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Committee for Medicinal Products for Veterinary Use

## Committee for Medicinal Products for Veterinary Use (CVMP)

# CVMP assessment report for a grouped type II variation for Zuprevo (EMEA/V/C/002009/II/0006/G)

International non-proprietary name: Tildipirosin

**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 7.2(b) 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 grouped type II variation for Zuprevo.

## 1.2 Scope of the variation

- Deletion of a warning in section 4.5: "The safety in piglets less than 4 weeks of age has not been established. Use in young piglets only according to the benefit-risk assessment by the responsible veterinarian."
- Addition of a new therapeutic indication for metaphylactic use.

| Current | Recommended by CVMP |
|---|---|
| **SPC (Pigs)**<br><br>**4.2 Indications for use, specifying the target species**<br><br>Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Bordetella bronchiseptica* and *Haemophilus parasuis* sensitive to tildipirosin. | **SPC (Pigs)**<br><br>**4.2 Indications for use, specifying the target species**<br><br>Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Bordetella bronchiseptica* and *Haemophilus parasuis* sensitive to tildipirosin.<br><br>The presence of the disease in the herd should be confirmed before metaphylaxis is implemented. |
| **4.4 Special warnings**<br><br>None | **4.4 Special warnings**<br><br>~~None.~~<br><br>In line with responsible use principles, metaphylactic use of Zuprevo is only indicated in severe outbreaks of SRD caused by the indicated pathogens. Metaphylaxis implies that clinically healthy animals in close contact with diseased animals are administered the product at the same time as the treatment of the clinically diseased animals, to reduce the risk for development of clinical signs.<br><br>The efficacy of metaphylactic use of Zuprevo was demonstrated in a placebo controlled multi-centre field study, when outbreak of clinical disease was confirmed (i.e. animals in at least 30% of the pens sharing the same airspace showed clinical signs of SRD, including at least 10% animals per pen within 1 day; or 20% within 2 days or 30% within 3 days). Following metaphylactic use, approximately 86% of the healthy animals remained free of clinical signs of disease (as |

<table>
<tr><td></td><td>compared to approximately 65% of animals in the untreated control group).</td></tr>
<tr><td>4.5 Special precautions for use<br><br>Special precautions for use in animals<br><br>The safety in piglets less than 4 weeks of age has not been established. Use in young piglets only according to the benefit-risk assessment by the responsible veterinarian.</td><td>4.5 Special precautions for use<br><br>Special precautions for use in animals<br><br>~~The safety in piglets less than 4 weeks of age has not been established. Use in young piglets only according to the benefit-risk assessment by the responsible veterinarian.~~</td></tr>
<tr><td>5.1 Pharmacodynamic properties</td><td>5.1 Pharmacodynamic properties<br><br>The following proposed preliminary tildipirosin breakpoints have been determined for swine respiratory disease:<br><br>
<table>
<tr><th rowspan="2">Species</th><th rowspan="2">Disk content</th><th colspan="3">Zone diameter (mm)</th><th colspan="3">MIC breakpoint (µg/ml)</th></tr>
<tr><th>S</th><th>I</th><th>R</th><th>S</th><th>I</th><th>R</th></tr>
<tr><td>A. pleuropleumoniae</td><td rowspan="3">60 µg</td><td>–</td><td>–</td><td>–</td><td>16</td><td>–</td><td>–</td></tr>
<tr><td>P. multocida</td><td>≥ 19</td><td>–</td><td>–</td><td>4</td><td>–</td><td>–</td></tr>
<tr><td>B. bronchiseptica</td><td>≥ 18</td><td>–</td><td>–</td><td>8</td><td>–</td><td>–</td></tr>
</table>
S: susceptible; I: intermediate; R: resistant<br><br>Corresponding sections of labelling and package leaflet have been updated accordingly.<br>In addition, all annexes have been updated in line with the current QRD template.</td></tr>
</table>

# 2. Scientific discussion

## 2.1 Assessment

### ***Deletion of the warning to use Zuprevo in young piglets***

In support of the proposed deletion of the warning in regard to the use of Zuprevo in young pigs, the applicant submitted two new target animal safety studies, as well as some references from published literature.

