



Paul-Ehrlich-Institut

Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

Versifel FeLV

Zulassungsdatum:	19.11.2010
Zulassungsnummer:	PEI.V.11457.01.1
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(Reference Member State)**

**MUTUAL RECOGNITION PROCEDURE
PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

Versifel FeLV

PRODUCT SUMMARY

EU Procedure number	DE/V/0254/001/MR
Name, strength and pharmaceutical form	Versifel FeLV, suspension for injection
Applicant	Zoetis Deutschland GmbH Schellingstraße 1 10785 Berlin Germany
Active substance(s)	Inactivated Feline Leukaemia Virus (FeLV) subtypes A, B and C (Kawakami-Theilen strain) including gp70 sub-unit antigen, inducing anti-gp70 antibodies GMT $\geq 8.1 \text{ Log}_2^*$ *As determined by mouse potency test (anti-gp70 antibodies, GMT denotes: geometric mean titre) <u>Adjuvants:</u> Quil A 20 µg Cholesterol 20 µg DDA (Dimethyl-dioctadecyl ammonium bromide) 10 µg Carbopol 0.5 mg
ATC Vetcode	QI06AA01
Target species	Cats
Indication for use	For active immunisation of susceptible cats from 9 weeks of age to reduce the number of cats infected with FeLV and presenting clinical signs of the related disease. No data are available in the studies to demonstrate protection against related clinical disease but prevention of infection is associated with protection against related clinical disease.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Versifel FeLV,
suspension for injection for cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 1 ml contains:

Active substance:

Inactivated feline leukaemia virus (FeLV) subtypes A, B and C (Kawakami-Theilen strain) including gp70 sub-unit antigen, inducing anti-gp70 antibodies

GMT \geq 8.1 log₂*

* As determined by mouse potency test (anti-gp70 antibodies, GMT denotes: geometric mean titre)

Adjuvants:

Quil A	20 µg
Cholesterol	20 µg
DDA (Dimethyl-dioctadecyl ammonium bromide)	10 µg
Carbomer	0.5 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Slightly opaque suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Cats.

4.2 Indications for use, specifying the target species

For active immunization of susceptible cats from 9 weeks of age to reduce the number of cats infected with FeLV and presenting clinical signs of the related disease.

No data are available in the studies to demonstrate protection against related clinical disease but prevention of infection is associated with protection against related clinical disease.

Onset of immunity occurs within four weeks of the completion of the primary vaccination course.

The duration of immunity is at least one year after the primary course and three years after the booster.

4.3 Contraindications

None.

4.4 Special warnings for each target species

Only healthy animals should be vaccinated.

Do not vaccinate FeLV antigen positive cats.

Therefore a test for presence of FeLV before vaccination is recommended.

No data are available for the efficacy of the product in presence of maternal derived antibodies.

4.5 Special precautions for use

Special precautions for use in animals

Not applicable.

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)

Commonly, small subcutaneous swellings have occurred at the injection site, (diameter usually smaller than 10 mm, maximal diameter 20 mm) and very rarely may be associated with a brief period of discomfort and/or pain. The majority of these

swellings resolve within a short period (2 weeks). A small proportion may remain detectable for 1 to 2 months however, by this time they are very small.

Commonly, following the first subcutaneous administration in the target species, transient increases in temperature could occur (up to 40.5°C after administration of an overdose); such temperature rises are however expected to be of short duration (resolving within 48 hours). Frequency and duration of any temperature rise is usually lower following subsequent administrations.

When administered concurrently or simultaneously with Zoetis' Versifel CVR transient increases in temperature (up to 40.5 °C) are common following first vaccination lasting up to 5 days.

Following the second dose administration, on rare occasions transient enlargements of the pre-scapular lymph nodes have been observed; such enlargements are small in size (0.5 cm diameter) and only detected upon palpation of the area following injection.

Very rarely, a brief period of general malaise or mild or moderate depression is observed immediately post vaccination but normally resolves within 24 hours; health of animals is not adversely affected.

Very rarely, digestive tract disorders such as: vomiting, diarrhoea or anorexia has been observed.

