8 October 2015
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Velactis (EMEA/V/C/003739/0000)

International non-proprietary name: cabergoline

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

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Introduction

On 30 August 2013, the applicant CEVA Santé Animale submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Velactis, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the CVMP on 9–11 April 2013 as the applicant showed that the product would provide a significant therapeutic innovation. The CVMP appointed W. Schlumbohm as rapporteur and E. Persson as co-rapporteur for the assessment of the application.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

Velactis is a solution for injection for dairy cattle, containing 1.12 mg/ml cabergoline as the active substance. Velactis is presented in single dose vials of 5 ml and multidose vials of 25 ml or 50 ml.

The applicant initially applied for the following indication: *Prevention of new intra-mammary infections during the dry period. Reduction in milk leakages at drying-off. Reduction in pain and discomfort after the drying-off due to a reduction in udder engorgement and udder pressure.*

The proposed withdrawal period for meat and offal is 23 days; for milk, the proposed withdrawal period after calving is zero or four days, when the dry period is at least 32 days or less than 32 days, respectively.

On 8 October 2015, the CVMP adopted an opinion and CVMP assessment report.

On 9 December 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for Velactis.

Scientific advice

The applicant received scientific advice from the CVMP on 10 March 2010, 17 June 2010 and 27 April 2010, followed up by another scientific advice on 13 September 2012. The scientific advice concerned the establishment of the MRL, quality and clinical aspects of the dossier, and was largely followed by the applicant.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated October 2012) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person (QP) responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

A QP declaration has been provided by the QP of the manufacturer of the finished product stating that the active substance manufacturer operates in compliance with the detailed guidelines on Good Manufacturing Practice for starting materials. The finished product is manufactured and packed in the EU. Batch release is carried out by CEVA Santé Animale, Libourne, France. The manufacturing site complies with GMP requirements; a corresponding GMP certificate has been provided.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system is considered in line with legal requirements.

The GMP certification of both the active substance and finished product manufacturing sites have been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is a clear, pale yellow, non-aqueous (oily) solution for injection for intramuscular use. It contains the active ingredient cabergoline and two excipients, dimethyl sulfoxide (DMSO) and medium chain triglycerides (MCT). Each ml contains 1.12 mg cabergoline.

Container

The product is presented either in single dose amber (brown) type I glass vials containing 5 ml of solution or in multidose amber (brown) type II glass vials containing 25 or 50 ml of solution. The vials are closed with bromobutyl rubber stoppers and sealed with aluminium crimp seals with plastic flip tops.

The vials and the rubber stoppers comply with the requirements of the relevant European Pharmacopoeia (Ph. Eur.) monographs (No 3.2.1 and No 3.2.9, respectively). Specifications, certificates of analysis and technical drawings for the vials and bromobutyl rubber stoppers have been provided demonstrating compliance with the proposed specifications. Results of migration and extraction studies demonstrate the good compatibility of the rubber stopper with the finished product.

The validation of the sterilisation process of the glass vials has been sufficiently demonstrated.

The validation of the sterilisation process of the rubber stoppers has been demonstrated.

Development pharmaceutics

The aim was to develop a solution for injection, containing cabergoline as the active substance. On the basis of experience gained during the development of similar products authorised in the EU, an oily solution using MCT as the vehicle was developed.

The finished product contains no preservative. It has however been demonstrated that the formulation fulfils the A criteria of the Ph. Eur. general chapter, 5.1.3. 'Efficacy of antimicrobial preservation', both before first broaching and also during an in-use stability test. The applicant has therefore demonstrated that the formulation provides adequate protection against expected levels of microbiological contamination both during storage and use after first opening/broaching. The following general advice is nevertheless included in the SPC (and package leaflet) "Normal aseptic procedures for administration of an intramuscular injection should be followed. Only use a dry sterile needle and avoid the introduction of

humidity/water during use". The omission of an antimicrobial preservative in the formulation has therefore been justified.

Sterilisation method of the finished product has been justified.

The use of amber glass vials has been justified by the poor light sensitivity of cabergoline.

The pharmaceutical development section is considered comprehensive.

The choice of the raw materials incorporated in the formulation is discussed and justified.

Method of manufacture

The finished product is a simple non-aqueous solution formulation. Validation of the manufacturing process, has been performed. Appropriate in-process controls are carried out.

The manufacturing process cannot be considered as a standard process. The batch size is therefore limited to the biggest batch size used for process validation.

The manufacturing process is considered reliable and able to produce a consistent finished product.

Control of starting materials

Active substance

The active substance cabergoline is described in the European Pharmacopoeia (Ph. Eur.) and a copy of the current EDQM Certificate of Suitability for the active substance manufacturer has been presented.

In addition to the Ph. Eur. parameters a limit for any unspecified impurity and limits for the residual solvents are specified in the CEP. Residual solvents are determined by a headspace GC-method as described in the CEP.

The drug substance is tested in accordance with both the requirements of the Ph. Eur. monograph and the additional testing required by the Certificate of Suitability.

Certificates of analysis from the finished product manufacturer of three batches of cabergoline are presented. All results conform to the Ph. Eur./CEP specification. Limits for solvents are appropriate and in line with the VICH guidelines on residual solvents.

Excipients

Both the excipients, dimethyl sulfoxide and medium chain triglycerides, are described in the European Pharmacopoeia and are controlled according to the relevant current monograph.

Representative certificates of analysis of the excipients have been provided demonstrating compliance with the specifications.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01-Rev.3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests during production

Not applicable.

Control tests on the finished product

The proposed finished product specification at release is appropriate to control the relevant parameters of the dosage form. The test parameters include appearance, freedom from foreign particles, relative density, identification of cabergoline, clarity of the solution, degree of colouration, extractable volume, water content, assay of cabergoline and sterility, and will be routinely checked at release. The specified limits have been justified.

The shelf life specification also includes limits for the degradation products of cabergoline. Limits for known impurities, unknown impurities and total impurities have been specified and justified by the stability data presented. All the differences and the associated limits have been justified by batch analyses and stability data.

Analytical test methods used for the control of the finished product are well described and adequately validated in accordance with current VICH guidance.

The results of the analysis of three industrial batches and one pilot batch of finished product are presented which comply with the release specification.

Stability

For the active substance, the Ph. Eur. Certificate of Suitability states a re-test period of 5 years when stored at 2–8 °C in a sealed double polyethylene bag inside an aluminium container.

Stability studies on the finished product were conducted in accordance with the relevant EU and VICH stability guidelines. One pilot batch and three industrial scale batches were included in the stability studies. The bulk solution of the industrial batches was split into three sub-batches, one for each of the three different vial sizes (5 ml, 25 ml and 50 ml). The final container/closure system was used. Some vials from each batch were stored in the inverted position. Results covering 36 months at 25 °C/60% RH and 30 °C/65% RH and 6 months at 40 °C/75% RH are available; all results comply with the shelf life specification. A shelf life of 3 years without any specific storage conditions has therefore been justified.

Photostability study data show that both the drug substance and the finished product are sensitive to light. The results from samples of the drug product in the marketing packaging exposed to light comply with the specifications. The chosen primary packaging has therefore been demonstrated suitable for the protection of the finished product and no warning in the product information is therefore necessary that the product needs to be protected from light.

In-use stability studies have been performed with three batches of the finished product (tested both during and at the end of its shelf life). The in-use shelf life specification is identical to the shelf life specification. All results are in compliance with the specification. The results of the in-use stability studies support an in-use shelf life of 28 days.

Overall conclusions on quality

The finished product is a non-aqueous (oily) solution of 1.12 mg/ml cabergoline for intramuscular use presented in amber glass single dose (5 ml) and multidose vials (25 and 50 ml). The omission of a

preservative has been adequately justified. The composition has been justified. The chosen immediate container is demonstrated to be suitable.

The active substance and the two excipients meet their current respective Ph. Eur. requirements.

The active substance is the subject of Ph. Eur. certificate of suitability, which includes some additional (to the Ph. Eur. monograph) tests.