The first study was a non-GLP (good laboratory practice) pilot target animal safety study from 2011 investigating the general tolerance of 30 healthy suckling piglets treated within 3 days of birth either with a single intramuscular administration of Zuprevo at 4 mg tildipirosin/kg bodyweight (bw), or a mixture (in the same syringe) of Zuprevo at 4 mg tildipirosin/kg bw and an iron dextran containing product (Myofer) or the iron dextran containing product alone. From birth until 8 days after administration the piglets were assessed twice daily throughout the study for common clinical parameters, and were also observed continuously during the first hour and then approximately 2, 4 and 8 hours after injection of each test item to detect possible adverse reactions. Bodyweights of the piglets were determined on the day of administration (day 0) and at study end (day 8). All piglets remained healthy throughout the study and no adverse reactions were seen after administration of the test items. The results indicate that concomitant administration of Zuprevo and iron dextran as mixture in one syringe is as safe as the single administration of Zuprevo or the iron dextran containing product alone. However, the study size was

small and thus sound conclusions regarding tolerance in newborn piglets during co-administration of Zuprevo iron-dextran could not be made.

The pivotal study was a well-designed GLP compliant target animal safety study from 2013. Zuprevo was administered intramuscularly to 30 newborn piglets at two occasions 11 days apart at doses corresponding to the recommended treatment dose (RTD) of 4 mg tildipirosin/kg bodyweight, and multiples thereof (12 mg/kg bw, i.e. 3X RTD), with maximum injection volumes of 0.63 ml (first administration) and 1.80 ml (second administration). All piglets received concomitant medications. Common clinical parameters used for the safety evaluation were performed twice daily, and haematological, coagulation and clinical chemistry parameters, and gross necropsy and histopathological examinations were performed. Injection site tolerance was investigated by clinical examinations in vivo and gross and histopathological examinations of the injection sites. All piglets were euthanised at day 18.

The observed systemic adverse reactions related to Zuprevo administration, i.e. transient subdued behaviour, transient tremor, are already known from overdose studies submitted with the initial marketing authorisation application and mentioned in section 4.10 of the SPC. However, in the present study subdued behaviour and tremor occurred already after administration of the RTD. Body tremors were considered not treatment related as they were observed intermittently in both control and treated animals and even observed in an animal that was a non-study littermate, that is, it was not treated with test or control item. The adverse reaction 'transient lethargy' was added to section 4.6 with a frequency classification of 'very rare'.

Clinical examinations of the injection sites revealed no signs of swelling, pain, heat or erythema at any of the time points. This is unexpected since according to the product information during clinical trials, pain on injection and injection site swellings were seen very commonly in treated pigs. Head-shaking and blood/reddening at the injection site were observed in both saline and test item treated animals and are deemed treatment but not substance related. The haematological and clinical chemistry analyses showed some test substance related changes which are not considered of clinical significance. For bodyweight no statistical significant differences were observed between control and treated animals. Gross necropsy findings at the injection site were limited to one group (12 mg/kg bw, i.e. 3X RTD) and consequently histological findings do origin only from this group only. The pathological findings were indicative for an inflammatory process. Overall, injection site reactions were less than expected given the information from previous studies submitted with the original application and the product information.

It can be concluded that the intramuscular administration of Zuprevo at 4 and 12 mg tildipirosin/kg bw (1X and 3X RTD) given on 2 occasions, 11 days apart was well tolerated in suckling piglets.

## Overall conclusions on target animal safety in young pigs

The new target animal tolerance studies did not indicate a health risk in piglets treated with Zuprevo at the RTD, and provide sufficient support to conclude that a particular warning for use in piglets younger than 4 weeks is not necessary. Consequently, the CVMP considered it acceptable to delete the wording 'The safety in piglets less than 4 weeks of age has not been established. Use in young piglets only according to the benefit-risk assessment by the responsible veterinarian' from section 4.5 of the SPC (special warnings) and the product information.

Additionally, in order to take into account the findings in the target animal safety (TAS) study related to subdued behaviour, the sentence "In very rare cases, transient lethargy in piglets has been observed." was included in section 4.6 of the SPC (adverse reactions). Furthermore, the frequency of individual shock reactions was amended from 'rare' to 'very rare' and reads now as follows: "In very rare cases, individual shock reactions with a potentially fatal outcome might occur." The CVMP considers the proposed amendments acceptable.

In summary, the proposed type II variation (No C.I.6) was accepted, subject to changes in the SPC and product information.

## ***New indication: Metaphylaxis***

The proposed type II variation concerned the addition of a new claim:
"Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Bordetella bronchiseptica* and *Haemophilus parasuis* sensitive to tildipirosin".

