Ústav pro státní kontrolu veterinárních biopreparátů a léčiv
Institute for State Control of Veterinary Biologicals and Medicaments
Czech Republic

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT

CZ/V/0101/001/MR

PRODUCT DETAILS	
Name of product	**CASTOREX**
Indication for use/target species	For active immunization of rabbits to prevent mortality caused by RHD virus
APPLICATION(S) DETAILS	
Type of application	Mutual recognition
Concerned member states	Germany (DE)
Applicant	Pharmagal Bio, s.r.o. Murgašova 5 949 01 Nitra Slovak Republic
RMS DETAILS	
Member state responsible for preparing the assessment report	Czech Republic
Date of preparation	May 2006
Date product first authorised in the reference member state	April 2000
CONTACT WITH THE RMS	
Address	ÚSKVBL, Hudcova 56a, 62100 Brno, Czech Republic

Summary of Product Characteristics (SPC)

1. Name of the immunological veterinary medicinal product

CASTOREX
Inactivated adsorbed vaccine against rabbit haemorrhagic disease

2. Qualitative and quantitative composition

One dose of vaccine (0,5 ml) contains:

Active substances :
Inactivated Rabbit haemorrhagic disease virus ……min. 1280 HAU

Adjuvant :
Aluminium hydroxide gel ..... 0,75- 1,50 mg

Excipients:
Formaldehyde …… max. 0,90 mg
Thiomersal …… max. 0,06 mg

3. Pharmaceutical form

Suspension for injection.

4. Clinical particulars

4.1. Target species
Rabbit .

4.2. Indications for use , specifying the target species
For active immunization of rabbits to prevent mortality caused by RHD virus
Onset of immunity: 7 to 14 day
Duration of immunity: 1 year

4.3. Contra-indications
Do not vaccinate animals sick or suspected from any disease.
The vaccination is not recommended during the last week of pregnancy as the incautious fixation may cause fetus impairment.

4.4. Special warnings for each target species
No tests on safety and efficacy have been performed in dwarf rabbits. Therefore, vaccination of these races is not recommended.

4.5. Special precautions for use

i) Special precautions for use in animals

None.

ii) Special precautions to be taken by the person administering the medicinal product to animals

In case of accidental self-injection, seek medical advice immediately and show the package insert or the label to the physician.

iii) Other precautions

None.

4.6. Adverse reactions (frequency and seriousness)

None.

4.7. Use during pregnancy , lactation or lay

Can be used during pregnancy and lactation.

The vaccination is not recommended during the last week of pregnancy ,as the incautious fixation may cause fetus impairment.

4.8. Interaction with other medicinal products and other forms of interaction

No information is available on safety and efficacy from the concurrent use of this vaccine with any other vaccine except for the myxomatosis vaccine Pharmavac MXT inj. sicc a. u. v. Therefore, it is recommended not to use any other vaccine than Pharmavac MXT inj. sicc a. u. v. within 14 days before or after vaccination with this product.

4.9. Amounts to be administered and administration route

The vaccine dose for all age categories is 0,5 ml.

1 dose of 0.5 ml per rabbit, administered subcutaneously, it is recommended to localize the site of administration in the lateral thoracic wall.

Primary vaccination: 1 injection in rabbits from the age of 10 weeks.
Booster: 1 injection every 12 months

With respect to the epizootological situation, it is possible to vaccinate rabbits younger than 10 weeks (but not earlier than at the age of six weeks) with subsequent revaccination 4 weeks after the first vaccination.

Where intensive breeding under commercial farming conditions is undertaken it is recommended to vaccinate breeding does every 6 to 12 month, depending of the turn-over and the sanitary situation of the farm.

4.10. Overdose (symptoms, emergency procedures, antidotes), if necessary
Following the administration of a double dose of vaccine, no systemic undesirable effects have been observed.

4.11. Withdrawal periods
Zero days.

5. Immunological properties

ATCvet.: QI 08 AA 01

To stimulate active immunity against rabbit haemorrhagic disease .

Environmental properties

The virus component is inactivated- non infectious thus the spreading of immunizing antigen between susceptible animals is prevented. The vaccine is parenteral preparation that should be administered by individual subcutaneous injection to each vaccinated animal. The inactivated vaccine cannot be excreted into the environment.

6. Pharmaceutical particulars

6.1. List of excipients:
Phosphate buffered solution (PBS)
Aluminium hydroxide gel
Formaldehyde
Thiomersal

6.2. Incompatibilities
Do not mix with any vaccine or other medicinal products.

6.3. Shelf- life
1 year
Once broached the content of the vial must be used within 24 hours, or discarded
Do not use the medicinal product after expiry date as indicated on label.

