Paul-Ehrlich-Institut

Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

Nobivac Tricat Trio
In Deutschland: Nobivac RCP

Zulassungsdatum:	21.06.2006
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Paul-Ehrlich-Institut
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Nobivac Tricat Trio
In Germany: Nobivac RCP

INTRODUCTION

Nobivac Tricat Trio is a freeze-dried combined vaccine containing live attenuated feline calicivirus (strain F9), live attenuated feline herpes virus type 1 (strain G2620A) and live attenuated feline panleucopenia virus (strain MW-1) for the active immunisation of cats to reduce the signs of the disease caused by infection with feline calicivirus and feline herpesvirus type 1 and to prevent the signs of the disease, leucopenia and virus excretion caused by infection with feline panleucopenia virus. Nobivac Tricat Trio is indicated for cats of 8-9 weeks of age onwards and was authorised in Germany on 21. June 2006.

The relevant EP (European Pharmacopoeia) monographs for this application are:

- Vaccina ad usum veterinarium
- Vaccinum panleucopeniae felinae infectivae vivum (251)
- Vaccinum rhinotracheitidis viralis felinae vivum cryodesiccatum (1206)
- Vaccinum calicivirosis felinae vivum cryodesiccatum (1102)

The relevant EU requirements

* Directives; 2001/82/EC as amended; 87/22; 91/412
* Guidelines: GRLMV, General requirements for the production and control of live mammalian bacterial and viral vaccines for veterinary use

I. SUMMARY OF THE DOSSIER

I. A. ADMINISTRATIVE DATA

I. A. 1Product

Name of Product	Nobivac Tricat Trio
Active Ingredient(s)	live attenuated feline calicivirus, strain F9 live attenuated feline herpes virus type 1, strain G2620A live attenuated feline panleucopenia virus, strain MW-1
Pharmaceutical Form	Lyophilisate and solvent for suspension for injection.
Indications	Active immunisation of cats: - to reduce the clinical signs caused by infection with feline calicivirus and feline herpes virus type 1, - to prevent clinical signs, leucopenia and virus excretion caused by infection with feline panleucopenia virus.
Dose and Method of	1 ml twice at intervals of 3-4 weeks, minimum age: 8 to 9 weeks,

Administration	Booster injections: feline calicivirus and feline herpesvirus type 1: once a year, feline panleucopenia virus: every three years
Route of Administration	Subcutaneous injection
Target Species	Cats from 8 to 9 weeks of age

I. A. 2Source

The Manufacturing Authorisations and GMP (Good Manufacturing Practice) certificates of all manufacturing sites are presented.
Countries where the application was submitted for Mutual Recognition: AT, BE, CZ, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, SE, SI, SK, UK.

II. ANALYTICAL INFORMATION

II. A. 1 Composition

Active substances per dose after freeze-drying

Name of ingredients	Quantity per dose	Function	Reference
Active substances			
Live attenuated feline calicivirus, strain F9:	4.6 – 6.4 $\log_{10}$ PFU*	antigen	Ph.Eur. 1102
Live attenuated feline herpesvirus type 1, strain G2620A:	5.2 – 7.0 $\log_{10}$ PFU	antigen	Ph.Eur. 1206
Live attenuated feline panleucopenia virus, strain MW-1:	4.3 – 6.4 $CCID_{50}$	antigen	Ph.Eur. 0251

***** PFU: Plaque forming units

DILUENT (Nobivac Solvent)

Phosphate buffered solution.

Container
The vaccine is filled in glass vials (type I, Ph.Eur.). After filling the vials are closed with a rubber stopper. After freeze-drying, the stoppers are sealed with coded aluminium cap.

Development of Pharmaceutics

Live attenuated vaccines to protect kittens against diseases caused by the most important viral feline pathogens have been available for decades. Intervet developed the lyophilised vaccine Nobivac Tricat Trio which contains live attenuated vaccine strains of FCV, FVR virus and FPLV. This vaccine has been on the European market for more than 25 years now. In the 1990s the same vaccine concept was introduced in the USA but with another FPLV vaccine strain for which three year duration of immunity was documented. This trivalent vaccine will be known as Nobivac Tricat Trio in Europe.