The manufacturing process of the finished product has been sufficiently described. To date the process has been validated using production batches. As the manufacturing process cannot be considered as a standard process, the batch size is therefore limited to the biggest batch size used for process validation.

The proposed finished product specifications, both at release and end of shelf life, are acceptable.

Stability data from up to 36 months under long-term and intermediate storage conditions and from up to 6 months under accelerated storage conditions have been presented. The proposed shelf life of 3 years without any storage precautions is accepted.

The proposed in-use shelf life of 28 days has been adequately justified.

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate the consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Part 3 – Safety

The safety of cabergoline has been documented by published data and experimental studies in laboratory animals. Cabergoline was assessed by the CVMP in the context of the establishment of MRLs, and the key findings of the toxicity studies are described in the European public MRL assessment report (EPMAR – EMA/CVMP/656490/2013). Therefore, only a summary of the toxicology data is given in this assessment report.

Safety documentation

Pharmacodynamics

The potent and long-lasting prolactin inhibiting effects of orally administered cabergoline was demonstrated by published data in laboratory animals.

Cabergoline acts primarily directly on the pituitary lactotrophic cells by stimulating specifically dopaminergic D2 receptors, causing inhibition of prolactin secretion and, consequently, inhibition of lactation in rats, dogs and rabbits. The dog was the most sensitive species in respect to primary pharmacodynamic effects of cabergoline: the average daily weight gain of puppies declined with increasing levels of administered cabergoline in lactating bitches. The NOEL for effects on lactation was 1 µg/kg bw. Data gained from humans are comparable: no effects on serum prolactin levels were seen at 1.7 µg/kg bw in man, whereas the lowest therapeutic dose is 2 µg/kg bw.

Secondary pharmacodynamic effects as emesis (in dogs) and gastric emptying (in rats) occurred at doses somewhat higher than those inhibiting prolactin secretion in laboratory animals. The potential of cabergoline to affect the digestive tract has also been described in cows.

In several animal species prolactin is important for the maintenance of a functioning corpus luteum during pregnancy. However, in ruminants, functioning of the corpus luteum is believed to depend on substances

secreted by the embryo/foetus, and prolactin is possibly not essential for normal luteal function during the oestrus cycle in ruminants.

In cows, the clinically most relevant consequence of the prolactin-inhibitory activity of cabergoline is the reduction of milk production, as demonstrated in an explorative dose determination study at drying-off at three different doses close to the proposed treatment dose of approximately 2 µg/kg bw (i.e. 1.333, 4, and 12 µg/kg bw). However, there was no clear treatment effect on udder pressure, perimeter of the inter-teat distance or cistern diameter. Cabergoline reduced prolactin plasma levels for 8 to 14 days without significant differences between doses tested. Prolactin can, therefore, not serve as a biomarker for the efficacy of cabergoline. In addition, prolactin plasma levels could not be correlated with specific clinical endpoints. A dose effect relationship was indicated in the explored dose range but dose dependency of milk yield was demonstrated with a statistically significant difference only between placebo and the highest dose (12 µg/kg bw) tested. Based on pk/pd considerations (MPK/C646.0/0944), a dose range between 4.8–8.7 µg cabergoline/kg bw resulted in a 51% reduction of milk production. A notable seasonal variation of prolactin plasma levels with low basal prolactin levels in cows in winter was observed, but cabergoline inhibited prolactin equally in winter and in late summer.

Pharmacokinetics

Absorption:

Cabergoline is rapidly absorbed after oral administration in rats and dogs. Oral bioavailability is at least 50%. AUC and C_{max} increased approximately in proportion to the dose. More than 60% of administered cabergoline is bound to plasma proteins in vivo. During repeated (oral) treatment of rats for 21 days, steady state plasma radioactivity concentration was found to be reached after 14 daily administrations. The mean concentrations of radioactivity were 1.8 times higher compared with those seen after single administrations.

(Plasma/Tissue) Distribution:

Cabergoline is rapidly and extensively distributed in tissues and organs following oral administration to rats. Highest concentrations of cabergoline were found in the liver, followed by the pituitary gland, adrenals, spleen, kidneys and lungs. At seven days (168 hours), residues were also seen in milk.

Metabolism:

Cabergoline is rapidly metabolised: in rats the metabolites reached their plasma peak levels already 1 to 2 hours after administration, whereas the unchanged active substance reached peak levels at 8 hours.

Excretion:

The main route of elimination of cabergoline is faecal (> 80%), largely as a result of extensive biliary excretion. A relevant amount of cabergoline undergoes enterohepatic circulation. Urine accounted for only 4 to 15% of the administered dose (oral or intravenous) in rats, and elimination was practically complete within 48 to 72 hours. Exhalation is not a relevant excretion route for cabergoline. Elimination half-lives were 17 to 40 hours. Unchanged drug plasma levels decreased with a plasma half-life of approximately 10 hours.

In cattle (non-lactating, non-pregnant adult cows), a GCP-compliant bioavailability single dose study was provided, using a randomised two-period, two-treatment parallel design at the recommended dose of 5.6 mg cabergoline/animal following intramuscular or intravenous administration. Blood sampling was performed once before treatment and at defined intervals after treatment. A wash-out period of 14 days was kept. Analysis of data was done descriptively. This study confirmed that cabergoline is rapidly and

readily absorbed following intramuscular administration. Peak plasma concentrations of 150 ± 21.6 pg/ml were reached at 3 hours post dosing. The AUC_{0-4} values following intramuscular administration and intravenous administration were 2363 ± 246 h*pg/ml and 2570 ± 213 h*pg/ml, respectively. A similar pattern was determined for the $AUC_{0-\infty}$, i.e. 2488 ± 257 (i.m.) and 2758 ± 233 (i.v.) h*pg/ml. From these data an absolute bioavailability of 91±10% has been deduced. After intramuscular administration the terminal plasma half-life was found to be 19 hours. The mean residence time of about 23 hours was similar to that for the intravenous administration.

Furthermore, deduced from the data of a combined pharmacodynamic and pharmacokinetic study the dose linearity for AUC and C_{max} of cabergoline has convincingly been shown at a dose range of 1.33–12 µg/kg.

For more information on pharmacokinetics in cows, see also part 3B.

Toxicological studies

Single dose toxicity

Cabergoline showed a moderate acute oral toxicity (LD_{50} in mice: 331 mg/kg, in rats: 588 mg/kg) in the data submitted with sialorrhea and prostration in rats, and hyperactivity and convulsions in mice.

Repeat dose toxicity

After repeated oral administration, cabergoline showed a low potential for toxicity, when given at doses up to 50 µg/kg bw/day in rats, and up to at least 320 µg/kg bw/day in monkeys, respectively.

The main effects were seen in the ovaries in female rats. An overall NOEL of 5 µg/kg bw/day was established for repeat dose toxicity in the rat, based on increased ovarian weights associated histopathologically with an increase in the number and size of corpora lutea at 50 µg/kg bw/day in females. Minor effects were a slight but significant reduction of cholesterol concentrations and decreased pituitary weights in females and a decreased urea serum concentration in males at 50 µg/kg. At higher oral doses (400 µg/kg bw/day and higher) additional toxic effects were observed such as neurological excitation, poor general condition, changes in clinical chemistry and haematology, and hyperplasia of the reticular and fascicular zones in the adrenals. In monkeys, high oral doses of cabergoline caused mortality (at 1250 µg/kg bw/day and higher).

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

For data in the target species, see part 4 (target animal tolerance).

Effects observed in one generation and two generation studies in rats at 12 µg/kg bw/day were due to the pharmacodynamic mode of action of cabergoline causing a low fertility rate. An overall NOEL of 6 µg/kg/day was established for reproductive performance in rats of the F0 and F1 generations. Maternal effects were limited to decreased food consumption in lactating females of the F0 and F1 generation. A NOEL of 3 µg/kg/day was established for maternal effects. For developmental toxicity of offspring an overall NOEL of 3 µg/kg/day was established, based on the reduced body weights/body weight gains in F2 pups during lactation.