6.4. Special precautions for storage
Store and transport refrigerated (+ 2° C - + 8° C). Protect from frost.
It is important to minimize even short-term deviations from indicated storage temperature.

6.5. Nature and composition of immediate packing

Glass vials made of neutral borosilicate glass with high hydrolytic resistance (Type 1) closed with a rubber plug suitable for parenteral preparations and an aluminium cap.

Size of package:
10 doses (5 ml) in one vial
20 doses (10 ml) in one vial
40 doses (20 ml) in one vial

6.6. Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Any unused veterinary medicinal products or waste materials derived from such veterinary medicinal products should be disposed of in accordance with relevant legislation requirements.

7. Marketing authorisation holder

PHARMAGAL BIO, s. r. o.
Murgašova 5
949 01 Nitra
Slovak Republic

8. Marketing authorisation number

Slovak Republic	97/119/99-S
The Czech Republic	97/030/00-C

9. Date of first authorisation / Renewal of the authorisation

Date of first authorization:
In the Slovak Republic in October 26,1999
In the Czech Republic in April 7 ,2000

Renewal of the authorization:
In the Slovak Republic in October 26, 2004
In the Czech Republic in April 7, 2005

10. Date of revision of the text

25.09.2006

Analytical part

II.A. QUALITATIVE AND QUANTITATIVE PARTICULARS

The detailed composition is provided. The product is filled in 12,20 and 23,00 ml, type I neutral borosilicate glass vials closed with a rubber chlorobutyl stopper and sealed with aluminium cap. The particulars of the containers and controls performed are provided and conform to European Pharmacopoeia requirements. The dossier provides a sufficient description of the materials, the sterilization procedures used and the additional physical tests. Analysis certificates are provided as well as certificates from producers of each material.
The development of this product is adequately described. The choice of the vaccine strain, of the inactivating agent, of the adjuvant and the preservative are justified. The inactivation process and the detection limit of the control of inactivation are correctly validated.

II.B. METHOD OF PREPARATION

The steps of the production process are detailed. The production is based on a seed lot system; the antigen is then inactivated and blended with the other ingredients (adjuvant and excipient).
The production is performed on accordance with Good Manufacturing Practice (GMP).
The validation study monitors individual steps of vaccine production. In the validation study of the manufacturing procedure of the vaccine Castorex the production and control parameters were observed. The results show that on the condition of complying with all directives of the production and control procedures of the vaccine the required quality parameters are gained.

II.C. PRODUCTION AND CONTROL OF STARTING MATERIALS

All the starting materials used for the production of the vaccine are tested for quality and absence of extraneous agents according to the current regulation.

II.D. MINIMISING THE RISK OF TRANSMITTING AGENTS CAUSING SPONGIFORM ENCEPHALOPATHY

Starting materials do not represent any risk of transmission of agents causing TSE. The veterinary medicinal product Castorex is designed for prophylaxis of RHDV in animals, for which up to now natural transmission of prion infection TSE has not been confirmed.

II.E. CONTROL TESTS DURING PRODUCTION

The tests performed during production are described including the timing and frequency of the testing and including description of each test and limits of acceptance of results.

II.F. CONTROL TESTS ON THE FINISHED PRODUCT

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

II.F. STABILITY TESTS

The stability of the finished product is demonstrated by a 15-month real time stability study, performed on 5 batches of vaccine. All these batches were stored according to the specifications and tested until 15 months of storage for sterility, efficacy and stability of chemical parameters of the vaccine. The parameters conform to the release specifications, these results justify a shelf-life of 12 months of the final product. Three batches were tested 24 hours after opening an original container, test parameters were sterility and pH value. The stability for 24 hours after broaching as indicated in the SPC is acceptable.

Safety

Laboratory tests

All studies were performed with the target species, rabbits at the age of six weeks, ten weeks, four months and nine months, clinically health, serologically negative for antibodies against rabbit haemorrhagic disease. The safety of the administration of one dose, an overdose and the repeated administration of one dose is demonstrated. The examination of the reproductive performances was performed, the treatment by the vaccine Castorex has no negative impact on the reproductive performance of vaccinated does. The vaccine Castorex has no negative impact on the immune system of vaccinates as well as their progeny. The absence of negative impact of the vaccine on immune system is supported by the results of trial aimed at examination of concurrent administration of two vaccines. Special requirements for live vaccines are not fulfil, the vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable. There is used the aluminium adjuvans in this vaccine and after application of larger volumes a weak inflammatory reaction occurs at the site of injection. For this reason there has been established a withdrawal period of 7 days for meat. No information is available on safety and efficacy from the concurrent use of this vaccine with any other vaccine except for the myxomatosis vaccine Pharmavac MXT inj. sicc. Therefore, it is recommended not to use any other vaccine than Pharmavac MXT inj.sicc. within 14 days before or after vaccination with this product.

