FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

EMEDOG, 1 mg/ml, solution for injection for dogs

FR/V/0281/001

Date: 25/05/2023

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0281/001
Name, strength and pharmaceutical form	EMEDOG, 1 mg/ml, solution for injection for dogs
Applicant	DOMES PHARMA 3 rue André Citroën 63430 PONT DU CHATEAU FRANCE
Active substance(s)	Apomorphine
ATC Vetcode	QN04BC07
Target species	Dogs
Indication for use	Induction of emesis.

MODULE 2

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

MODULE 3

PUBLIC ASSESSMENT REPORT

Basis of original application	Well established veterinary use application in accordance with Article 13 (a) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	11/06/2015
Concerned Member States for original procedure	AT – BE – DE – ES – IT – LU – NL – PT – UK
Concerned Member States for subsequent recognition procedure	DK, EL, FI, IE, NO, PL, RO, SE

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 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 was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 1,0 mg/ml apomorphine (hydrochloride hemihydrate) as active substance and excipients sodium metabisulfite (E223), hydrochloric acid concentrated and water for injections.

The container is a glass ampoule. The particulars of the containers and controls performed are provided and conform to the regulation.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

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.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is Apomorphine hydrochloride, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

A re-test period for the active substance is set in the certificate of suitability issued by EDQM.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

H. Genetically Modified Organisms Not applicable.

I. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

See part IV.

Toxicological Studies

Most of the data that were provided in the dossier on the toxicological profile of apomorphine are bibliographic ones.

Acute toxicity
Whatever the route of administration, the acute toxicity of apomorphine can be considered as low with high LD_{50} values (the lowest LD_0 was 13 mg/kg after subcutaneous injection in mouse).
After a single administration of apomorphine, main observed signs were central behavioural and gastro-intestinal effects.

Repeated dose toxicity
Studies were carried out in rats, mice and dogs. In all species, behavioral changes were reported and consisted in stereotypic reactions, decreased activity, rearing, circling and development of aggressive behavior only observed in rodents. These changes were due to “dopamine” effects of apomorphine.
Mortality was observed in mouse (from 30 mg/kg in a 13-week study) and in rats (at 8 mg/kg in a 9-week toxicity study). No mortality was noted in dogs up to 0.4 mg/kg in a 26-week toxicity study.
Decrease in liver weight and increase in adrenal gland weight were recorded in mice and rats. In mice, focal corneal atrophy was reported at 14 mg/kg in one 13-week toxicity study. Stereotypical behavior, temporary and/or reduced sleeping times were also considered attributable to the substance. Such a finding was not recorded in rats and dogs.

Reproductive toxicity
Effects of subcutaneous administration of apomorphine on fertility in rats and dogs were investigated in 3 studies (2 in rats, one in young male Beagle dogs).
No effect on male reproductive system or indices of fertility were reported up to 8 mg/kg in rats and up to 0.4 mg/kg in dogs.

No apomorphine data on embryotoxicity/foetotoxicity and teratogenicity are available. Only information on the modification of behavior in lactating rats administered with apomorphine was provided. Treated lactating mothers showed hyperactivity and stereotypic behaviors that interfered with the normal sequence of maternal behavior by exaggerating some components and delaying others.

The safety of the product has not been assessed in pregnant/lactating bitches. If recommendations of the current guideline of SPC are strictly followed, the use of the product should be strictly contra-indicated in dogs during pregnancy and lactation. However, the benefits of apomorphine administration treatment may be greater than the potential risks associated with ingestion of a toxicant or foreign body that can be fatal for the pregnant bitch. Consequently, the use of the product in pregnant bitch should be the subject to a benefit/risk assessment by the veterinarian.

Mutagenicity
Apomorphine showed mutagenic and clastogenic potential in *in vitro* tests (Ames test and test for chromosomal abnormalities on Chinese hamster lung cells). This mutagenic potential is ascribed to an oxidized derivative of apomorphine, 8-oxo-apomorphine-semiquinone. It can be considered as a metabolite that appears specifically in *in vitro* study. Thus, in *in vivo* condition it should not raise any mutagenic concern.
In an *in vivo* test in mouse bone marrow or in unscheduled DNA synthesis in rat hepatocytes, there was no increase in clastogenicity/aneuploidy.
The applicant provided a GLP mutagenicity study in mice.

Carcinogenicity
Carcinogenic studies were conducted in rats and mice, respectively for approximately 100 and 26 weeks.
In all studies, survival at termination was satisfactory.

In both species, the incidence of tumors was not significantly different between control and treated groups, only benign tumors were observed. They were specific to species and should not raise concerns for dogs and the user.
Furthermore, it should be kept in mind that the product should be used very occasionally in dogs and only a veterinarian should handle the product.
If the product is used as recommended, the carcinogenic risk for the user and the treated animal can be considered as negligible.

Other Studies

In well conducted GLP *in vitro and in vivo* studies, apomorphine was shown to be non-irritant to skin, non-irritant to eyes and to induce delayed contact hypersensitivity.