In support of the proposed new claim, the applicant provided two new pharmacodynamic studies to determine the in vitro activity of tildipirosin against recent target bacteria isolated from swine suffering from respiratory disease, and two new field studies. Reference was also made to two field studies previously submitted and assessed during the initial application procedure.

## Pharmacodynamics

In two GLP compliant studies (S12021-00-MCR-MIB-SW and S13303-00-MCR-MIB-SW) a total of 679 field isolates were investigated for tildipirosin minimum inhibitory concentrations (MICs) of *A. pleuropneumoniae* (31), *B. bronchiseptica* (209), *H. parasuis* (239) and *P. multocida* (201). The isolates were collected within the scope of two field studies i.e. strains came from the same episode(s) of the disease(s)/herd(s). Therefore, it is very likely that a considerable number of isolates are epidemiologically related and consequently interpretation of distribution profiles is limited. Nevertheless, MIC data came from 17 different sites of 3 different countries and, when comparing these data, large consistencies are found for MIC values suggesting that distribution profiles are representative for the recent susceptibility situation in target pathogens. For reasons of comparison, the data of both studies were pooled and $MIC_{50}$/$MIC_{90}$ values were calculated even though calculations may be biased by epidemiological relation.

In conclusion, the MIC data of target pathogen strains, isolated in 2011 and 2013 from swine suffering from respiratory disease indicate that the susceptibility pattern is similar to what was reported in the dossier in support of the initial application for market authorisation of Zuprevo.

In section 5.1 of the SPC tildipirosin breakpoints according to Clinical and Laboratory Standards Institute (CLSI) Guideline VET02-A3 are provided for the target pathogens. The CVMP noted that these breakpoints are not publically available yet. Therefore, the reference to CLSI was deleted and the breakpoints indicated as "proposed preliminary breakpoints" instead. The applicant will provide the published references as soon as they are available.

## Field studies

In support of the new indication, the applicant submitted two new clinical studies, investigating the efficacy of Zuprevo administered intramuscularly at a single dose of 4 mg tildipirosin/kg bw in the metaphylaxis of swine respiratory disease (SRD) associated with *A. pleuropneumoniae*, *B. bronchiseptica*, *P. multocida* or *H. parasuis* under field conditions, compared with a negative control (0.9% saline solution).

Both new field studies were good clinical practice (GCP)-compliant, and conducted in 2013 in France, Germany and Spain (one study only) as a negative-controlled, multi-centred, randomized and investigator-blinded study in farms with confirmed history of (re-)occurring swine respiratory disease (SRD). The relevant CVMP Guidelines on GCP (CVMP/VICH/595/98-FINAL), the current CVMP guideline on

efficacy testing of antimicrobials (EMEA/CVMP/627/01-FINAL) and the CVMP Guideline on statistics (EMEA/CVMP/816/00-FINAL) were taken into account.

***Study 1 (Fresnais)***

An SRD outbreak was declared within an air space if at least 20% of all the pens of the same air space were affected and included. The outbreak of SRD was then further confirmed when the presence of at least one of the four target pathogens was evidenced in diseased (sentinel) animals and 10% of the animals of the negative control group within a site showed signs of SRD and met the failure criteria within 14 days after initiation of treatment.

Study enrolment was initiated and continued for a period of maximum 7 days when an SRD outbreak was evidenced and inclusion criteria were met. A pen was considered as affected and eligible for inclusion if at least 20% of the animals within the pen met the following clinical criteria of SRD: rectal temperature ≥40 °C (score ≥ 1) and abnormal respiration (score ≥ 1) and abnormal general attitude (score ≥ 1). The animals meeting these criteria were considered ill and identified as "sentinels". The other animals of the pen were defined as "exposed" animals having at least one score=0.

In total, 722 pigs aged from 52 to 133 days (10.6–114.4 kg bw at inclusion) were enrolled with 227 sentinel pigs and 495 exposed pigs of which 468 animals were suitable for per protocol analysis with 229 in the Zuprevo group and 239 in the negative control group.

Sentinel pigs were treated with enrofloxacin (using Baytril 1nject). These animals stayed within the pen and were not housed separately. On day 0, the exposed pigs were treated with either Zuprevo (4 mg tildipirosin/kg bw) or 0.9% saline solution as a single intramuscular injection. The treatment randomization was performed at a pen level, and the same treatment was administered to all the exposed animals in the same study pen.