II. B. METHOD OF PREPARATION OF FINISHED PRODUCT

II. B. 2 Detailed description of the production steps

Expansion of production cells

To expand the production cells, these are thawed, resuspended in growth medium and seeded into culture vessels. Then, cells are incubated. When the monolayers are confluent, the cells are collected, resuspended into fresh growth medium and seeded again. The above described steps are repeated until the amount of cells required for the virus production is obtained. The cells are transferred from the clean cell production unit to a virus production unit.

FCV, FVR and FPV antigen production

Production cells are seeded into culture vessels and incubated. After sufficient time the cells are infected with FCV, FVR or FPV seed virus. After adequate incubation, the antigen is harvested. The harvests are pooled, sampled and filled in sterile bottles and stored.

Final product preparation

Aliquots of antigen which have passed the in-process control are selected and mixed with stabiliser. Vaccine is filled into glass vials and freeze-dried. Finally, the vials are closed and secured with a coded aluminium cap. Vials are stored between 2-8 °C or lower for shipment. When quality control tests are passed satisfactorily, the product can be released on the market.

II. B. 3 Validation

Based on the data of 3 consecutive batches of each bulk antigen and of three batches finished product the conclusion seems justified that the method of manufacturing leads to a product of consistent quality.

II. C. PRODUCTION AND CONTROL OF STARTING MATERIALS

II. C. 2 Starting materials not listed in a pharmacopoeia or used in tissue culture media

II. C. 2.1a. Starting materials of biological origin

The source, passage history, preparation and control of the seed lots and other materials of animal origin have been described in sufficient details. All materials comply with the appropriate requirements as laid down in European legislation, including TSE aspects.

II. C. 2.1b Starting materials of non biological origin

Amphotericin B

II. E. CONTROL TESTS DURING PRODUCTION

In-process tests on antigen bulk:
- Sterility of the antigen bulk
- Titration of the bulk antigen

In-process tests during preparation of the finished product:
- Checking the filling volume
- Monitoring freeze drying

II. F. CONTROL TESTS ON THE FINISHED PRODUCT

- Sterility according to Ph.Eur. monograph 2.6.1./0062.
- Absence of mycoplasmas according to Ph.Eur. 2.6.7.
- Batch safety test
- Test of absence of extraneous agents.
- Titration of the antigen components
- Identification
- Residual moisture
- Cap code and vacuum

II. G. STABILITY

The stability of the finished product was tested over 36 months at 2-8 °C. The data of this study indicate good stability for all components of Nobivac Tricat Trio All results were above the minimum titre set. The provided data justify the proposed shelf life of 33 months at 2-8 °C.

Stability of the reconstituted product was tested over 30 minutes at 20-25 °C. The data of this study are valid to support the stability of Nobivac Tricat Trio vaccine and justify a shelf life of 30 minutes for reconstituted vaccine stored at room temperature. Based on the data presented, a short period (transport) without cooling is acceptable.

III. SAFETY

III. A + B. INTRODUCTION/GENERAL REQUIREMENTS

Nobivac Tricat Trio is a live, attenuated vaccine intended for cats of 8-9 weeks of age or older. Before use, the freeze-dried vaccine should be reconstituted with the solvent Nobivac Solvent. One dose of 1 ml contains at least 4.6 $\log_{10}$ PFU of FCV, at least 5.2 $\log_{10}$ PFU of FVR and at least 4.3 $\log_{10}$ $TCID_{50}$ of FPLV. The vaccine should be injected subcutaneously.
Nobivac Tricat Trio is indicated for the active immunisation of cats against the consequences of an infection with feline calicivirus, feline rhinotracheitisvirus and feline panleukopeniavirus.
The safety has been examined in young kittens. The ten times maximum dose of the FCV, FVR and FPLV antigen components used in the main safety studies are 7.4 $\log_{10}$ PFU, 8.0 $\log_{10}$ PFU and 8.1 $\log_{10}$ $TCID_{50}$, respectively.
Safety studies were performed both in the laboratory and in the field.
Sufficient information on animal welfare and GLP (Good Laboratory Practice) is provided for each single laboratory trial.