Data from developmental toxicity studies have shown that pregnant rats are far more sensitive to the effects of cabergoline than pregnant rabbits: the administered doses in rats were approximately 1 to 2 orders of magnitude lower than in rabbits.

A reduced fertility rate was seen in rats at 20 µg/kg bw/day caused by pre-implantation losses, which were considered a result of the inhibition of prolactin secretion in the dams. At 40 µg/kg bw/day only 2 dams became pregnant. At this dose severe inhibition of implantation and/or early embryonic death were seen. In rabbits, no substance-related effects of cabergoline on fertility or development were seen.

In rats and rabbits, a dose-dependent decrease of body weight gain was observed during the early treatment stage (GD6 to GD9). In does, these effects were already seen at the lowest dose (0.5 mg/kg bw/day) and were associated with a dose-dependent decrease of mean food consumption and caused body weight losses in both highest dose groups (2 and 10 mg/kg bw/day).

The following NOELs were established from the developmental toxicity studies: in rats 10 µg/kg bw/day for maternal toxicity and 20 µg/kg bw/day for developmental toxicity. In rabbits, no NOEL for maternal toxicity was established due to effects on body weight at all doses, and 10 mg/kg bw/day for developmental toxicity (the highest dose tested).

Cabergoline did not show teratogenic potential.

Mutagenicity/genotoxicity

Cabergoline was tested in two assays for mutagenic activity (bacterial and mammalian cells) and in an in vivo test for clastogenic activity, the mouse micronucleus test. Cabergoline did not show a genotoxic potential.

Carcinogenicity

No carcinogenicity studies have been conducted with cabergoline. This is acceptable as cabergoline has no structural similarity with known carcinogens, no pre-neoplastic lesions were identified in toxicity studies and no mutagenic potential was detected in a battery of genotoxicity tests.

Studies of other effects

No signs of immunotoxicity and neurotoxicity were observed in repeat dose toxicity studies. Therefore, no specific studies were performed.

Three acute toxicity studies were performed with the commercial formulation of Velactis according to OECD-Guidelines. These demonstrated that the final formulation has no skin or eye irritation potential, but that the product was a skin sensitizer in the murine local lymph node assay (LLNA).

Cabergoline is used therapeutically in humans for its inhibitory effect on prolactin secretion for the treatment of prolactinomas, for the inhibition of puerpal lactation and for the treatment of parkinsonism. Its safety profile in humans is well known. There were no effects of cabergoline reported in more than 400 pregnant women treated for hyperprolactinaemia. The safety and efficacy of cabergoline in children less than 16 years has not been established, which is considered acceptable for this type of product. When given twice weekly, a dose of 2 µg/kg bw has been shown to be effective in inhibition of prolactin secretion in some patients suffering of hyperprolactinaemia.

User safety

A user safety risk assessment was performed in line with the CVMP Guideline on User Safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

The most likely user is a veterinarian or a farmer. Possible exposure scenarios are considered to be acute based on the single event of administration. Accidental self-injection and accidental dermal contact due to spillage during handling and administration of the product are considered to be the most relevant exposure routes.

In pharmacological and toxicological studies, effects observed at lowest effective doses are related to the mode of action of cabergoline. Therefore, the pharmacological oral NOEL of 1.7 µg/kg bw and the lowest oral therapeutic dose in humans of about 2 µg/kg bw are considered most relevant for the quantitative user risk assessment. The calculated acute exposure due to accidental self-injection is clearly above these limit values: 10% of the injected volume of 5 ml of Velactis may be assumed as a worst case scenario containing 0.56 mg of cabergoline, which corresponds to 9.3 µg/kg bw cabergoline systemically available. Therefore, care should be taken when handling the veterinary medicinal product. A general warning sentence is included. In addition, due to the mode of action of the cabergoline (inhibition of prolactin secretion) and the demonstrated effects on lactation as well as on fertility and intrauterine survival, pregnant women, women attempting to conceive and breastfeeding women should avoid contact with the product. Relevant warnings are included in the SPC.

Dermal exposure is considered not relevant for a pharmacological or systemic toxicological effect. However, since the product has been shown to be a skin sensitizer, it is proposed, that persons with a known hypersensitivity to the active ingredient or any of the excipients should avoid contact with Velactis. Additionally, the user is directed to wash hands after administration of the product.

In relation to risks for children, the warning on the outer box "Keep out of the sight and reach of children" is considered satisfactorily.

The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the VICH guidelines. The predicted environmental concentration (PEC) for soil was calculated in accordance with the guideline on environmental impact assessment for veterinary medicinal products – Phase I (VICH GL6,CVMP/VICH/592/98-FINAL) and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1). The initial PEC in soil (PEC_{soil}, initial=0.021 µg/kg and 0.013µg/kg for pasture animals and intensively reared animals, respectively) is far below the trigger value of 100 µg/kg soil.

However, the active ingredient cabergoline is considered a substance with potential endocrine disrupting properties. Cabergoline is a synthetic ergot derivate and acts as dopamine receptor agonist on D2-receptors. When administered to dairy cows at drying-off as recommended, approximately 66% of the treatment dose is released into the environment, mainly in metabolised form. Dopamine receptors are found in a wide range of wildlife animals including invertebrates and vertebrates like fish.

There is strong scientific evidence from publicly available literature that dopamine receptor agonists have an impact on reproduction, sexual development and behaviour. Consequently an increase of cabergoline

in the environment could have adverse effects on reproduction in wildlife below a PEC_{soil} of 100 µg/kg. Therefore, further assessment was considered necessary to address specifically the concerns related to the potential endocrine disruptive activity of the product.

A targeted Phase II environmental risk assessment was submitted in accordance with VICH GL38 (CVMP/VICH/790/03-FINAL), which included tests on physico-chemical properties, the environmental fate and behaviour of cabergoline in soil, terrestrial effects (toxicity to *Collembola* and earthworms) and aquatic effects studies.

Based on the data provided, it could be concluded that cabergoline is rapidly metabolised and degraded in soil, and unlikely to pose a risk to terrestrial organisms.

In regard to the aquatic effects studies, no Fish Full Life Cycle Test according to US EPA OPPTS 850.1500 and OECD Detailed Review Paper on Fish Life-Cycle Test (ENV/JM/MONO (2008) 22) was submitted. In order to address specific concerns related to the potential endocrine disrupting properties of cabergoline such information was considered necessary. However, a Fish Sexual Development Test (OECD 234) and a Fish Short Term Reproduction Assay (OECD 229) were provided with the argumentation that both tests together would cover all but one endpoint of the Fish Full Life Cycle Test, and would be appropriate to fully evaluate the endocrine disrupting properties of cabergoline in aquatic species.

The Committee, however, disagreed with this argumentation, and considered that all the life stages potentially exposed to cabergoline and the endpoints to be measured should be covered in one test, and not be collected from different tests. In addition, the time until first spawning, which is likely of relevance given the mode of action of cabergoline, was not covered in any of the two studies. The results of the short Term Reproduction Assay clearly indicate that anything related to reproduction is population relevant. However, this would need to be assessed in a test, where juvenile and adolescence life stages are exposed as well, as dopamine receptor agonists like cabergoline are effecting also puberty and early steps of gametogenesis. This can only be assessed in a Full Life Cycle test, were fish are exposed from early life stages up to the reproduction stage. Without the results of a Fish Full Life Cycle Test a knowledge gap still exists.

The CVMP concluded that cabergoline is unlikely to pose a risk to terrestrial organisms, but might have harmful effects on aquatic species. Therefore, as a precautionary principle, appropriate risk mitigation measurement has been included in the SPC for treated cows not to have access to open water, and not to contaminate watercourses with faeces until at least 5 days after administration of the product.