Clinical examinations were performed on the day of inclusion (day 0) and afterwards daily from day 1 to day 14±1 and again on day 21±2. Clinical examination included scoring of respiration, attitude and temperature as well as injection site observation.

The primary efficacy variable was the metaphylaxis success rate in the exposed population on day 14, defined as the percentage of "clinically healthy" animals (as defined in the study protocol) remaining in the study on day 14±1.

Superiority of the metaphylaxis success rate of the Zuprevo group in comparison to negative control group was investigated using a generalized linear mixed model using a binomial distribution and a logit link, with site and country as random variables. The level of significance was $\alpha$= 0.05 (two-sided).

As secondary efficacy variable, the "late metaphylaxis success rate" was defined using the same parameters but for day 21±2. Additional secondary efficacy variable were mortality rate, rectal temperature, respiratory score and attitude score, and average daily weight gain. Additional criteria were microbiological results for exposed pigs (intent to treat (ITT) and per protocol (PP) population) and sentinel pigs. Microbiological results for exposed study animals (ITT and PP population) and microbiological results for sentinel animals were summarized as additional criteria descriptively per study group.

For the primary efficacy criterion (metaphylaxis success on day 14±1), mean success rates were significantly different between the two study groups: 86.0% (PP) and 85.7% (ITT) in the Zuprevo group compared to 70.7% (PP) and 70.8% (ITT) in the 0.9% saline group (PP and ITT population, p<0.0001). For the secondary efficacy criteria (late success on day 21±2), success rates in the Zuprevo group were 83.3% (PP) and 83.0% (ITT) compared to 63.9% (PP) and 64.0% (ITT) in the 0.9% saline group (PP and ITT population, p<0.0001). The mortality rate was nil in both the Zuprevo group and the saline group.

Animals in the Zuprevo group had a lower rectal temperature, higher daily weight gain, better respiratory and attitude scores than the saline group.

Adverse events observed in both treatment and control group were comparable. Episodes of mild to moderate diarrhoea of unknown aetiology were reported in less than 3% of the cases in both study groups, and regarded as possibly related to the administration of the treatment. None required any concomitant treatment.

**Conclusions:**

The CVMP noted major shortcomings in terms of the study design of Frénais (2013): Pigs assigned to the metaphylactic treatment showed clinical signs of SRD at a non-negligible proportion (about 25% had a temperature of more than 40 °C, more than 40% showed respiratory scores above 0, and about 20% had an attitude score above 0 at inclusion). However, according to the definition of metaphylaxis all animals with a sum score above 0 should have been excluded from the analysis of metaphylaxis effect. Also the definitions of prevention success and late prevention success (pigs with sum of scores $\leq 1$) are considered not appropriate, since according to this definition pigs with fever or impaired attitude were considered as success which is not correct.

Furthermore, the CVMP considered the chosen threshold of 5% for success in metaphylactic treatment as too low and therefore not relevant. Considering the high success rate of Zuprevo as a benefit without referring to the also high success rate in the placebo group is not acceptable, even if it was biased upwards to an unknown extent due to the study design

On request of the CVMP the applicant re-analysed the data excluding one site where target pathogens were not found and re-defining success by allowing at most mild respiratory signs (but no temperature >40 °C and no attitude score >0) resulted in mean "metaphylaxis" success rates of 76.7% (Zuprevo) and 62.4% (placebo) on study day 10 with 5.3% as the lower confidence limit for the rate difference. The CVMP considered this difference as not being clinically relevant. A re-analysis by exclusion of pigs with any clinical sign of SRD at day 0 revealed no statistically significant difference between pigs treated with saline or Zuprevo. The lack of significance might be due to a too small number of clinically healthy animals.

***Study 2 (Petersen)***

Outbreak of SRD was confirmed if at least within one day 10%, within two days 20% or within three days 30% of the animals (sentinel animals) sharing the same pen met at least the following criteria: rectal temperature ≥ 40 °C and abnormal respiration (respiratory score ≥ 1) and abnormal general attitude (attitude score ≥ 1). This prevalence had also to be shown in at least 30% of the pens in the same air space. Further confirmation was given through post-mortem examination and by bacteriological sampling of sentinels. Sentinels stayed within the pen and airspace. The infection pressure at the site was considered to be adequate if at least 10 % of the animals injected with 0.9% saline solution developed signs of SRD during the first 7 days and there was evidence for the presence of at least one of the four target pathogens.