III. C. LABORATORY STUDIES

Overview of the safety-studies

Safety of the administration of one dose, an overdose and a repeated one dose to the target animal
Examination of immunological functions
Spread of the vaccine strains
Reversion to virulence FCV strain
Reversion to virulence FVR strain
Reversion to virulence FPLV strain
Field Studies

III. C. 1-3 Safety of administration of one dose, an overdose and a repeated single dose to the target animal

Local and systemic reactions are described after the administration of one dose, an overdose, and a repeated single dose in cats of 9 weeks of age.
Vaccinated kittens were monitored daily for local and systemic reactions from -2 to +14 days for the primary vaccination and days -2 to +21 for the second and third vaccination. Temperatures (rectal) of all kittens were monitored once daily and immediately before, 4 and 8 hours post vaccination. Serum samples were collected from all kittens prior to each vaccination and three weeks after the last vaccination and tested for antibody titres to all components.
It is concluded that subcutaneous vaccination in cats at a minimum age of 9 weeks is safe.
The observed adverse reactions are described in the SPC (Summary of Product Characteristics).

III. C. 4 Examination of reproductive performance

The use of the vaccine in pregnant queens and during lactation has not been investigated. Therefore, the use of Nobivac Tricat Trio during pregnancy and lactation is not recommended. An appropriate comment can be found in the SPC.

III. C. 5 Examination of immunological functions

FPLV is known to induce leucopenia in cats and may consequently adversely affect the immunological function of the cat. Therefore, the properties of Intervet's FPLV vaccine strain were evaluated. The studies show that the FPV component does not negatively affect the immunological functions.
The other two vaccinal antigens are not known to adversely affect immunological functions. Therefore studies for these two antigens are considered not to be relevant.

III. C. 6 Special requirements for live vaccines

III. C. 6.1 Spread of the vaccine strains

After subcutaneous administration of Nobivac Tricat Trio, none of the components were shed or spread to susceptible in-contact kittens. Therefore, the recommended subcutaneous route can be considered safe.

III. C. 6.2 Dissemination in the vaccinated animal

All three pathogens (FCV, FVR and FPLV) do not cause zoonotic disease and the vaccine is not intended for food producing animals. According to EP monograph 5.2.6 “Evaluation of safety of veterinary vaccines” dissemination studies are therefore not necessary.

III. C. 6.3 Reversion to virulence

FCV is reisolated for up to five passages in cats. The amount of FCV reisolated from tissue homogenates is rather stable, and enhancement of clinical signs was not observed. Reisolation of the viral vaccine strains FVR and FPLV was possible for up to three and two passages, respectively, in low amounts. No clinical signs attributed to FVR were observed. No clinical signs, no leucopenia, no virus excretion, and no increase in gross pathological or histological abnormalities were found that could be attributed to FPLV. From these studies, it is concluded that the avirulent nature of all three vaccine strains is stable.

III. C. 6.5 Recombination or genomic reassortment

For each of the three viral agents concerned, the occurrence of recombination cannot be excluded. It is evident that recombination can occur only if two different genomes of the same viral species are present in the same cell but opportunities for recombination between vaccine virus and field strains of the same viral species do exist. Hence, sooner or later any live vaccine strain may recombine with field virus. This should not be a matter of concern: the event is natural as a recombination between two field strains, and it is not to be expected that the recombinant will have any virulence factors that are not already present in contributing parent field strain. Each of the three viruses concerned has a single genome. Therefore, no genomic reassortment can occur.

III. C. 7. Residues

Nobivac Tricat Trio is a vaccine which is indicated solely for use in cats. Therefore, the issue of residues is not applicable.

