Annex I

Scientific conclusions and grounds for suspension of the marketing authorisation

Overall summary of the scientific evaluation of Velactis

1. Introduction

Velactis is a veterinary medicinal product which was authorised in the European Union (EU) in December 2015 through the centralised procedure. The product is indicated for use in herd management programme of dairy cows as an aid in the abrupt drying-off by reducing milk production to reduce milk leakage at drying off; to reduce risk of new intramammary infections during the dry period; and to reduce discomfort. The active substance is cabergoline which blocks the release of prolactin and as a consequence reduces milk production. Velactis is presented as a solution for injection for intramuscular use with a recommended dose of 5.6 mg of cabergoline (corresponding to 5 ml of solution for injection) per animal to be given in one single injection at the day of drying off, within 4 hours after the last milking.

Velactis was placed on the EU market in March 2016, first in Denmark and The Netherlands. Analysis of the pharmacovigilance data available conducted by the CVMP indicated serious animal health concerns following the use of Velactis due to the number and severity of the adverse event reports including recumbency and death occurring in a short period after placing on the market. Taking into consideration that the product is intended for use in healthy pregnant cows the clinical signs reported were particularly notable. Consequently it was considered appropriate to determine if the benefit-risk balance of the product remained favourable and if regulatory actions were required; therefore, on 16 June 2016 the European Commission triggered a procedure in accordance with Article 45 of Regulation (EC) No. 726/2004, accordingly.

On 21 and 24 June 2016, respectively, the national competent authorities (NCAs) in Denmark and The Netherlands suspended the use of the product on their territories.

On 21 June 2016 the Agency was informed by the marketing authorisation holder (MAH) that the release of any further products into the distribution chain had been halted.

2. Discussion of data available

Between 16 March and 12 July 2016, 198 cases involving 319 animals were reported to EudraVigilance Veterinary (EVVet). Of these, 135 cases (208 animals affected) involved recumbency and 57 of these cows died or were euthanised. A further 14 deaths were reported in animals without recumbency. Adverse events were reported in 12 EU Member States, the majority of which occurred in Denmark.

The CVMP considered the adverse event reports, data from clinical and field studies and literature provided by the MAH, including information on the possible role of factors that may contribute to the occurrence of the adverse events. These included, for example, as animal related factors (e.g. breed, age/number of lactations, milk yield at the time of drying off, health status of animals, including intramammary infections); management factors (feed, husbandry, housing etc.); interactions with other medicines; quality (batch)-related effects; and/or geographical factors. A definitive conclusion could not be drawn concerning potential association between these factors and the adverse events.

The potential association between hypocalcaemia, recumbency and death and the use of the product was considered. However, the information appeared insufficient to allow a definitive conclusion on this hypothesis and further investigations were considered necessary to elucidate the underlying mechanism and potential factors that may contribute to the adverse events.

The Committee considered the measures proposed by the MAH to mitigate the risk of recumbency following use of the product to add special warnings for management of cows, in particular feed intake,

as part of an 'abrupt dry-off process'. However, supporting data were not considered sufficient to allow firm conclusion on the possible effect and/or potential interaction between dietary changes (e.g. feed restriction) and treatment with Velactis at drying-off, to support the proposed changes to the product information.

In addition, the MAH proposed updates to the product information to include recumbency as a new adverse reaction and the potential association with hypocalcaemia. However, the changes proposed were considered premature as the underlying mechanism and potential risk factors associated with these have yet to be determined.

Further investigations to identify the underlying aetiology of the adverse events and potential contributory factors, including hypocalcaemia, associated with these were considered necessary. These should include but not be limited to investigation of calcium status in late lactation in cows, for example, comparing treated and untreated cows and those with and without feed restrictions; investigation of conditions that could trigger milk fever/postparturient hypocalcaemia in late lactation and the prevalence of this condition (with or without cabergoline treatment). Appropriate scientific justification should be provided to support the proposals for feeding regimes when administering Velactis.

The CVMP considered the MAH's ongoing or planned studies relating to the safety and efficacy of Velactis. However, no firm conclusions could be drawn relating to these studies based on the data available.

The number and severity of the adverse events reported was considered remarkable particularly taking into consideration the relatively short time frame in which they occurred. Recumbency is not considered to be an event commonly associated with drying-off in cows.