Overall conclusions on the safety documentation

Cabergoline showed a moderate acute oral toxicity (LD_{50} in mice: 311 mg/kg, in rats: 588 mg/kg) with sialorrhea and prostration in rats and hyperactivity and convulsions in mice. After repeated oral administration, cabergoline showed a low potential for toxicity, when given at doses up to 50 µg/kg bw/day in rats and up to at least 320 µg/kg bw/day in monkeys, respectively. The main effects were seen in the ovaries in female rats. A NOEL of 5 µg/kg bw/day was established for repeat dose toxicity in the rat.

An overall NOEL of 6 µg/kg/day was established for reproductive performance in rats based on a low fertility rate seen at 12 µg/kg bw/day in the F0 and F1 generations. Maternal effects were limited to decreased food consumption in lactating females of the F0 and F1 generation with the NOEL for maternal effects established as 3 µg/kg/day. For developmental toxicity a NOEL of 3 µg/kg/day was established, based on the reduced body weights/body weight gains in F2 pups during lactation.

The doses administered in developmental toxicity studies were approximately 1 to 2 orders of magnitude lower in rats than in rabbits. In rats, a NOEL of 10 µg/kg bw/day was established for maternal toxicity

based on a low fertility rate at 20 µg/kg bw/day and a NOEL of 20 µg/kg bw/day was established for developmental toxicity based on early embryonic deaths. No NOEL could be established for maternal toxicity in rabbits, since a decreased body weight gain was observed during the early treatment stage (GD6 to GD9). A NOEL of 10 mg/kg bw/day was established for developmental toxicity in rabbits. Cabergoline did not show a teratogenic potential.

Cabergoline was not genotoxic and was considered to have no carcinogenic potential.

The product has no skin or eye irritation potential, but it was a skin sensitizer in the murine local lymph node assay (LLNA).

Cabergoline is used therapeutically in humans for its inhibitory effect on prolactin secretion in the treatment of prolactinomas, for the inhibition of puerpal lactation and for the treatment of parkinsonism. The lowest therapeutic dose is 2 µg/kg bw.

The excipients in the final formulation are dimethyl sulfoxide (DMSO) and medium chain triglycerides (MCT). Both are generally recognized as safe.

The product does not pose an unacceptable risk to the user when standard personal hygiene is maintained and the product is used in accordance with the SPC. However, a warning relating to the potential risk for women attempting to conceive or breastfeeding has been added to the SPC and product information.

Cabergoline is unlikely to pose a risk to terrestrial organisms, but might have harmful effects on aquatic species. Therefore, advice has been included in the SPC and other product literature that treated cows should not have access to open water and should not contaminate watercourses with faeces for at least 5 days after administration.

Residues documentation

Identification of the product concerned

Cabergoline (N-[3-(dimethylamino)propyl] N-[(ethylamino)carbonyl]-6-(-propenyl)-8ß-ergoline-8-carboxamide) is a specific D2 dopamine receptor agonist and acts as a prolactin inhibitor (it inhibits prolactin secretion which leads to the inhibition of lactation).

The formulation used in the residue studies was representative of the commercial formulation.

Residue studies

Four ^{14}C-radio tracer studies were conducted to investigate the pharmacokinetic behaviour and biotransformation in target animals, dairy cattle. Further, these studies provided information/data on total residue concentrations of cabergoline in tissues and milk of dairy cows. The identification of the marker residue and marker to total ratios was based on the results of these studies. The studies, which were all performed according to GLP were provided in the MRL application dossier for cabergoline, and descriptions and assessments of the studies are included in the European public MRL assessment report (EPMAR) for cabergoline (EMA/CVMP/646490/2013).

Pharmacokinetics

The pharmacokinetics of cabergoline were studied in two absorption, distribution, metabolism and elimination (ADME) studies following a single intramuscular injection of 10 µg ^{14}C-cabergoline in lactating cattle. Cabergoline was shown to be rapidly absorbed, distributed and excreted. The maximum

concentration of total residues in plasma was reached between 0.5 and 6 hours after administration. Parent cabergoline in plasma peaked between 4 and 8 hours after administration and declined to below detectable concentrations at 120 hours after administration.

The highest concentrations of ^{14}C-total residues were measured in injection site, lungs, kidney, bile and liver at 12 hours after administration. Concentrations of total radioactivity declined quickly in most tissues except for pituitary gland and liver. By contrast, the concentration of parent ^{14}C-cabergoline detected in the liver declined significantly over 120 hours indicating that radioactive residues were mainly associated with metabolites of cabergoline. The extraction recovery of total radioactive residues in liver decreased with increasing sample time and declined from 69.9% at 0.5 hours after administration to 15% at 20 days post dosing. Results indicated a relatively high portion of non-extractable residue. Although it was not possible to quantify the amount of bioavailable/non-bioavailable residues of the bound residues, residues in liver appear to be less than completely bioavailable. ^{14}C-total residue concentrations in fat, skeletal muscle and milk were very low. In plasma and milk parent cabergoline was detected in very low quantities.

Three tissues metabolites M1, M2 and M3 were found. The major metabolite M2, which could not be chemically identified, represented 22–27% of total extractable metabolites in liver and 10% of total extractable metabolites in kidney up to 5 days after administration. The other metabolites, M1 (also not identified) and M3 (a carboxylic acid derivative of cabergoline) were minor components in liver and kidney and represented less than 10% of total extractable metabolites. Data indicate that the M2 metabolite is produced by both rat and cow microsomes, and that it has negligible activity on D2 receptors.

Depletion of residues

In radiometric absorption, distribution, metabolism and elimination (ADME) studies in dairy cows (n=6) tissues and milk were investigated following a single intramuscular injection of approximately 10 µg ^{14}C-cabergoline per kg bw. The animals were slaughtered at 12, 72 and 120 hours and in a second study at 10 and 20 days after treatment.

Mean concentrations of total radioactivity were highest in kidney (140 µg equivalents/kg), liver (87.5 µg equivalents/kg) and at the injection site (189 to 217 µg equivalents/kg) at 12 hours after administration, low concentrations were detected in fat (1.7 µg equivalents/kg) and muscle (4.56 µg equivalents/kg). Radioactivity depletion was rapid in kidney and injection site core but less rapid in liver.

Parent ^{14}C-cabergoline was detected in relevant concentrations in all edible tissues with highest mean concentrations at 12 hours after administration (kidney 92.6 µg/kg, liver 31.4 µg/kg and injection site core 180.3 µg/kg). Parent drug concentration declined rapidly in all tissues to values below the limit of quantification of the analytical method at day 20 after administration.

In a non-radiolabelled residue depletion study in dairy cows (n=20) liver, kidney muscle, fat and injection site (core and surround) were investigated following a single intramuscular injection of an average of 8.6 µg cabergoline per kg bw. The animals were slaughtered at 3, 6, 11, 16 and 21 days after treatment. Cabergoline concentrations were highest in kidney and liver at all slaughter days with maximum levels seen at day 3. Residue concentrations at the injection site (core and surround) were below the limit of quantitation (LOQ) of the analytical method in all samples at day 16 for the first time.

Two radiometric residue studies in milk were conducted in pregnant dairy cows (each n=4). Milk was investigated following a single intramuscular injection of 9 to 11 µg ^{14}C-cabergoline per kg bw at drying-off, on average forty to sixty days before calving. Milk was collected twice a day as colostrum and at the first milk release for the first 10 days following calving. Concentrations of total ^{14}C-radioactivity expressed as µg cabergoline equivalents/kg were in the range of 0.025 to 0.050 µg equivalents/kg at day

1 and declined to less than 0.017 to 0.021 µg equivalents/kg at day 2. After this time, concentrations of radioactivity in milk remained below the limit of detection. The concentration of parent ^{14}C-cabergoline in milk was below the limit of quantification (0.00625 µg/kg) at all times from the first milking onwards.