Pigs sharing the same pen with sentinel pigs showing no signs of SRD, i.e. rectal temperature ≤ 39.9 °C and normal respiration and normal attitude were enrolled.

In total 842 pigs of either sex and any breed were enrolled; 468 pigs were sentinel pigs. Pigs aged from 3 to 24 weeks including 113 pigs younger than 4 weeks and weighed from 3.4 to 122 kg at inclusion.

Clinical examinations were performed daily from day 0 to day 10 and on day 17±1, including scoring of respiration and attitude, measuring of rectal temperature as well as observations of (pain at the) injection

site. Animals that were less than 4 weeks old were additionally examined on day 0 after administration of Zuprevo or saline.

The primary efficacy variable was the metaphylaxis success rate in the exposed population on day 10, defined as the percentage of animals without any clinical sign (temperature ≤ 39.9 °C and normal respiration and normal attitude). Animals that were withdrawn from the study between day 1 and day 10 were regarded as "failures" (temperature ≥ 40 °C and abnormal respiration and abnormal attitude), withdrawn animals between day 11 and day 17±1 were regarded as "late failures".

Super-superiority of the metaphylactic success rate of the Zuprevo group in comparison to the 0.9% saline group was investigated using a one-sided shifted asymptotic $X^2$-test for comparing two rates with the maximum likelihood estimation for the unknown parameters. The level of significance was $\alpha = 0.025$ and the minimum difference in favour for the Zuprevo group determined as $\delta = 0.10$. The secondary efficacy variable was defined as metaphylaxis success on day 17, i.e. animals which completed the study on day 17, which was analysed like the primary efficacy variable. Additional secondary efficacy criteria were late failure rate, mortality rate, rectal temperature, respiratory score and attitude score, and daily weight gain. Further additional criteria were microbiological and serological results for exposed pigs and sentinel pigs (ITT and PP population) as well as microbiological results from sentinel pigs. Microbiological and serological results were summarised descriptively per study group.

Eight hundred and forty two pigs were considered suitable for intent to treat (ITT) analysis with 422 in the Zuprevo group and 420 in the 0.9% saline group. Four hundred and fifty six (456) pigs were suitable for per protocol analysis with 229 in the Zuprevo group and 227 in the 0.9% saline group. For the primary efficacy variable (metaphylaxis success on day 10), the mean success rates were 83.8% (PP) and 77.2% (ITT) in the Zuprevo group as compared to 69.2% (PP) and 67.8% (ITT) in the control group. Overall, significant super-superiority of Zuprevo compared to saline was not documented (PP: p=0.1164, ITT: p=0.5755). Superiority of Zuprevo compared to saline could only be demonstrated for two sites. Metaphylaxis success rates were higher, but not significantly, on all other sites with the exception of one site, where the metaphylaxis success rate was approximately 17% higher in the negative control group. For the secondary efficacy variable (late metaphylaxis success on day 17), success rates in the Zuprevo group were 75.6% (PP) and 67.7% (ITT), as compared to 62.1% (PP) and 56.7% (ITT) in the control group. Significant super-superiority of Zuprevo compared to saline was not demonstrated (PP: p=0.2128, ITT: p=0.3823). Late failure rates were 9.6% (PP) and 12.3% (ITT) in the Zuprevo group compared to 10.2% (PP) and 16.3% (ITT) in the saline group. Mortality rates were comparable and below 0.5% in both treatment and control group. Mean rectal temperatures from inclusion until day 10 were comparable and below 40 °C in both treatment and control group. The serology results indicate that infections with *Mycoplasma hyopneumoniae*, porcine respiratory coronavirus (PRCV), influenza virus and porcine reproductive and respiratory disease virus (PRRSV) were present at the start of the study on day 0. The antibody titres indicated that, besides influenza A, *M. hyopneumoniae*, PRRSV and porcine circovirus (PCV 2) were present as concomitant infections in a large proportion of animals that were withdrawn from the study.

Pain on injection was observed in 160 animals treated with Zuprevo (38.2%) and in 121 animals treated with 0.9% saline (28.8%). Swelling was only seen in one animal treated with 0.9% saline.