The data evaluated indicated a potential association between use of Velactis and adverse events including recumbency, although the underlying mechanism and potential contributory factors associated with the events have yet to be determined. The proposed risk mitigation measures and further studies planned by the MAH do not appear to adequately address the potential risks to healthy cows in calf at present, and further investigations to minimise the risk of such adverse events are required.

3. Benefit-risk evaluation

Velactis is a recently authorised veterinary medicinal product containing the active substance cabergoline. The product has been shown to be efficacious when used as an aid in the management of dairy cows the day of abrupt drying-off by reducing milk production, and as a consequence to reduce milk leakage at drying off, to reduce the risk of new intramammary infections during the dry period and to reduce pain and discomfort. Additional benefits include facilitation of drying-off management and reduction of the incidence of development of new intramammary infections and as a consequence it can be expected that it may reduce the need for antimicrobial treatment.

Velactis was known to be generally well-tolerated on the basis of the assessment of the application of granting of the marketing authorisation. Within the first 4 months of placing the product on the EU market, between 16 March and 12 July 2016, 198 cases involving 319 animals were reported. Of these, 135 cases (208 animals affected) involved recumbency and 57 of these cows died or were euthanised. A further 14 deaths were reported in animals without recumbency. Adverse events occurred in 12 EU Member States, the majority of which in Denmark.

The data evaluated indicate a potential association between use of Velactis and adverse events including recumbency, which is notable in some EU Member States. The underlying mechanism and

potential contributory factors associated with the events remain unclear at present. Risk management measures proposed by the MAH were not considered sufficient to minimise the risk of healthy pregnant cows experiencing such adverse events which were considered serious. The underlying mechanism and potential contributory factors associated with the adverse events have yet to be determined and therefore further investigations are required.

The CVMP considered that the potential risk of serious unexpected adverse events such as recumbency, some of which are fatal, following administration of Velactis as recommended to healthy cows, was unacceptable and that the risks outweigh the benefits of the product. The risk mitigation measures proposed by the MAH were considered to be insufficient since the underlying mechanism for the events observed and potential contributory factors have yet to be determined and further investigations were considered necessary. Consequently, the CVMP concluded that the benefit-risk balance of the product was considered unfavourable, at present, under the authorised conditions of use and therefore recommended suspension of the marketing authorisation.

In addition on the basis of the benefit-risk evaluation in view of the estimated amount of product available within the distribution chain and the severity and frequency of the observed adverse events, as a precautionary measure to prevent further exposure and thereby minimise the risk of further adverse events, the CVMP recommended that the product should be recalled at all levels of the distribution chain - wholesaler, retail and user (veterinarians/farmers) - to ensure timely removal of product and that further use is prevented.

Grounds for suspension of the marketing authorisations

Whereas

- serious adverse events including recumbency and death reported after the use of Velactis appear to indicate an association with use of the product;
- the underlying mechanism and potential contributory factors associated with the adverse events have yet to be determined;
- no specific risk management measures could be recommended to ensure that the product is not associated with an unacceptable risk of serious adverse events under the authorised conditions of use;
- the CVMP concluded that the risks outweigh the benefits of the product and therefore the benefit-risk balance for Velactis is unfavourable under the authorised conditions of use;

therefore the CVMP recommended the suspension of the marketing authorisation for Velactis.

In addition, the CVMP considered that in view of the estimated amount of product available within the distribution chain and the severity and frequency of the observed adverse events, as a precautionary measure to prevent further exposure and thereby minimise the risk of further adverse events, the product should be recalled at all levels of the distribution chain - wholesaler, retail and user (veterinarians/farmers) - to ensure timely removal of product so it does not get used.

Annex II

Conditions for lifting the suspension of the marketing authorisation

The following conditions should be fulfilled by the marketing authorisation holder to provide the CVMP with scientific evidence to:

- elucidate the underlying cause of the adverse events and potential contributing factors, which may include but should not be limited to hypocalcaemia;
- demonstrate that the administration of the product to cattle does not lead to an unacceptable risk of serious adverse events, including recumbency and death and if necessary, to propose management measures to mitigate this risk that can be included in the product information; and
- demonstrate a favourable benefit-risk balance for the product.

It is recommended that the authorisation be suspended until all conditions are satisfactorily addressed by the submission of data (via an appropriate variation application).

The above-mentioned data should be provided to the CVMP for assessment as soon as available but no later than 6 months before the due date for submission of the renewal application for the marketing authorisation for the product.