Observations in Humans

Apomorphine is used in human medicine in the control of Parkinson's disease, by subcutaneous route.
Patients typically require 3 to 30 mg daily, the recommended maximum total daily dose being 100 mg.
Apomorphine can cause drowsiness, nausea, vomiting, orthostatic hypotension, fatigue, pallor, salivation, perspiration, psychiatric disorders, requiring dose reduction or even termination of treatment. Itching at the injection site is also reported.
The use of the human French product is not recommended in pregnant women due to the lack of relevant data on safety during pregnancy.
Apomorphine is excreted in breast milk and patients should therefore not breastfeed whilst using it.

Ecotoxicity

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

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to the users of the product.

III.B Residues

documentation

Not applicable

III. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The applicant has provided many bibliographic data to describe the mode of action of apomorphine.

Apomorphine is an aporphine derivative of the dibenzoquinoline class and a synthetic derivative of morphine with no analgesic, opiate or addictive properties. At low doses, apomorphine induces emesis by stimulation of the dopamine receptors in the chemoreceptor trigger zone (CTZ).
Higher doses of apomorphine, however, may suppress vomiting by stimulating the µ receptors in the vomiting centre in the brain.

Pharmacokinetics

The pharmacokinetic (ADME) profile of apomorphine is documented through bibliographic references and through one study performed with the product.
The plasmatic profile of apomorphine was investigated in the target species, the dog, after administration of the product at the recommended dosage (0.1 mg/kg once).
After subcutaneous administration apomorphine is rapidly absorbed. Peak plasma concentration (C_{max}) is of 28.10 ± 7.58 ng/ml and is reached after about 20 minutes.
Apomorphine is very lipophilic and equilibrates rapidly between blood and tissue. Apomorphine binds extensively to plasma proteins.
Apomorphine is conjugated in the liver (glucuronidation and methylation) into non-active metabolites.
Apomorphine is excreted in urine, mostly as the metabolites with some unchanged (<2%). It is also excreted in breast milk. The half-life of the product is 25.9 ± 4.4 minutes.

Tolerance in the Target Species of Animals

The applicant conducted a tolerance study in dogs in accordance with VICH GL 43.
Observed effects were increased salivation, vomiting and expulsive effort. They were due to pharmacological properties of apomorphine. Locally, the product caused minimal to slight irritation with dose-relationship and with severity reduction in the time. Same effects were described in literature and in a recent retrospective survey.
In the field clinical study, minor adverse reactions were noted: drowsiness (very common), modification of appetite (very common), increased salivation (very common), mild to moderate pain on injection (very common), slight dehydration (common), change in cardiac frequency (tachycardia followed by bradycardia) (common). They are transient and may be related to the physiological response to expulsive efforts.

IV.B Clinical Studies

The applicant supplied bibliographical data to support the dose of apomorphine to administer to the dogs. Based on these data, the most relevant dose to administer is 0.1 mg apomorphine /kg BW.
The applicant provided a GCP field study in dogs.
This study was well conducted and showed the ability of the product to rapidly induce vomiting in 100 % of the treated dogs.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

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 in the Union Product Database (UPD).

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.

Summary of change	Approval date
FR/V/0281/001/IA/001/G B.III.1.a.2 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability	17/08/2018
FR/V/0281/001/IA/002 C.I.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006	24/05/2019
FR/V/0281/001/IB/003 B.II.e.5.a.2 Change in the number of units (e.g. tablets, ampoules, etc.) in a pack	14/06/2019
FR/V/xxxx/WS/056 C.II.7.b Introduction of a new Pharmacovigilance system Which has been assessed by the relevant national competent authority/EMA for another product of the same MAH	12/10/2020
FR/V/0281/001/IA/005 A.8 Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance (*)	13/11/2020
FR/V/xxxx/IA/155/G A.1 Change in the name and/or address of the MAH	12/03/2021
FR/V/0281/001/IB/007 B.III.1.a.2 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability	09/05/2021
FR/V/0281/001/IA/008 C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics.	24/09/2021
FR/V/xxxx/WS/071 C.II.7.b Introduction of a new Pharmacovigilance system Which has been assessed by the relevant national competent authority/EMA for another product of the same MAH	10/01/2022
FR/V/0281/001/IA/010 B.III.1.a.2 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability	26/11/2021
FR/V/0281/001/IB/011 B.II.f.1.b.1 Stability - Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	18/01/2022
FR/V/0281/001/IB/012/G B.II.b.3. Manufacture - Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product - Other changes	04/02/2022

Other

Summary of change	Approval date
VNRA B.44: Submission of a new or updated Ph. Eur. CEP from an already approved manufacturer for a non-sterile active substance; starting material, reagent or intermediate used in the manufacturing process of the active substance; or excipient	05/10/2022
FR/V/0281/001/A/013- VRA G.I.18 One-off alignment of the product information with version 9.0 of the QRD templates i.e. major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicinal products placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004.	19/01/2023