Overall, 18 adverse events were seen of which two were seen after end of individual animal phase. For animals treated with Zuprevo, seven adverse events were seen; three of them were probably related to the medication (immediately after injection: paddling movements in lateral position, shock syndrome; sudden death; following injection pig laid down on his site for some seconds without movement). Two of the seven adverse events were severe. For animals treated with 0.9% saline, eleven adverse events were seen; seven of them were regarded as severe, none of them were probably related to the medication.

**Conclusions:**

The study design of this pivotal field study was deemed appropriate, and inclusion and efficacy criteria were endorsed; however, the time when metaphylaxis success was evaluated (study days 10 and 17) might have been too short. On study day 10, 83.8% (192 of 229) of the animals treated with Zuprevo and 69.2% (157 of 227) of the animals treated with 0.9% saline were free of signs of SRD (metaphylaxis success). Overall, super-superiority of Zuprevo compared to 0.9% saline could not be demonstrated (PP population, p= 0.116) even at the chosen margin of 10%, which was considered to be low in the view of the CVMP. Safety of administration of Zuprevo was confirmed. The observed injection site reactions after intramuscular injection of Zuprevo are adequately addressed in the SPC and other product information.

**Overall conclusions:**

Based on the two clinical field studies provided, the CVMP expressed concern as to the limited support for metaphylactic efficacy. In account of the high response rates in some placebo groups it was suspected that study sites with low infection pressure had been included, which may have made the study less sensitive to detect differences in response between test treated and placebo treated animals. The applicant was requested to review the data taking into account only those study sites where a severe outbreak of SRD could be substantiated from a clinical point of view in order to assess if the subpopulation for which metaphylaxis is clinically justifiable can be identified.

The applicant reviewed the data and selected from both studies, Frénais (2013) and Petersen (2013), those study sites with a severe outbreak of SRD, defined by a mean respiratory score of at least 1.5 (out of 0–3) in the diseased animals (sentinels). Overall, 9 out of 17 study sites were selected as having had a severe SRD outbreak with an actual mean respiratory score of 1.68 (range of 1.5–2.1), the difference to the remaining 8 study sites with a non-severe outbreak was however small (actual mean respiratory score of 1.13, range 1.0–1.4). By pooling the study sites with severe SRD outbreak from both studies, mean success rates were 86.4% (range 73.5% – 100%) for Zuprevo compared to 67.1% (range 42.9% – 97.9%) for placebo. Super-superiority of Zuprevo for the chosen margin of 10 percent was shown for that subpopulation (lower confidence limit 11.5%). In addition, the applicant provided a separate post hoc analysis of the study sites with severe SRD outbreak in the study of Petersen (2013): 6 out of 10 study sites had a severe SRD outbreak according to the applicant's definition. The mean success rate following metaphylactic treatment with Zuprevo was 86.5% (range 76.7% – 94.4%) compared to 65.3% (range 42.9% – 83.3%) in saline treated animals. Super-superiority of Zuprevo over placebo could be demonstrated based on a lower confidence limit of 10.8% for the difference of metaphylaxis success rates.

The CVMP considered the selected threshold respiratory score for the classification in severe and non-severe outbreaks as being arbitrary but the rationale for the choice of threshold was acknowledged that there is no standard threshold that could be applied as to when metaphylactic treatment should be initiated. The CVMP did not accept the merging of the data due to the different design of the field studies and the major shortcomings in the design of the study of Frénais (2013). Therefore the CVMP focused on the separate re-analysis of the study sites with severe outbreak from Petersen (2013). The effect size of Zuprevo compared to saline-treated animals at these study sites was considered marginal from a clinical point of view. However, further review of the data from Petersen (2013) provided evidence that increasing differences in success rates between Zuprevo and placebo can be observed at study sites with a higher mean respiratory score of 1.8 or above, indicating a more severe outbreak of SRD.

In conclusion, the CVMP considered that the data provided were somehow weak; however, the CVMP acknowledged that there is currently no agreed study design for this type of treatment, and that the applicant had put adequate efforts into the study design that was submitted for the pivotal study of Petersen (2013). The CVMP also recognised that the type of disease (SRD) is known to benefit from

metaphylactic treatment, and that the efficacy of Zuprevo in the therapeutic treatment of SRD associated with the target pathogens has been established. Hence, the CVMP considered the metaphylactic claim approvable on condition that precautionary sentences warranting prudent use and information about clinical efficacy that can be expected are added in the SPC and other product information.