Field studies

Approximately 700 rabbits were included into the field trials of safety. In vaccinated animals of various age categories no adverse post-vaccination reactions were recorded, all parameters of clinical evaluation of health status stayed unchanged throughout the whole period of observation.

Ecotoxicity

This is an inactivated vaccine, injected to the animal; unused vaccine is disposed according to national requirements. Therefore, the risk of possible ecological effects of the inactivated antigens, the adjuvant and the other substances present in the vaccine is considered as effectively zero.

Conclusions on safety

The trials reported in the safety dossier carried out during the development of the product and in accordance with recommendations of Directive 2001/82 EC as amended by Directive 2004/28/EC, Ph.Eur. and OIE Manual of Standards for Diagnostic Tests and Vaccines. The results of tests proved that the vaccine Castorex is safe for target animals of all age categories including the youngest category of 6-week-old rabbits. The vaccine Castorex is safe for target animals even when overdose is administered. Treatment by the vaccine Castorex has no negative impact on the reproductive performance of vaccinated does, the vaccine is not immunosuppressive and no adverse effect attributable to the vaccine was observed during the safety testing. The use of excipients (formaldehyde and thiomersal) is satisfactory, with respect to the weak inflammatory reaction occurring at the site of injection (inflammatory reactions that adjuvant substance evoke), a withdrawal period of 7 days for meat was established.
The trials carried out in accordance with guideline EMEA/CVMP/550/02 – "Requirements for Concurrent Administration of Immunological Veterinary Medicinal Product" provided information for Interaction and has impact in the proposed SPC.
The safety of Castorex vaccine was also demonstrated in the field.
Within more than five years of use of the vaccine Castorex in the territory of the SR and the CR more than 7 million vaccine doses have been applied. During this period no report concerning unsatisfactory safety of vaccine have been announced.

Efficacy

Efficacy testing was performed on target animals of the following age categories : minimum six weeks, ten weeks, older than three months.
Efficacy testing was performed by challenge trials and also by examination of post-vaccination humoral immunity. Onset of post-vaccination immunity in target animals and duration of post-vaccination immunity has been tested too.
The results of control test on efficacy confirm that on condition of keeping the technological procedure of manufacturing, the vaccine retains the efficacy as it is given in OIE Manual of Standards for Diagnostic Tests and Vaccines for Terrestrial Animals, 5th Ed., 2004, chapter 2.8.3. "Rabbit haemorrhagic disease" and also in the monograph of European Pharmacopoeia that is under preparation.

Field studies

Evaluation of efficacy was done on conditions of a rabbit-breeding farms. The results under these conditions gave evidence on efficacy of the vaccine Castorex. By vaccination of rabbits of various age categories the reliable protection against challenge infection was reached, the vaccine evoked solid humoral immunity as it was confirmed by consequential challenge trials on randomly selected vaccinated animals. After vaccination no adverse reactions were developed. No deviations from standard physiological status were recorded; vaccination had no negative effect on performance of animals.

Conclusions on efficacy

The trials reported in the efficacy dossier were carried out during the development of the product and in accordance with the recommendations of Directive 2001/82 EC as amended by Directive

2004/28/EC, Ph.Eur. and OIE Manual of Standards for Diagnostic Tests and Vaccines and with guideline EMEA/CVMP/682/99 “Duration of protection achieved by veterinary vaccines”. The results of tests proved that the vaccine Castorex is efficacious for target animals of all recommended age categories. The protection after vaccination was tested even after administration of diluted vaccine by challenge, and immune response was tested also by the detection of antibodies. The onset of immunity and the duration of immunity have been tested as well. The safety of Castorex vaccine has also been demonstrated in the field.
During more than five years of use of the vaccine Castorex in the territory of the SR and the CR many vaccine doses have been applied. In this period no report concerning unsatisfactory efficacy of vaccine has been announced.

Overall conclusion

The vaccine is produced and controlled using validated methods which ensure the consistency of the product released on the market. The vaccine was demonstrated as safe using as recommended in the target species. The efficacy of the vaccine was demonstrated according to the claims made in the SPC. The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk / benefit analysis for the target species is in favour of granting a marketing authorization.