In a non-radiolabelled residue depletion study in pregnant dairy cows (n=10) milk was investigated following a single intramuscular injection of approximately 10 µg cabergoline per kg bw at the beginning of the dry period, on average 63 days before calving (range: 46–91 days). Milk was collected as colostrum and twice a day at the first milk release for the first 14 days following calving. Neither the parent drug, cabergoline, nor its metabolite des-ethylcarbamoyl cabergoline were detectable from the first milking to the 28th milking after calving.

In a second non-radiolabelled residue depletion study ten pregnant cows were treated with a single injection of cabergoline at the dose of 5 mL per animal (7.00-0.036 µg/kg) at the beginning of the dry period. Intervals between treatment and calving ranged from 36 to 62 days (mean 49.5). Milk samples were collected after calving, twice a day until the 10th milking. All measured values were below the limit of detection (0.099 ng/kg) or the limit of quantification (5 ng/kg).

An additional residue study in milk was conducted in lactating cows. Twenty lactating dairy cows received a single injection of cabergoline at the therapeutic dose (maximum of 10.08 µg/kg bw).

Milk was sampled from day 0 evening milking (11 hours after treatment) until day 10 evening (251 hours after treatment).

- From day 0 evening to day 1 evening, all cabergoline concentrations were above the MRL (0.1 µg/kg).
- From day 3 evening, all cabergoline concentrations were below the MRL.
- From day 4 evening, all cabergoline concentrations were below the LOQ (0.050 µg/kg).

Selection of marker residue and ratio of marker to total residues

The parent compound cabergoline has been established as the marker residue, and marker to total residues ratios are: 0.04 µg/kg for liver, 0.28 µg/kg for kidney, 0.473 µg/kg for muscle, 0.111 µg/kg for fat, 0.303 µg/kg for injection site (core) and 0.20 µg/kg for milk.

MRL status

The MRL status of cabergoline, the active constituent of Velactis is as follows:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
cabergoline	cabergoline	Bovine	0.10 µg/kg 0.25 µg/kg 0.50 µg/kg 0.15 µg/kg 0.10 µg/kg	Fat Liver Kidney Muscle Milk	NO ENTRY	Prolactin inhibitor

The other components of the product (dimethylsulfoxide and triglycerides, medium chain) are also covered by existing entries in Table I of the Annex to Commission Regulation (EU) No 37/2010. Dimethyl sulphoxide has a "No MRL required" status for all food producing species and triglycerides, medium chain

is covered by the entry for myglyol, which also has a "No MRL required" status for all food producing species.

An analytical method for the determination of residues of cabergoline in tissues and milk of cattle based on HPLC with MS/MS detection was available and was validated according to Volume 8 of The rules governing medicinal products in the European Union.

Withdrawal periods

Based on the proposed MRLs and using the results from the marker residue studies withdrawal periods for the target tissues of cattle including the injection site were calculated in accordance with the CVMP Note for guidance: Approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95) and the CVMP Guideline on injection site residues (EMEA/CVMP/542/03).

Using the statistical approach, withdrawal periods were estimated separately for all tissues by linear regression analysis of the residue data and defined at the time point when the one-sided upper 95% tolerance limit with 95% confidence falls below respective MRLs. The longest of these withdrawal periods is proposed as the overall withdrawal period. A withdrawal period of 23 days was calculated for edible tissues.

No residues in milk were detected in the residue and ADME studies conducted with cows at the point of drying-off. The shortest time period between treatment and calving was 32 days. Consequently the following withdrawal period for milk is proposed: zero hours after calving when the dry period length is 32 days or more.

In line with the "Note for guidance for the determination of withdrawal period for milk" (EMEA/CVMP/473/98), data from the study in lactating cows were used to calculate a withdrawal period (using the statistical approach) for cases with dry periods of less than 32 days after treatment, or when lactating cows have been treated accidentally. The resulting withdrawal period is 4 days or 8 milkings. This result justifies the addition of the following sentence to section 4.11 of the SPC (withdrawal period): "4 days (8 milkings) after calving when the dry period length is less than 32 days". The withdrawal period of 4 days after calving includes a significant safety margin as substantial excretion of cabergoline will already occur during the dry period.

Overall conclusions on the residues documentation

Parent ^{14}C-cabergoline was detected in relevant concentrations in all edible tissues. Highest mean concentrations of parent drug were detected 12 hours post application in kidney, liver and injection site-core and declined rapidly to concentrations below the LOQ of the analytical method at day 20 post application.

In a non-radiolabelled residue depletion study in dairy cows cabergoline concentrations were highest in kidney and liver at all slaughter days, whereas residue concentration in fat and muscle were significantly lower. Residue concentrations at the injection site (core and surround) were below the LOQ in all samples at day 16 for the first time.

Mean total ^{14}C-radioactivity concentrations in milk samples were low. Neither cabergoline nor the main metabolite in milk, desethylcarbamoyl cabergoline, was detected in any milk sample at any sampling point after administration at the point of drying off (earliest sampling 32 days after application).

In a non-radiolabelled depletion study in milk, both the parent drug cabergoline and its main metabolite desethylcarbamoyl cabergoline were not detectable from the first milking (earliest sampling 46 days after

application) until the 28th milking after calving (the last sampling timepoint). In a second non-radiolabelled depletion study in milk cabergoline was not detectable from the first milking (earliest sampling 36 days after application) until the 10th milking after calving (the last sampling timepoint).

In a non-radiolabelled residue study in milk from lactating cows, cabergoline was detected in quantifiable amounts until the eighth milking, values were below the MRL for milk from the sixth milking onwards.

Parent cabergoline is accepted as an appropriate marker residue as it comprises the majority of the tissue residues and is detected over a sufficiently long period after administration (up to ten days). Liver, kidney and injection site are the target tissues of cabergoline.

For tissues and milk the marker to total ratios were calculated at 5 days as 0.473 µg/kg for muscle, 0.111 µg/kg for fat, 0.044 µg/kg for liver, 0.280 µg/kg for kidney, 0.303 µg/kg for injection site (core) and 0.202 µg/kg for milk respectively.

Based on the MRLs the following withdrawal periods can be set: 23 days for edible tissue, 0 hours for milk, provided the dry period is 32 days or longer, and 4 days (8 milkings) for milk if the dry period is less than 32 days.

Part 4 – Efficacy

Velactis is intended for use in the 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 the risk of new intramammary infections during the dry period, and to reduce discomfort.

The proposed dose is a single intramuscular administration of 5.6 mg cabergoline per animal (i.e. the lowest therapeutic dose is approximately 6.6 µg/kg bw) for a cow weighing 850 kg on the day of drying-off. The product should be administered within 4 hours after the last milking.

Pharmacodynamics

See part 3.

Development of resistance

Not applicable.

Pharmacokinetic

See part 3.

Dose determination/justification

Initially, no conventional dose determination/confirmation studies were conducted. The dose of 5.6 mg cabergoline/cow (corresponding to 7–10 µg/kg bw) was chosen on the basis of an exploratory dose determination study, which provided the data for a pk/pd analysis that indicated that a dose range of 4.8–8.7 µg/kg bw would result in a 51% reduction in milk production. As the study was explorative and of limited value for establishing the treatment dose, the pk/pd considerations based on this study were considered inconclusive. Thus, another pk/pd analysis was generated retrospectively based on the same data of the exploratory dose determination study demonstrating that cabergoline doses of 4.8–9.2 µg/kg bw resulted in milk reductions of about 4 kg at the next milking. However, as the new pk/pd assessment was based on the same exploratory study, this approach was also not considered meaningful.

Further dose justification was provided by a dose confirmation study in which efficacy of the recommended treatment dose of 5.6 mg/cow was confirmed. In this study, Holstein dairy cows of three different milk production categories: low (< 16 kg milk/day), medium (16–22 kg milk/day) and high (≥ 22 kg milk/day) were treated either with cabergoline at the recommended treatment dose of 5.6 mg/cow or saline. For the parameter "reduction in milk production 24 hours after drying-off", superiority of cabergoline versus saline was successfully demonstrated. The cabergoline effect was not impacted by the level of milk production before drying-off. The study confirmed that cabergoline at a single intramuscular dose of 5.6 mg per cow was effective in reduction of the milk production in dairy cows at drying-off.