***Cross reference to already assessed data***

Additionally, the applicant referred to two studies already presented with the original application for Zuprevo in support of its initial authorisation. From these studies the CVMP concluded:

- In the negative-controlled study (Rohdich 2009 (V-0045-0149)) success was high after metaphylactic treatment with both tildipirosin and the placebo control. Superiority of tildipirosin over saline could not be shown.
- In the positive-controlled study (Petersen 2009 (V-0045-0225) ) success was high after metaphylactic treatment with tildipirosin and with the positive control (tulathromycin). Non-inferiority of tildipirosin (40 mg/ml solution for injection) compared to the positive control was shown. However, no healthy untreated animals (sentinels) were included in the study. Thus the risk for disease occurrence during the study period could not be determined and internal validity of the study was thus not confirmed. Furthermore, microbiological confirmation of SRD in the herds was weak. Data presented suggests the infectious pressure was low which would lead to erroneous conclusions.

The CVMP considers the earlier assessment of these two studies as still valid, and being not supportive for the metaphylactic treatment claim.

## Overall conclusions on the proposed new indication

MIC data of recently isolated target pathogen strains indicate unchanged susceptibility compared to MIC data determined before Zuprevo first was launched. According to preliminary breakpoints proposed for tildipirosin and target pathogens in swine respiratory disease the percentage of clinically resistant isolates was 0%. Information on the CLSI breakpoints is included in section 5.1 of the SPC. However, tildipirosin breakpoints have not been published yet and should therefore be indicated in the SPC as "proposed preliminary breakpoints" without mentioning a reference.

Two new clinical field studies (Frénais 2013, Petersen 2013) were submitted in support of the new metaphylactic treatment claim to be included in the indication. While the study of Frénais (2013) was considered not suitable due to the major shortcomings of the study design, the CVMP considers that the study of Petersen (2013) showed some support for the new claim of metaphylactic treatment of animals in contact with pigs suffering from SRD. On request of the CVMP post-hoc analyses were performed on the data collected in the Petersen study (2013) with the aim to explore the potential influence of disease severity on treatment outcome. This study was a placebo controlled multi-centre field study where outbreak of clinical disease was confirmed according to the following criteria: animals in at least 30% of the pens sharing the same airspace showed clinical signs of SRD, including at least 10% animals per pen within 1 day; or 20% within 2 days or 30% within 3 days. The post-hoc analyses demonstrated that in the herds with more severe clinical signs of respiratory disease among affected animals (more than 1.5 on a 3 graded scale) approximately 86% of the animals that were clinically healthy at time of treatment did not develop clinical signs of disease (i.e. metaphylaxis success rate was 86%) as compared to approximately 65% of animals in the untreated control group. The difference between placebo and Zuprevo treated groups was statistically significant.

The CVMP considered that the data to support a metaphylaxis claim was somehow weak given that efficacy evaluations were partly based on post-hoc analyses. However the CVMP acknowledged that there

is currently no agreed study design for this indication, and the applicant had put adequate efforts into the design of the pivotal clinical field study. It was also noted that there is no standard threshold that could be applied as to when metaphylactic treatment should be initiated, but the applicant had provided an adequate rationale for their choice of threshold. The CVMP also considered that, in line with the outcome of the post-hoc analyses, metaphylactic use is only indicated in cases of highly contagious and/or severe disease, and severe outbreaks of SRD are known to benefit from metaphylactic treatment. Taking also into account that pharmacodynamic studies and the agreed "treatment" indication had already demonstrated that Zuprevo would be effective against the causing pathogens in the proposed dose and posology, the CVMP considered that Zuprevo would also be effective when used metaphylactically.

The product information (SPC section 4.4) has been updated, stating precautionary sentences warranting prudent use and information about clinical efficacy that can be expected: "In line with responsible use principles, metaphylactic use of Zuprevo is only indicated in severe outbreaks of SRD caused by the indicated pathogens. Metaphylaxis implies that clinically healthy animals in close contact with diseased animals are administered the product at the same time as the treatment of the clinically diseased animals, to reduce the risk for development of clinical signs".

