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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MUSTELIGEN D

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0394/001/DC
Name, strength and pharmaceutical form	MUSTELIGEN D, lyophilisate and solvent for suspension for injection for ferrets
Applicant	VIRBAC, France
Active substance(s)	Live attenuated distemper disease virus, Lederle strain
ATC Vetcode	QI20DD01
Target species	Ferret
Indication for use	Active immunisation of ferrets from 9 weeks of age to prevent mortality and clinical signs caused by distemper virus Onset of immunity : 3 weeks Duration of immunity : 1 year

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended
Date of completion of the original decentralised procedure	01/04/2020
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	AT, BE, CZ, DE, ES, HU, IE, IT, LU, NL, PL, SK, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed – transient slight apathy, hyperthermia or digestive disturbance / moderate swelling at the injection site or erythema - are indicated in the SPC.
The product is safe for the user and for the environment when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product – prevention of mortality and clinical signs caused by distemper virus in ferrets - was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

The vaccine is classified as a minor use / minor species product and the dossier has been assessed taking into account the relevant guideline.

II. QUALITY ASPECTS

A. Composition

The product is constituted of a freeze-dried fraction containing attenuated distemper virus, strain Lederle ($10^{2.9}$ to $10^{5.1}$ $CCID_{50}$ per dose) and excipients (saline and buffered isotonic solutions) to be reconstituted with water for injection before use.

These two fractions of the vaccine are filled in vials made of neutral borosilicate type I glass closed with butyl elastomer stoppers and aluminium capsules. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain, the production process and the formulation are justified.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance - distemper virus strain Lederle - is manufactured in accordance with the principles of good manufacturing practice.
The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.
The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Starting materials of non-biological origin used in production comply with European Pharmacopoeia monographs where relevant or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur.; any deviation was adequately justified.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control tests during production

The tests performed during production are described and the results of 2 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified.
For the freeze-dried fraction, the tests include in particular physicochemical tests, identification and titration of the active ingredient, bacterial and fungal sterility and test for mycoplasma according to Ph. Eur. and residual humidity. Testing of the liquid fraction include physico-chemical characteristics, sterility and endotoxins.

The demonstration of the batch-to-batch consistency is based on the results of 2 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its 2 years shelf life when stored under the approved conditions (refrigerated 2-8°C).

III. SAFETY ASSESSMENT

Vaccine batches used in the following studies are representative of the production process. Vaccine batches contain the maximal claimed titre.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the ferret is demonstrated in groups of ferrets free of antibodies against distemper virus of 9 weeks of age [8 ferrets receiving 2 doses 4 weeks apart / 12 ferrets receiving 10 doses followed by 2 additional doses 4 weeks and 8 weeks later respectively]. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. No adverse reactions were observed after vaccination. Mild local reactions were observed at the injection site (transient oedema, swelling or nodule disappearing spontaneously) in the group receiving 10 doses of vaccine. These reactions have been adequately described in the SPC (section 4.10).

In the absence of the required demonstration data, it is recommended not to use the vaccine during pregnancy or lactation.

Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain. No transmission of the vaccine strain from vaccinated ferrets to in-contact animals was evidenced. Stability of the vaccine strain and absence of reversion to virulence is established in compliance with Ph. Eur. requirements.

The excipients used in the vaccine formulation are in annex II of MRL regulation and the live vaccine strain is not associated to zoonotic disease. Based on this information, no withdrawal period is proposed.

No specific assessment of the interaction of this product with other medicinal products was made. Therefore, an appropriate warning in the SPC is included.

Field studies

Safety of the vaccine was confirmed in field situation where 153 ferrets from 8 weeks of age from 18 veterinary clinical sites were vaccinated. The study confirms the good tolerance of the vaccine in ferrets. Common adverse reactions observed consist commonly in local reactions [swellings, pain or erythema at injection site] or systemic reactions such as slight and transient hyperthermia, digestive disorders and/or lethargic states.

These reactions are adequately described in the SPC.
As it has been observed that the vaccine may be not well tolerated when administered to too young and weak animals, a warning has been included in the SPC.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed in the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show the efficacy of the vaccine in preventing mortality and clinical signs of distemper disease. Vaccines used in the studies contain the minimum titre and were administered as recommended by subcutaneous route using 2 doses 4 weeks apart.

A preliminary dose determination study allowed to set the minimal titre of virus for formulation.
Efficacy was established in clinical studies including challenge. Prevention of mortality and clinical signs was demonstrated in 6 vaccinated ferrets challenged 3 weeks after vaccination (in a study including 2 controls). Duration of immunity has been established through a challenge protection study conducted in 6 vaccinated ferrets and 6 controls one year after vaccination. Efficacy of a single booster vaccination applied one year after primary vaccination was confirmed in a study conducted in 8 vaccinated ferrets and 8 controls challenged one year after the booster vaccination.

Field Trials

The applicant has conducted a field study involving 42 ferrets from 7 veterinary practices. The study allows to confirm the ability of the vaccine to induce a serological response in vaccinated ferrets. Field investigation in 8-or 9-week old ferrets also shows that most of the ferret population is seronegative at the time of vaccination (9 weeks of age) and that maternal derived immunity should not be regarded as a problem for vaccine intake.

V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit-risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Quality changes

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change (Type; application number)	**Section updated in Module 3**	**Approval date**
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	