The dose is considered to be sufficiently justified given the level of efficacy demonstrated and on basis of the fact that this dose is not related to any safety concern.

Target animal tolerance

The target animal safety (TAS) of the product has been examined in non-pregnant cows in a GLP-and VICH GL43-compliant TAS-study. Target animal safety of the product was furthermore investigated in two reproduction safety studies in cows during early pregnancy at month 3 and prior to drying-off at month 7. Observations in the two latter studies covered the dry period, calving, and early lactation. In addition, the safety of the product was observed during the field efficacy studies. In one study, also the subsequent reproduction cycle until next calving was covered.

Cows enrolled in most safety studies were high performance dairy cows in their 1st to 6th lactation, which are representative of the intended target population for Velactis. In the TAS-study the product was administered at the proposed recommended treatment dose (RTD) of 5.6 mg/cow, and at overdoses (3xRTD and 5xRTD) for 3 days each. In the reproduction safety studies cabergoline was administered once at the therapeutic dose and at overdoses (1.5xRTD, 3xRTD). In all studies the product was injected as intended; i.e. intramuscularly into the neck at a maximum volume of 10 ml per site.

Common safety parameters were monitored in the TAS-study, while in the reproductive safety studies in pregnant cows specific parameters related to reproduction and lactation were observed. Pregnancy-related hormone levels were determined in some cows at month 3 and at month 7 of pregnancy in order to examine any potential luteolytic or foetotoxic effect of cabergoline. While deficiencies were identified in the safety studies regarding the study design, the reporting of data, the statistical analyses and the documentation data allow a conclusion that Velactis did not produce severe adverse events in cows, when administered at drying-off as intended.

In general, Velactis was well-tolerated, apart from local reactions to injection site (swelling) persisting up to 7 days in some animals, which were commonly observed. The occurrence of local injection site reactions is adequately reflected in section 4.6 of the SPC. Plasma levels of progesterone were not affected, suggesting that Velactis had no luteolytic effect in cows at pregnancy month 3 or at drying-off. Pregnancy-associated glycoprotein (PAG) and oestrone sulphate levels in plasma, which are correlated with placental function and the viability of the foetus, were also not affected by treatment. Clinical observations at calving revealed normal pregnancy length in treated cows, and no treatment-related abnormalities in the calves or in the rate of abortions or calving or post-calving complications. Milk parameters determined in the subsequent lactation were also not significantly affected by treatment.

Overdoses of the product resulted in some cases in slight and transient decrease of appetite. This was observed following 1.5–2 times of the recommended dose and was more pronounced at higher doses. The administration of three or five times the recommended dose for 3 consecutive days resulted in addition in some cases in transient and reversible diarrhoea. At 9 times the recommended dose a decrease in ruminal

activity may be observed. Fatal meteorism has been observed in a single cow following a second administration of 5 times the recommended dose. Three consecutive administrations of 1, 3 or 5 times the recommended dose may result in transient and reversible slight elevation of plasma glucose levels. Results from overdoses are properly reflected in section 4.10 of the SPC. Administration of Velactis at drying-off had no apparent impact on the subsequent reproduction cycle.

Cabergolin induces a reduction of milk production. Therefore, a precautionary advice has been added to section 4.5 of the SPC that the product should only be used in dairy cows at the time of drying off.

Field trials

The applicant provided three pivotal clinical field studies, and several supportive pilot or experimental studies, in support for the use of the product at the proposed single intramuscular dose 5.6 mg cabergoline (equivalent to 5 ml Velactis) per cow as an aid in the management of dairy cows the day of abrupt drying-off by reducing milk production to: reduce milk leakage at drying off, reduce the risk of new intramammary infections during the dry period, and reduce pain and discomfort.

In addition, the applicant claimed that Velactis would contribute to the reduction of the need for antimicrobial treatment.

Reduction of the risk of new intramammary infections during the dry period and reduction of milk leakage at drying-off

A GCP compliant multi-centre, double blinded study using a randomised three-armed design was conducted in France, Germany and Hungary in 2011–2012. A total of 917 cows were enrolled from preselected dairy cows of different breeds and cross breeds, approximately one week before drying-off, from a total of 80 commercial farms. At the day of drying-off, cows diagnosed free of subclinical mastitis were either given a single intramuscular dose of 5.6 mg cabergoline (i.e. 5 ml Velactis) per cow, a placebo or a positive control (dry cow product containing cefquinome).

Reduction of the risk of new intramammary infections:

The primary efficacy parameter was the percentage of new intramammary infections per quarter for Velactis versus placebo detected during the first week after subsequent calving. Clinical observations including examinations of cows, udders and milk samples for bacteriology and somatic cell count were performed at regular intervals at the day of drying-off and the day thereafter, and up to 7–10 days after calving.

Environmental streptococci spp (*Sr. uberis, Sr. dysgalactiae, Enterococcus*) were the most prevalent among the major pathogens causing new intramammary infections, followed by Coliforms (*Klebsiella, Enterobacter spp*.) and *S. aureus* (very low). The rate of new intramammary infections during the dry period was significantly lower in udder quarters of cows treated with cabergoline (20.5%) compared to placebo (26%), although higher than in the positive control group (14.3%).

To support the clinical relevance of a 5.5% difference in occurrence of new intramammary infections (95% confidence interval for the difference 0.5%–10.4%) between the cabergoline group and placebo a meta-analysis of publications was submitted dealing with dry cow management including altogether 34 comparisons of antibiotic herd treatment to placebo (Halasa et al., 2009). The results of this meta-analysis revealed that the effect size noted for Velactis was within the effect range obtained with some antimicrobial dry cow treatments. It was noted that some of the publications were quite old and would not represent the current field situation. Overall, the Committee considered the effect of Velactis in reducing new intramammary infections as modest.

Milk leakage:

Milk leakage is a major risk factor for new intramammary infections and consequently reduced milk leakage among Velactis treated animals would constitute a benefit as to a reduced risk for new intramammary infections during the dry period. Milk leakage was therefore also investigated, as a secondary parameter. The percentage of cows presenting milk leakage was significantly lower in the cabergoline group (2.0% in the ITT population) compared to placebo (10.7%; confidence interval for the difference 4.9%–12.6%) and the positive control (14.8%). This was confirmed in another GCP compliant multicentric randomised clinical trial where incidence of milk leakage was significantly lower among Velactis treated animals (3.9%) as compared to placebo treated animals (17.6%).

No effect of cabergoline treatment was noted for any of the other secondary efficacy criteria (somatic cell count (SCC), percentage of cows with SCC higher than 200 000 cells/ml at 7–10 day after calving, percentage of clinical mastitis during drying-off or in the week after calving, clinical aspects of milk and udder after calving).

Reduction of the need for antimicrobial treatment:

The applicant also considered that Velactis is a new treatment concept which may potentially reduce the need for antimicrobial dry cow treatment. However, no data is presented to support this assumption. The applicant argued that although milk quality and mastitis control programs have been improved for several years to reduce the risk of new intramammary infections during the dry period, antibiotic treatment is still frequently used in many EU member states (if permitted) irrespective of the udder health status to further reduce the risk of new intramammary infections. In cows diagnosed to be free of mastitis in which antibiotic treatment would not be justified/ permitted, Velactis was demonstrated to significantly reduce the risk of new intramammary infections. Hence, in this situation, Velactis would contribute to the reduction of antimicrobial dry cow treatments. In cows with diagnosed subclinical mastitis at drying-off in which antimicrobial treatment would be justified, concomitant administration of Velactis would further reduce the risk of new intramammary infections during the dry period. In this situation, the reduction of milk leakage induced by Velactis would contribute to reduce the spread of antimicrobials in the environment and maintain optimum antibiotic concentrations in the mammary gland.