In addition, the CVMP considered that some details from the outcome of the clinical study should be included in the SPC to provide more information to the prescribing veterinarian: "The efficacy of metaphylactic use of Zuprevo was demonstrated in a placebo controlled multi-centre field study, when outbreak of clinical disease was confirmed (i.e. animals in at least 30% of the pens sharing the same airspace showed clinical signs of SRD, including at least 10% animals per pen within 1 day; or 20% within 2 days or 30% within 3 days). Following metaphylactic use, approximately 86% of the healthy animals remained free of clinical signs of disease (as compared to approximately 65% of animals in the untreated control group)."

Taking into account the above consideration, the CVMP agreed that the proposed type II variation (No C.I.4; new indication) was accepted subject to changes in the SPC and product information.

# 3. Benefit-risk assessment

## *3.1. Benefit assessment*

*Deletion of safety warning (piglets):*

The applicant has now demonstrated the safe use of the product in young piglets less than 4 weeks of age, and the special warning in the current SPC in regard to this population can be removed, widening the range of animals in which the medicine can be used.

*Metaphylactic use:*

The proposed direct benefit is use of the product for (treatment and) metaphylaxis of swine respiratory disease (SRD) associated with *A. pleuropneumoniae*, *P. multocida, B. bronchiseptica* and *H. parasuis* sensitive to tildipirosin, at the same dose and duration as already authorised for the current indication.

A clear and statistically significant effect of treatment was noted among herds with more severe clinical signs of respiratory disease but given that this information was generated post-hoc this weakens their supporting value. The CVMP acknowledged that there is currently no agreed study design to investigate for this indication however the study design that was submitted for the pivotal study was sufficiently justified. It was noted that there is no standard threshold that could be applied as to when metaphylactic treatment should be initiated and an adequate rationale for the choice of threshold had been provided. The CVMP also considered, in line with the outcome of the post-hoc analyses, that metaphylactic use is

only indicated in cases of highly contagious and/or severe disease and that severe SRD outbreaks are known to benefit from metaphylactic treatment. Taking into account also that pharmacodynamic studies and the agreed indication for use as treatment already demonstrated that Zuprevo is effective against the pathogens at the proposed dose and posology, the CVMP therefore concluded that Zuprevo would also be effective when used metaphylactically.

The product information has been updated, stating clearly new precautionary sentences warranting prudent use and information about clinical efficacy that can be expected.

### *3.2. Risk assessment*

The MIC data of target pathogen strains, isolated in 2011 and 2013 from swine suffering from respiratory disease indicate unchanged susceptibility when compared to MIC data determined before Zuprevo first was launched. None of the isolates were found to be clinically resistant to tildipirosin. With respect to resistance it is unlikely that the variation of Zuprevo 40 mg/ml saline for injection in pigs gives rise to animal health concerns.

Target animal safety has been demonstrated for piglets less than 4 weeks of age. However, some of the adverse reactions previously only noted at doses higher than the recommended therapeutic dose were seen in this young age group, and an appropriate warning was therefore added to section 4.6 (adverse reactions). No additional risks are associated with the inclusion of the new claim 'metaphylaxis' in section 4.2 of the SPC, as it follows the same posology as the already authorised "treatment" claim.

No additional risk to the user and the environment is associated with the inclusion of the new claim 'metaphylaxis' in section 4.2 of the SPC or the deletion of the warning sentence 'The safety in piglets less than 4 weeks of age has not been established. Use in young piglets only according to the benefit-risk assessment by the responsible veterinarian.' in section 4.5 of the SPC.

**Risk management or mitigation measures**

Appropriate warnings sentences are already included in the SPC to mitigate possible risks to the user, other animal species and the environment. A new warning has been added to address adverse reactions seen at the RTD in very young piglets.

### *3.3. Evaluation of the benefit-risk balance*

No changes to the risk for the user, target animal and the environment are envisaged.

Type II variation, No C.I.6 (deletion of warning):
The benefit-risk balance for use of Zuprevo in very young piglets is considered positive.

Type II variation, No C.I.4 (new indication):
The benefit-risk balance for the metaphylactic use of Zuprevo is considered positive.

## 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, is acceptable concerning the following changes:

- Type II variation, No C.I.6: Deletion of a warning in section 4.5: "The safety in piglets less than 4 weeks of age has not been established. Use in young piglets only according to the benefit-risk assessment by the responsible veterinarian."

- Type II variation, No C.I.4: Addition of a new therapeutic indication for metaphylactic use.

## *4.1. Changes to the community marketing authorisation*

Changes are required in the following Annexes to the Community marketing authorisation:

Annexes I, IIIA and IIIB.