In very rare cases allergic reactions have been observed. In case of anaphylactic shock appropriate treatment should be administered.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment).
- common (more than 1 but less than 10 animals in 100 animals).
- uncommon (more than 1 but less than 10 animals in 1,000 animals).
- rare (more than 1 but less than 10 animals in 10,000 animals).
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy and lactation or lay

Do not use in pregnant and lactating cats.

4.8 Interaction with other medicinal products and other forms of interaction

Safety and efficacy data are available which demonstrate that this vaccine can be either mixed with Zoetis' Versifel CVR and administered at a single site or administered on the same day as Zoetis' Versifel CVR but at different sites.

No data are available on the duration of immunity of Versifel FeLV when administered together with Versifel CVR, this should be taken into account when considering re-vaccination intervals.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the product mentioned above. 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

Subcutaneous use.

Shake the vial well immediately before use.

Primary vaccination:

Two doses of 1 mL should be administered subcutaneously to cats from nine weeks of age, with an interval of 3-4 weeks between doses.

Re-vaccination:

A single booster dose should be administered 1 year after the completion of the primary vaccination course. Thereafter a single booster dose should be administered to cats once every 3 years.

For concurrent vaccination with Zoetis' Versifel CVR, a single dose of Versifel FeLV should be administered as described above. A single dose of Zoetis' Versifel CVR should then be administered at a separate site via the subcutaneous route.

For simultaneous vaccination with Zoetis' Versifel CVR, the contents of a single vial of Zoetis' Versifel CVR should be reconstituted with the contents of a single vial of Versifel FeLV in place of the diluent. Once mixed, the contents of the vial should appear as a slightly coloured (pink/orange) opaque suspension ; the mixed vaccines should be injected immediately via the subcutaneous route.

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

Following the administration of an overdose, a larger proportion of animals might be expected to show a transient rise in rectal temperature (up to 40.5°C). Such transient rises are however expected to be of short duration (resolving within 48 hours). Frequency and duration of any temperature rise is usually lower following subsequent single dose administrations.

In the laboratory overdose study, in which an overdose, comprising double (2 ml) the recommended dose was administered, a larger proportion of animals developed a swelling at the injection site, (max. diameter up to 21 mm). The majority of these

swellings resolved within a short period (within 2 weeks). A slightly larger proportion had swellings which remained detectable for 1 or 2 months however, by this time they were very small.

4.11 Withdrawal period

Not applicable.

5. IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: immunologicals for Felidae, inactivated viral vaccines for cats.

ATC vet code: QI06AA01

Vaccination stimulates active immunity against FeLV infection in healthy cats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Quil A
Cholesterol
DDA (Dimethyl-dioctadecyl ammonium bromide)
Carbomer
Phosphate buffered saline

6.2 Incompatibilities

Safety and efficacy data are available which demonstrate that this vaccine can be mixed with, or administered at the same time as, Zoetis' Versifel CVR. Do not mix with any other veterinary medicinal product.

6.3 Shelf-life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life after first opening the immediate packaging: use immediately.

6.4 Special precautions for storage

Store and transport refrigerated (2 °C - 8 °C).
Do not freeze.
Protect from light.

6.5 Nature and composition of immediate packaging

Single dose type I (Ph. Eur.) glass vials, closed with rubber stoppers (Ph. Eur.) and sealed with aluminium caps.

Pack sizes:

Clear plastic tray containing 10 x 1 ml dose.

Clear plastic tray containing 25 x 1 ml dose.

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

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

7 MARKETING AUTHORISATION HOLDER

To be completed nationally.

8 MARKETING AUTHORISATION NUMBER

To be completed nationally.

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

To be completed nationally.

10 DATE OF REVISION OF THE TEXT

To be completed nationally.