III. C. 8 Interactions

No interactions with other products have been investigated. It is therefore recommended that no other parenteral vaccine should be administered shortly before or after vaccination with Nobivac Tricat Trio. A corresponding warning can be found in the SPC.

III. D. FIELD STUDIES

In the field studies conducted it is shown that the vaccine, administered to cats subcutaneously on two occasions, causes only a few mild transient systemic reactions. Therefore, it is concluded that Nobivac Tricat Trio is safe in young kittens kept under field conditions.

III. E. ECOTOXICITY

Nobivac Tricat Trio is a freeze-dried live vaccine, to be dissolved in a diluent, containing phosphate buffer, and to be administered by subcutaneous injection to individual cats. The product is used exclusively by professionals for the vaccination of cats. As the product is presented in single dose vials, it is prepared immediately before use and virtually no remnant remains. Any unused or waste material should be disposed of via the appropriate channels. The product contains as active ingredients live attenuated FCV, FVR and FPLV strains which are not pathogenic to cats and do not revert to virulence during experimental cat-to-cat passage. Hazards and risks from the active ingredients of Nobivac Tricat Trio are therefore likely to be negligible.
The risk of possible ecological effects of the live virus strains and of the substances associated with the product should be considered effectively zero.

CONCLUSIONS ON SAFETY

All accomplished investigations show that Nobivac Tricat Trio is well tolerable for cats. However, in some cases a slight painful swelling was observed at the injection site for 1-2 days. A slight transient rise in body temperature (up to 40°C) occurred for 1-2 days. In some cases, sneezing, coughing, nasal discharge, and a slight dullness or reduced appetite was found for up to 2 days post vaccination. In very rare cases, the vaccine may cause hypersensitivity reactions (pruritus, dyspnoea, vomiting, diarrhoea and collapse).
An appropriate warning reference was included in the SPC. The immune system is not affected negatively. Nobivac Tricat Trio is safe for the environment. None of the components spread to other cats. Serial passage in cats did not result in reversion to virulence.
No data was presented for use in pregnant and lactating cats. An appropriate warning has been included in the SPC
The studies carried out demonstrated the safety of this vaccine used at the requested minimum age of 8-9 weeks.

IV. EFFICACY

IV. A./B. INTRODUCTION / GENERAL REQUIREMENTS

Nobivac Tricat Trio is a live, attenuated vaccine indicated for the active immunisation of cats. Before use, the freeze-dried vaccine should be

reconstituted with the solvent Nobivac Solvent. One dose of 1 ml contains at least 4.6 log_{10} PFU of FCV, at least 5.2 log_{10} PFU of FVR and at least 4.3 log_{10} $TCID_{50}$ of FPLV. The vaccine should be injected subcutaneously to cats aged 8 to 9 weeks and older. It is used to reduce clinical signs and virus excretion caused by an infection with FCV and FVR, and to prevent clinical signs, virus excretion and leucopenia caused by FPLV. Protection in face of specific passive antibodies has been shown.
To evaluate the efficacy of Nobivac Tricat Trio vaccination/challenge studies under controlled conditions as well as field trials were performed.
Vaccinations were carried out in the target animal according to the prescribed vaccination route. For the initial vaccination course, two doses are required, injected subcutaneously at intervals of 3-4 weeks. The preferred age for initial vaccination of kittens is 8-9 weeks with the second injection at 12 weeks of age.
The efficacy studies were performed with vaccine containing the minimum titres (for FCV 4.6 log_{10} PFU, for FVR 5.2 log_{10} PFU and for FPLV 4.3 log_{10} $TCID_{50}$).
Sufficient information on animal welfare is provided for each single laboratory trial.