Based on the data provided, the committee considered the efficacy of Velactis in reducing the risk of new intramammary infections during the dry period in cows free of subclinical mastitis and in the absence of antimicrobial treatment as modest (5.5% difference between Velactis and placebo). To what extent this could contribute to the reduction of (unnecessary) antibiotic dry cow therapy remains to be explored. Moreover, the add-on effect of Velactis to further reduce the risk of new intramammary infections in cows with subclinical mastitis when compared to antimicrobial dry cow therapy alone was not explored in clinical trials. However, where Velactis reduces the incidence of development of new intramammary infections during the dry period, it can be expected that the use of Velactis may reduce the need for antimicrobial use.

Conclusions:

Velactis, when administered to cows diagnosed free of subclinical mastitis and in the absence of antimicrobial treatment, showed only modest efficacy (5.5%, 95% confidence interval 0.5–10.4%) in the reduction of new intramammary infections during the dry period compared to placebo (primary parameter).

The percentage of cows presenting milk leakage was significantly lower in Velactis treated cows (2.0%) compared to placebo (10.7%), i.e. a difference between groups of 8.7% (95% confidence interval

4.9%–12.6%). This was confirmed in another GCP compliant multicentric randomized clinical trial where incidence of milk leakage was significantly lower among Velactis treated animals (3.9%) as compared to placebo treated animals (17.6%), i.e. a difference between groups of 13.7% (95% confidence interval 6.4%–21.0%).

The efficacy of Velactis in reducing the risk of new intramammary infections during the dry period when administered to cows with subclinical mastitis in conjunction with antibiotic treatment was not explored in the clinical trials. Furthermore, no studies were presented which investigated if the use of Velactis would reduce the need for antimicrobial dry cow treatment. However, where Velactis reduces the incidence of development of new intramammary infections during the dry period, it can be expected that the use of Velactis may reduce the need for antimicrobial use.

Reduction in pain and discomfort after the drying-off due to a reduction in udder engorgement and udder pressure

The applicant provided two pivotal studies to support the efficacy of Velactis in the reduction in pain and discomfort after the drying-off due to a reduction in udder engorgement and udder pressure. In addition, a number of supportive pilot field or experimental studies were submitted to establish the methodology used in the pivotal studies. Generally, udder engorgement, lying time and milk leakage after drying-off increased with increasing milk production at late lactation.

First clinical field study:

The initial, pivotal field study was a GCP-compliant, blinded, randomised, parallel, multi centre (France, Hungary, Germany), controlled pivotal clinical field study conducted in 2012 in 263 dairy cows with a mean daily milk production the week before drying-off of approximately 20 kg/day. The objective was to assess the efficacy of a single dose of 5.6 mg cabergoline/cow (intramuscular) after the last milking on the reduction of udder engorgement and pressure, as well as in milk leakages following drying-off. The observation period started 7 days before drying-off, the day of treatment/drying-off (D0) and the post treatment observations (D1, D2, D3, D7, D10 and D14).

Parameters included milk yield before drying-off, milk leakages, metrology of the udder, udder pressure, pain on udder palpation, adverse events and local tolerance. Primary efficacy criterion was udder "over-engorgement (i.e. higher milk engorgement during the dry period than during the lactation period) on D1", and the percentage of cows with udder "over-engorgement on D1" was significantly lower in the cabergoline group compared to the placebo group in both the all randomised population (AR) and the per protocol (PP) populations. The main secondary criterion was "milk leakage on D1", and the percentage of cows with milk leakages on D1 was significantly lower in the cabergoline group (3.9%) compared to the placebo group (17.6 %, p=0.0004) in both the AR and the PP populations. Other secondary criteria during the engorgement phase (D1 to D3) also showed significant lower results for cabergoline versus placebo in regard to udder "over-engorgement" (D2, D3), inter-teat perimeter values/udder engorgement (D1), udder pressure (D1, D2), udder "over-pressure" (D1), and pain (D1). "Pain" was measured by palpation of all quarters of the cows during the engorgement phase on D1, D2 and on D3, also any potential pain while the cow moved was also recorded.

Signs of pain were observed in 1.6% animals in the cabergoline group and in 11.5% animals in the placebo group in the first two days after drying-off. The difference in occurrence of pain was 9.9% (95% confidence interval 4.0%–15.9%) in the Velactis treated cows compared to placebo treated animals. No statistical difference between treatment groups was found on D2 and D3 for signs of pain. During the regression phase (D7 to D14), no significant difference was observed in udder engorgement or udder pressure for both study populations.

The CVMP did not consider the primary parameter ("over-engorgement on D1") as a suitable parameter, but considered one of the secondary parameter ("udder engorgement" measured by the inter-teat perimeter) as a more objective and, therefore, more suitable parameter. Also, the significant reduction of udder pain on D1 was questioned since the assessment was based on udder palpation only. All other parameters were not considered to be suitable since methods appear not validated and resulted in unclear findings ("udder pressure") or their clinical relevance was unclear (e.g. reduction of udder "over-engorgement", udder engorgement, and milk-leakage at the utmost for 3 days after drying-off). The main secondary criterion was milk leakage on D1. The percentage of cows with milk leakages on D1 was significantly lower in the cabergoline group compared to the placebo group (3.9% versus 17.6%). It should be noted that mastitis, which served as a safety parameter, was detected with the same incidence in both groups (2 cows per group=1.5%) despite the claimed reducing effect of cabergoline on udder engorgement. In this study the cows were treated with intramammary antibiotics in accordance to the routine practice of the farm.

Overall, the CVMP considered that an effect of Velactis on mastitis occurrence could not accurately be determined in this study.

Second pivotal clinical field study :

A second clinical field study was performed. The objective of this GCP-compliant, blinded, randomised, parallel, multi centre (France, Hungary, Germany), pivotal clinical field study was to assess the efficacy of one intramuscular injection 4 hours after the last milking at a dose of 5.6 mg cabergoline/cow in improvement of animal welfare by reducing the animal pain and discomfort the days following drying-off compared to placebo. 228 dairy cows were enrolled with a mean daily milk yield during the week before drying-off of approximately 20 kg. Cows were grouped into three equal-sized groups based on their milk yield (< 18.4 kg/d, 18.4–22.2 kg/d and > 22.2 kg/d). The primary efficacy criterion was the daily lying time (as an indicator for reduction of discomfort) from D1 to D4. The daily mean lying time from D-4 to D-1 was considered as the before drying-off baseline. Other parameters included the daily milk yield recorded in the last 4 days (D-4) before drying-off, lying and standing behaviour recorded from 4 days before to 7 days after drying-off, and udder pain on palpation (D-7, up to D7).

Results of the study showed that daily lying time was on average only about 24 minutes higher for the cabergoline treated cows than for placebo treated cows (not statistically significant). The mean changes to baseline were also not statistically significant different according to calculations by the CVMP. Thus, the study was not successful in demonstrating statistical significance for the pre-defined primary endpoint daily lying time, and the difference between groups was smaller than what was considered clinically relevant. A further post-hoc analyses showed a significant effect of Velactis on the daily lying time of approximately 143 minutes. However, this effect was only demonstrated for the first day after drying-off.

Statistically significant changes in the Velactis group compared to placebo were also noted in regard to some of the secondary criteria at certain days following drying off, i.e. a lower number of lying bouts (D3 and D4), higher mean duration of lying bouts per day (D1), reduction of udder pain score (D1 and D2). No changes were seen in regard to the number of lying bouts on D1 and D2, mean duration of lying bouts per day (D2–4), and reduction of udder pain scores at D3–D7. Reduction of stress (indicated by faecal glucocorticoid metabolite 11, 17-dioxoandrostane [DOA]) was on average slightly lower in the cabergoline group than in placebo group on D2, but without significant difference.