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be completed nationally

PUBLIC ASSESSMENT REPORT

Legal basis of mutual recognition application	Mutual recognition application in accordance with Article 31 of Directive 2001/82/EC as amended.
Date of completion of the mutual recognition procedure	25.07.2012
Date product first authorised in the Reference Member State	19.11.2010
Concerned Member States for mutual recognition procedure	AT, BE, BG, CY, CZ, EL, ES, FR, HU, IE, IT, LU, PL, PT, RO, SI, 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 are indicated in the SPC (Summary of Product Characteristics). The product is safe for the user and for the environment, when used as recommended. The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. *Composition*

Composition per 1 ml dose:

Each 1 ml dose of Versifel FeLV contains the following:

Active substance:

Inactivated Feline Leukaemia Virus (FeLV) subtypes A, B and C (Kawakami-Theilen strain) including gp70 sub-unit antigen, inducing anti-gp70 antibodies

GMT \geq 8.1 Log₂ *

*As determined by mouse potency test (anti-gp70 antibodies, GMT denotes: geometric mean titre)

Adjuvants:

Quil A	20 µg
Cholesterol	20 µg
DDA (Dimethyl-dioctadecyl ammonium bromide)	10 µg
Carbopol	0.5 mg

Container/closure system:

The vaccine is filled in 3 ml glass type I containers.

The vials are closed with a pharmaceutical grade rubber stopper and an aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulations of Monograph 3.2.1 of the European Pharmacopoeia (Ph.Eur.).

The choice of the adjuvants (Quil A, Cholesterol, DDA, Carbopol) and the vaccine strain (Kawakami-Theilen strain) are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

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 (GMP) from a licensed manufacturing site. Corresponding manufacturing licences and GMP certificates are provided.

Process validation data on the product have been presented in accordance with the relevant European guidelines.
The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with the pharmacopoeia monograph 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 “Table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and control of mammalian veterinary vaccines” (Note for Guidance III/3427/93, 7Blm10a).
Seed lots and cell bank have been produced as described in the relevant guideline.

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

Scientific data and/or 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 in detail.

These tests are as follows:

Tests on harvested antigen fluids before inactivation

- sterility
- test for mycoplasma
- determination of virus titre

Tests on inactivated antigen fluids before concentration

- sterility
- identification and gp70 antigen content
- inactivation (residual live virus)
- residual sodium thiosulphate

Tests on inactivated antigen fluids after concentration

- sterility
- gp70 antigen content

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements.

The following tests are performed:

- appearance
- sterility: according to Ph.Eur. 2.6.1
- pH determination
- identity of FeLV antigen
- potency

The demonstration of the batch to batch consistency is based on the results of three batches produced according to the method described in the dossier.

G. Stability

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 (2 years) when stored under the approved conditions (at 2-8°C).

The vaccine must be used immediately after broaching.

III. SAFETY ASSESSMENT

Versifel FeLV is a third generation inactivated Feline Leukaemia vaccine to reduce the number of cats infected with FeLV and presenting clinical signs of the related disease.

This vaccine contains Quil A, Cholesterol, DDA (Dimethyl-dioctadecyl ammonium bromide) and Carbopol as adjuvants. The suspension for injection is administered subcutaneously. Cats from an age of 9 weeks can be vaccinated.

Laboratory trials

The trials have been performed in the target species (cat).
All animals used were seronegative to FeLV antigen.

The safety of the administration of one dose, an overdose (double dose) and the repeated administration of one dose in the target animal (cat) was demonstrated in a laboratory trial (involving 5 groups totalising 44 vaccinated animals and including a control group).

The animals were allocated to different groups and were administered either a single dose, an overdose or repeat single doses with an interval of several weeks. Unvaccinated animals were used as control group. All animals were monitored for local and systemic reactions during the study.

Overall, the vaccine Versifel FeLV proved to be well tolerated in the target species cat. The local and systemic reactions as well as the increase in rectal temperature observed are described in the SPC (Summary of Product Characteristics) and package leaflet under "adverse reactions".

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

No investigation of effect on reproductive performance was conducted because neither the FeLV antigen nor any of the excipients are thought to be associated with any pathological effects on the reproductive system of male or non-pregnant females. Furthermore, the vaccine is inactivated. The use of this vaccine therefore poses no obvious risk to reproductive performance. As no safety studies have been conducted in pregnant cats, this is reflected in the SPC and package leaflet.

Versifel FeLV is an inactivated vaccine. There is no reason to suppose that it might adversely affect immunological functions of the recipient. Therefore, no specific studies to examine the effect on immunological functions have been carried out.