Overview of the efficacy-studies

FCV-Challenge in kittens without antibodies
FVR-Challenge in kittens without antibodies
FPLV-Challenge in kittens without antibodies
Efficacy of the vaccine in the presence of antibodies
Duration of immunity - FCV component
Duration of immunity - FVR component
Duration of immunity - FPLV component
Field study

CONCLUSIONS ON EFFICACY

Vaccination with Nobivac Tricat Trio on two occasions at intervals of 3-4 weeks in kittens, aged 8-9 weeks or older, reduces clinical signs and virus excretion caused by an infection with FCV and FVR. Vaccination also prevents clinical signs, virus excretion and leucopenia caused by FPLV. Protection in the face of specific passively acquired antibodies has been shown and an effective immune response after vaccination under field conditions. The FCV and FVR components in Nobivac Tricat Trio are shown to be efficacious for at least one year after vaccination and the FPLV component for at least three years after vaccination. The studies were carried out with cats of minimum age and with low titres of the viral components.

Based on the data presented by the applicant, the following indication for use of the vaccine is justified:
Active immunisation of cats 8-9 weeks old:
- to reduce clinical signs caused by infection with feline calicivirus and feline herpes virus type 1,

- to prevent clinical signs, leucopenia and virus excretion caused by infection with feline panleucopenia virus.

Onset of immunity: for FCV and FHV: 4 weeks; for FPLV: 3 weeks.
Duration of immunity for FCV and FHV: 1 year, for FPLV: 3 years.

Basic vaccination:
Two single dose injections, 3-4 weeks apart.
The first injection can be given from the age of 8-9 weeks and the second injection from the age of 12 weeks.
Revaccination:
A single dose (1 ml) according to the following schedule:
Revaccination against feline calicivirus and feline herpesvirus type 1 must be given every year (with vaccines containing the F9 and G2620 strains, where available).
Revaccination against feline panleucopenia virus can be given every three years (with strain MW-1 as in Nobivac Tricat Trio, where available).

V. OVERALL CONCLUSIONS

Based on the data presented by the applicant, the qualitative and quantitative composition of this product and its properties, as well as the method to control product quality has been sufficiently substantiated.
The safety of the product is considered sufficiently proven.
The efficacy data sufficiently support the claim if the product is used according to the SPC, under normal field conditions.
The Applicant has provided satisfactory data on Quality, Safety and Efficacy to meet the requirements of Directive 2001/82/EC as amended by Directive 2004/28/EG and European Pharmacopoeia.

Annex

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nobivac Tricat Trio, lyophilisate and solvent for suspension for injection, for cats (AT, DE: Nobivac RCP; ES: Nobivac Tricat Novum, SE: Nobivac Tricat Novum* vet)

* The affix 'Novum' is added temporarily during transitional period between old and new product.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per dose of 1 ml:

Lyophilisate
Active substances:
live attenuated feline calicivirus, strain F9: ≥4.6 $\log_{10}$ PFU[1] ;
live attenuated feline herpes virus type 1, strain G2620A: ≥5.2 $\log_{10}$ PFU[1];
live attenuated feline panleucopenia virus, strain MW-1: ≥4.3 $\log_{10}$ $CCID_{50}$ [2]

[1]PFU: Plaque-Forming Units
[2]$CCID_{50}$: Cell Culture Infective Dose 50%

Excipients:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilisate and solvent for suspension for injection.
Off-white lyophilisate

4. CLINICAL PARTICULARS

4.1. Target species

Cats

4.2. Indications for use, specifying the target species

Active immunisation of cats:
- to reduce the clinical signs caused by infection with feline calicivirus (FCV) and feline herpes virus type 1 (FHV),
- to prevent the clinical signs, leucopenia and virus excretion caused by infection with feline panleucopenia virus (FPLV).

Onset of immunity: for FCV and FHV: 4 weeks; for FPLV: 3 weeks.
Duration of immunity for FCV and FHV: 1 year, for FPLV: 3 years.

4.3. Contraindications

See point 4.7

4.4. Special warnings

Maternal antibodies, which may persist up to the age of 9-12 weeks, can have a negative influence on the efficacy of vaccination. In the presence of maternal antibodies, vaccination may not completely prevent the clinical signs, leucopenia and virus excretion following an FPLV infection. In such cases where a relatively high level of maternally derived antibodies is expected, the vaccination schedule should be planned accordingly.