Conclusions:

In summary, discomfort in cows indicated by their daily lying time was reduced statistically significant and clinically relevant by Velactis at the first day after drying-off, only. The statistically significant reduction of udder pain on the first two days was noted. However, since the methods used to investigate udder pain

were poorly described and appeared to be only based on palpation technique or so called "pain response", the committee considered these data not sufficient to support the claimed indication "reduction of udder pain" after administration of the product. However, information on the efficacy of the product in reducing udder pain after treatment at drying-off derived from the clinical field studies has been included in section 4.4 of the SPC and the product literature.

Other studies

None.

Overall conclusion on efficacy

The applicant provided three pivotal and several supportive clinical field studies in support for the use of Velactis at a single intramuscular dose of 5.6 mg cabergoline per cow for a number of proposed indications i.e. prevention of new intramammary infections during the dry period, reduction in milk leakages at drying off, reduction in pain and discomfort after the drying off due to a reduction in udder engorgement and udder pressure. In addition, the applicant claimed that Velactis would reduce the need for antimicrobial treatment.

Data show only modest efficacy of cabergoline in reducing the risk of new intramammary infections during the dry period, when administered to cows diagnosed free of subclinical mastitis and in the absence of antibiotic treatment (5.5% difference between Velactis and untreated control animals in developing a new intramammary infection during the dry period). Whether this is connected to a clear clinical benefit with regard to a reduction in the need for antibiotic treatment has not been explored. An effect of Velactis in reducing the risk of new intramammary infections during the dry period in cows with subclinical mastitis that required antibiotic treatment was also not investigated in clinical trials. However, in all the pivotal clinical trials Velactis significantly reduced milk leakages in cows when compared to placebo. As milk leakage is, among others, a major risk factor for the development of new intramammary infections, the CVMP considered the data sufficient to support the efficacy of Velactis in the reduction of the risk of the development of new intramammary infections during the dry period. Where Velactis reduces the incidence of development of new intramammary infections during the dry period, it can be expected that the use of Velactis may reduce the need for antimicrobial use.

Velactis reduced discomfort after the drying-off as indicated by an increase in the daily lying time as an indicator for the animals' comfort. However, a clinically relevant and statistically significant effect on the lying-down period was only demonstrated for the first day after drying-off. The claimed indication "reduction of pain" was not sufficiently supported by data, since the methods used to investigate udder pain were unvalidated, poorly described and appeared to be only based on palpation technique or so called "pain response".

Based on the data provided the following indication for use is justified: "For use in the 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 the risk of new intramammary infections during the dry period, and to reduce discomfort". Whether a benefit of the product is obtained with regard to a reduced need for antibiotic dry cow treatment, was not explored. The effects confirmed were a reduction in the risk for new intramammary infection during the dry period in uninfected udders, and a reduction of milk leakage and discomfort. Given that the clinical benefit of these effects are regarded to be modest, clear information on the use of Velactis and its effect size is added to the SPC and other product literature in order to support the veterinarian in the decision on the use of the product in clinical practice. Based on the data provided the indication "reduction of udder pain" is not justified, but information on the efficacy of the product in

reducing pain at the time of drying off as derived from the clinical studies is included in section 4.4 of the SPC.

Part 5 – Benefit-risk assessment

Introduction

The application is for Velactis 1.12 mg/ml solution for injection for cattle. The application is supported by a full dossier.

Velactis contains as the active substance cabergoline, a synthetic ergot derivate, not hitherto authorised for use in cattle, and is presented in single dose vials of 5 ml and multidose vials of 25 ml or 50 ml.

Velactis is intended for use in the 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, reduce the risk of new intramammary infections during the dry period and to reduce discomfort.

The proposed dose is a single dose of 5.6 mg cabergoline/animal by the intramuscular route on the day of drying-off after the last milking. The product should be administered within 4 hours after the last milking. The proposed withdrawal period for meat and offal is 23 days, for milk, the proposed withdrawal period after calving is zero or four days, when the dry period is 32 days or more or less than 32 days, respectively.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

Cabergoline is a potent dopamine receptor agonist on D2 receptors of prolactin producing cells and was demonstrated to suppress the prolactin production in lactating cows, leading to the inhibition of prolactin secretion dependent processes, such as milk production. The reduction of milk production is the most relevant surrogate marker for the intended effect of cabergoline.

Velactis, when administered to low, intermediate and high yielding cows at abrupt drying-off at the recommended treatment dose, was demonstrated in several clinical studies to significantly reduce milk leakages at the day of drying-off and at the day thereafter, compared to placebo. The clinical benefit resulting from this is a reduction of the risk of the development of new intramammary infections in cows during the dry period.

In a pivotal clinical field study including cows diagnosed free of subclinical mastitis and in the absence of antibiotic treatment, Velactis was demonstrated to significantly reduce the rate of new intramammary infections during the dry period when compared to placebo. The effect size was modest (5.5% difference between Velactis and placebo), and the clinical benefit resulting from this, e.g. potential reduction of antimicrobial dry cow treatment, could not be derived from the data provided. The effect of Velactis when administered concomitantly with antibiotic treatment to cows with subclinical mastitis was not explored in clinical trials.

A modest benefit of Velactis in the reduction of discomfort after the drying-off due to a reduction in udder engorgement and udder pressure was demonstrated in clinical field studies. Velactis was shown to

increase the daily lying time to clinically relevant extent on the first day after treatment and, thus, reduced the animals' discomfort on the first day after drying-off, but not thereafter.

Based on the data provided, the benefits of Velactis are its use in the 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, reduce the risk of new intramammary infections during the dry period and to reduce discomfort. In addition, clear information on the use of the product and its effect size is included in section 4.4 of the SPC to help the prescriber in the decision on whether to prescribe Velactis.

Additional benefits

The use of this product may provide a benefit to farm management by facilitating the management of drying-off of dairy cows.

Where Velactis reduces the incidence of development of new intramammary infections, it can be expected that the product may reduce the need for antimicrobial treatment.

Risk assessment

Main potential risks

Concerning quality, the formulation and manufacture of Velactis is well described and satisfactory specifications have been set. The product is produced and controlled using validated methods and tests, which will ensure the consistency of the product.

For the target animal:

Velactis is well tolerated in cows at drying-off at the recommended treatment dose and local injection site reactions (transient swelling) at the injection site are adequately reflected in section 4.6 of the SPC. Moreover, information on adverse reactions following overdoses is provided in section 4.10 of the SPC.

For the user:

Cabergoline showed skin sensitising potential, but no skin or eye irritating properties. The substance has also been shown to reduce fertility and to be a developmental toxin. However, warning phrases are considered adequate to protect the user, particularly women attempting to conceive, and breastfeeding women. The user safety is therefore considered acceptable, when used as recommended, and taking into account the safety advice in the SPC.

For the environment:

Cabergoline is a substance with endocrine disrupting properties. It is a potent dopamine receptor agonist acting on D2 receptors common in a wide range of wildlife animals including invertebrates and vertebrates. A targeted phase II environmental risk assessment in accordance with VICH guidelines GL38 (CVMP/VICH/790/03-FINAL) was performed.

Cabergoline is unlikely to pose a risk to terrestrial organisms, but might have harmful effects on aquatic species. Therefore, advice is included in the SPC and other product literature that treated cows should not have access to open water and should not contaminate watercourses with faeces, for at least 5 days after administration.

For the consumer:

Based on the proposed MRLs, withdrawal periods were proposed for edible tissue and milk which are considered adequate to ensure consumer safety. The withdrawal period for meat and offal is 23 days, and

for milk zero hours after calving when the dry period length is 32 days or more and 4 days (8 milkings) after calving when the dry period length is less than 32 days.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of the product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall.

The product has been shown to be efficacious when used as an aid in the herd management programme of dairy cows in the abrupt drying-off by reducing milk production to reduce milk leakage at drying off, reduce the risk of new intramammary infections during the dry period and reduce discomfort.

The formulation and manufacture of Velactis is well described and specifications set will ensure that product of consistent quality will be produced.

The product is well tolerated by the target animals, and presents an acceptable risk for users, consumers and the environment, when used in accordance with the SPC. Appropriate withdrawal periods for meat and milk are established.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Velactis is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.