Some supporting serological data are, however, available which provide some evidence that the inactivated FeLV antigen does not adversely affect the immunological function or cause immunosuppression.

After vaccination, anaphylactic shock may occur. This is also described in the SPC and package leaflet.

Safety and efficacy data are available which demonstrate that this vaccine can be either mixed with Pfizer's Versifel CVR and administered at a single site or administered on the same day as Pfizer's Versifel CVR but at different sites. No data are available on the duration of immunity of Versifel FeLV when administered together with Versifel CVR. This should be taken into account when considering re-vaccination intervals. This is clearly indicated in the SPC and package leaflet.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

Field studies

Field studies, involving 182 vaccinated animals and 67 control animals, were performed to assess the safety of the vaccine Versifel FeLV.

Cats of different breeds, genders and ages were vaccinated with Versifel FeLV according to the vaccination scheme. All animals were observed for local or systemic reactions during the studies.

Overall, the vaccine Versifel FeLV proved to be well tolerated in the target species cat. The results confirm the observations made in the laboratory studies. The local and systemic reactions observed are described in the SPC and package leaflet under "adverse reactions".

Ecotoxicity

The applicant provided an environmental risk assessment which showed that the risk for the environment and other animals and species posed by this vaccine can be considered as very low.

No warnings are therefore required in the SPC and package leaflet.

IV. EFFICACY

IV.B Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the following Ph.Eur. monograph:

Vaccinum leucosis felinae inactivatum: monograph 1321

The efficacy in the target species cat was demonstrated by means of challenge trials using a heterologous challenge strain. In these trials (4 supportive studies), a total of 64 seronegative animals at the minimum vaccination age of 9 weeks were vaccinated with Versifel FeLV and challenged with virulent feline Leukaemia virus. Unvaccinated animals served as controls.

The results clearly demonstrate the efficacy of Versifel FeLV.

The following conclusions can be drawn from the results of the laboratory studies concerning onset and duration of immunity, indications for use and immunisation scheme:

Regarding the indications, the data are showing that the vaccine is able to lead to active immunisation of susceptible cats from 9 weeks of ages to reduce the number of cats infected with FeLV. Protection against clinical signs has not been demonstrated in studies but published data (McClelland et al 1980) is supporting the relation between absence of infection and protection against clinical signs.

Onset of immunity occurs within four weeks of the completion of the primary vaccination course (75% protection is achieved in the corresponding study).

The duration of immunity is at least one year after the primary course and three years after the booster. Taking into account the age related resistance, 82 to 100% protection is achieved in the corresponding studies.

No data about the efficacy in presence of maternal derived antibodies is available. An appropriate warning is included in the SPC.

Vaccination scheme:

Primary vaccination:

Two doses should be administered subcutaneously to cats from nine weeks of age, with an interval of 3-4 weeks between doses.

Re-vaccination:

A single booster dose should be administered 1 year after the completion of the primary vaccination course. Thereafter a single booster dose should be administered to cats once every 3 years.

For concurrent vaccination with Zoetis' Versifel CVR, a single dose of Versifel FeLV should be administered as described above. A single dose of Zoetis' Versifel CVR should then be administered at a separate site via the subcutaneous route.

For simultaneous vaccination with Zoetis' Versifel CVR, the contents of a single vial of Zoetis' Versifel CVR should be reconstituted with the contents of a single vial of Versifel FeLV in place of the diluent. Once mixed, the contents of the vial should appear as a slightly coloured (pink/orange) opaque suspension. The mixed vaccines should be injected immediately via the subcutaneous route.

Field Trials

The applicant has conducted field studies on the efficacy of Versifel FeLV involving 182 vaccinated animals and 67 control animals.

Cats of different breeds, genders and ages were vaccinated with Versifel FeLV according to the vaccination scheme. All animals were regularly bled during the study to determine antibodies to FeLV. The animals were also tested for FeLV p27 antigenaemia. The results confirm the observations made in the laboratory studies. The vaccine Versifel FeLV proved to be efficacious (to enhance antibody response) in the target species cat.

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.