4.5. Special precautions for use

Special precautions for use in animals

Only healthy animals should be vaccinated.

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

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

4.6. Adverse reactions (frequency and seriousness)

A slight painful swelling may be observed at the injection site for 1-2 days. A slight transient rise in body temperature (up to 40°C) may occur for 1-2 days. In some cases sneezing, coughing, nasal discharge, and a slight dullness or reduced appetite may be observed for up to 2 days post vaccination. In very rare cases, the vaccine may cause hypersensitivity reactions (pruritus, dyspnoea, vomiting, diarrhoea and collapse).

4.7. Use during pregnancy, lactation or lay

Do not use during pregnancy or lactation, as the product has not been tested in pregnant or lactating queens. Live FPL virus can cause reproductive problems in pregnant queens and birth defects in the progeny.

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

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

4.9. Amounts to be administered and administration route

Use 1 ml solvent to reconstitute the lyophilisate (= 1 single dose).
Bring the vaccine to room temperature and administer 1 ml of the vaccine per animal by subcutaneous injection.
Use sterile injection equipment, free from traces of disinfectants.

Vaccination schedule:
Basic vaccination:
Two single dose inoculations, 3-4 weeks apart.
The first inoculation can be given from the age of 8-9 weeks and the second inoculation from the age of 12 weeks. (See also section 4.4)
Revaccination:
A single dose (1 ml) according to the following schedule:
Revaccination against feline calicivirus and feline herpesvirus type 1 must be given every year (with vaccines containing the F9 and G2620 strains, where available).
Revaccination against feline panleucopenia virus can be given every three years (with strain MW-1 as in Nobivac Tricat Trio, where available).

4.10. Overdose (symptoms, emergency procedures, antidotes), if necessary

At ten-fold overdose, a slight painful swelling may be observed at the injection site for 4-10 days.
A slight transient rise in temperature (up to 40.8°C) may occur for 1-2 days.
In some cases general discomfort, coughing, sneezing, transient lethargy and reduced appetite may be observed for a few days post vaccination.

4.11. Withdrawal period(s)

Not applicable.

5. IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Live viral vaccine for cats
ATCvet-code: QI06AD04
To stimulate active immunity against feline calicivirus, feline herpesvirus type 1 (feline rhinotracheitis virus) and feline panleucopenia virus in cats.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lyophilisate:
Disodium phosphate dehydrate
Hydrolized gelatine
Pancreatic digest of casein
Sorbitol

Solvent:
Disodium phosphate dehydrate
Potassium dihydrogen phosphate
Water for injection

6.2. Incompatibilities

Do not mix with any other veterinary medicinal product.

6.3. Shelf life

Shelf life of the veterinary medicinal product as packed for sale:
Lyophilisate: 33 months.
Solvent: 5 years
Shelf life after reconstitution according to directions: use within 30 minutes.

6.4. Special precautions for storage

Lyophilisate: Store in a refrigerator (2 °C - 8 °C).
Protect from light.
Solvent: can be kept below 25°C if stored separately from the lyophilisate.
Do not freeze.

6.5. Nature and composition of immediate packaging

Lyophilisate: 1 dose vial of glass type I (Ph.Eur.) closed with a halogenobutyl rubber stopper and sealed with a coded aluminium cap.
Solvent fraction: 1 dose vial of glass type I (Ph.Eur.) closed with a halogenobutyl rubber stopper and sealed with a coded aluminium cap.

Pack sizes: Carton boxes with 5, 10, 25 or 50 doses of vaccine and solvent
Not all pack sizes may be marketed.

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

Dispose of waste material by boiling, incineration, or immersion in an appropriate disinfectant approved for use by the competent authorities.

7. MARKETING AUTHORISATION HOLDER

Intervet International BV
Wim de Körverstraat 35
5831 AN Boxmeer
The Netherlands

represented by the national companies in the CMS.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 June 2006 / 21 June 2011

10. DATE OF REVISION OF THE TEXT

June 2011

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.