmaniasis in an endemic area, including one multicentre study (Otranto et al, 2007). In the multicentre study, product was tested either once a month or every 2 weeks against a control group in two kennels. 2/209 dogs seroconverted when treated every month, 1/204 dog when treated every 2 weeks and 20/218 dogs in the control group. Both treatment groups demonstrated a significant decrease in leishmanial infection. Treatment every 2 weeks tended to be slightly more efficacious (90.73-100%), than treatment every month (88.9-90.73%) but infection in both treatment groups was significantly lower than in the control dogs. In the second study (Otranto et al, 2010) 111 young dogs (some positive and some negative tested for a large number of vector borne diseases) were divided in 2 groups. The treated group received 10% imidacloprid/50% permethrin as spot on every 3 weeks (50 mg permethrin/kg BW). Prevalence of *Leishmania* was 4/111 at onset of the study. After approximately 14 months, 100% protection from *Leishmania infantum* was observed, i.e. none of the negative testing animals at onset had seroconverted, compared to 20/42 in the control group.

From the data provided, it can be concluded that studies in literature demonstrate a protective effect of permethrin or deltamethrin against sand fly bites and therefore against *Leishmania* transmission. However, observed transmission rates of *Leishmania* during treatment period can vary significantly, e.g. between seasons in the same study. Besides treatment, other factors (e.g. weather circumstances or local conditions) are involved in *Leishmania* transmission by sand flies. Whilst the references cited by the applicant provide general information on the active substances and veterinary medicinal products used for the purpose of preventing sand fly bites (and consequently risk of transmission of canine leishmaniasis), it is evident that field studies using leishmaniasis as a surrogate efficacy parameter may be affected by many factors. Consequently, the conclusions that may be drawn from the cited literature are somewhat limited, therefore the cited literature cannot be relied upon to support the proposed indication.

CVMP overall summary and conclusions

Two laboratory studies investigated the repellent (anti-feeding) efficacy of Activyl Tick Plus against sand flies under controlled conditions and a field study investigated the reduction of leishmanial transmission in treated dogs under field conditions in a *Leishmania* endemic area. No treatment

related adverse events were observed.

The first controlled laboratory study (Murphy, 2012) studied the repellent efficacy of indoxacarb/permethrin. Dogs were exposed for one hour to a laboratory reared *Phlebotomus perniciosus* strain at weekly intervals for four weeks after treatment. Efficacy was measured by mean reduction in fed female sand flies in the treatment group compared with the negative controls. Repellent efficacy was higher than 80% at all time points. According to the Guideline "demonstration of efficacy of ectoparasiticides" (7AE17a), efficacy should preferably be >90%. Repellent efficacy was lower than 90% on day 21 and day 29, being 86 and 83% respectively.

At each time point the mean number of fed sand flies in the treatment group was significantly lower than in the placebo group ($p<0.0001$) but no insecticidal efficacy of indoxacarb/permethrin in non-repelled (i.e. engorged) sand flies was observed on day 21 and day 29 ($n=0$). The insecticidal efficacy of the combination in fed sand flies was very low at day 2 to 14. This indicates that indoxacarb does not have an insecticidal effect on sand flies.

In the additional GCP study (Doyle, 2016), the applicant demonstrated a repellent efficacy of more than 80% against sand flies for 4 weeks. However, efficacy was >90% for 3 weeks only. Also, repellent efficacy (>95%) was observed on day 1, where the dogs were exposed to sand flies just after clinical inspection at 24±2h.

In the negative controlled field study, *Leishmania* seronegative dogs were transported to an endemic area, known for a high prevalence of Canine leishmaniosis. The dogs were treated every four weeks with Activyl Tick Plus spot on in accordance with the existing dose in the approved SPC. After four months, the animals were moved back to an area with no occurrence of Canine leishmaniosis and they were followed serologically and parasitologically for 48 weeks.

The results from the field study did not demonstrate a statistically significantly different reduction of *Leishmania* transmission by sand flies between groups during the treatment period. The applicant points out that the study power was less than 80% caused by a relatively small size of both groups. However, it should be noted that a substantial number of dogs seroconverted in both control as well as test groups compared to reported seroconversion data in published literature. Given the proposed duration of repellent (anti-feeding) activity (up to 3 weeks), this would mean that the threshold of repellent or anti-feeding efficacy should be higher than 83% to give a significant reduction of *Leishmania* transmission.

Although not specifically commented upon by the applicant, it is noted that the dose rate of permethrin in Activyl Tick Plus (48 mg/kg) is comparable to that of other authorised veterinary medicinal products that include an indication for a repellent effect against sand flies. Consequently, the proposed dose rate is considered appropriate for the proposed indication.

The applicant has also referred to published literature in support of the proposed indication. The CVMP is of the opinion that whilst evidence of the established use of permethrin (and other active substances) for their repellent effect against sand flies has been provided, the cited literature cannot be relied upon to support the proposed indication.

In light of the above, the CVMP is of the opinion that based on the totality of data provided, the proposal of the applicant to introduce a claim for a repellent (anti-feeding) effect of the product for a period of up to 3 weeks is acceptable, given that a repellent efficacy at 21 days post-treatment application of 86% was demonstrated in one controlled dose confirmatory study and 92% in another.

Given the minimum efficacy acceptance criteria indicated in relevant guidelines to grant a claim (≥80% but preferably >90%) and the data from the two dose confirmatory studies, it is evident that not all sand flies will be repelled by the product. Whilst no specific claim for the prevention of

transmission of *Leishmania infantum* has been proposed, the possibility for transmission of *Leishmania infantum* cannot be excluded following use of the product. The existing warning/advice (originally located in SPC section 5.1 but now relocated to section 4.4), particularly given the percentage repellent efficacy reported (86% & 92%) and the proposed duration of repellent (anti-feeding) activity against *Phlebotomus perniciosus* (3 weeks) have been moved and strengthened to indicate that transmission of infectious disease cannot be completely excluded if conditions are unfavourable.

3. Benefit-risk assessment

3.1. Benefit assessment

The proposed additional indication reads: "**One treatment provides repellent (anti-feeding) activity against sand flies (*Phlebotomus perniciosus*) for up to three weeks"**. The relevant CVMP guideline specifies that a repellency of >80% (preferably >90%) is sufficient to grant a claim. Data was provided that demonstrates a repellent (anti-feeding) activity against sand flies of 86% in one dose confirmation study and 92% in a second dose confirmation study.

In the light of the data provided, the CVMP accepts that a benefit of the product for the indication repellency (anti-feeding) against sand flies has been shown.

3.2. Risk assessment

No change to the impact on the environment is envisaged.

The benefit-risk balance remains unchanged.

3.3. Evaluation of the benefit-risk balance

It is acknowledged that the reason why a product with repellent activity against sand flies is used, is generally to prevent transmission of *Leishmania* by biting sand flies. However, insufficient data has been provided to support any reference to leishmaniasis in the SPC. Although the possibility for transmission of *L. infantum* cannot be excluded following use of the product, the product was suitably demonstrated to have a repellent (anti-feeding) effect against sand flies for a period of 3 weeks. The CVMP agrees that this indication can be approved with specific relevant statements in the SPC.

4. Overall conclusions of the evaluation and recommendations

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met.

4.1. Changes to the community marketing authorisation

Changes are required in the Annexes to the Community marketing authorisation.

I, IIIA and IIIB