SCIENTIFIC DISCUSSION

I. SUMMARY OF THE DOSSIER.

Leucogen, already sold for many years worldwide, and in several countries of the European Union, is a highly purified vaccine against feline leukaemia produced by genetic engineering. The CVMP confirmed that Leucogen is eligible for the centralised procedure under Article 3.1 and the Annex to Regulation (EC) No 726/2004 because it contains a valence against feline leukemia virus developed by means of recombinant DNA technology. The Applicant Virbac S.A. gave a commitment at the time of submission to withdraw the national marketing authorisations for Leucogen (obtained via the ex-concertation procedure) once the Community marketing authorisation was granted.

In terms of the Leucogen vaccine, sequence of the envelope protein of FeLV was introduced via a plasmid in an appropriate *Escherichia coli*. FeLV envelope p45 protein is initially expressed in large quantities in inclusion bodies. These bodies are extracted and thoroughly purified. The final preparation includes the addition of aluminium hydroxide and highly purified extract of *Quillaja saponaria*. It is presented in vials containing one dose of 1ml as liquid preparation. Since the vaccine itself is highly purified and does not contain retraceable DNA, there are no concerns regarding potential recombination or reassortment.

The claim of the vaccine is: active immunisation of cats from eight weeks of age against feline leukaemia for the prevention of persistent viraemia and clinical signs of the related disease. Onset of immunity is 3 weeks after the primary vaccination and the duration of immunity is one year after the primary vaccination. The vaccine is to be administered subcutaneously according to the following vaccination scheme:

Primary vaccination:
- First injection in kittens from eight weeks of age
- Second injection 3 or 4 weeks later.

Revaccination:
Annual

2. QUALITY ASSESSMENT

Composition

Leucogen is an adjuvanted liquid vaccine for cats against feline leukaemia which is presented as a suspension for injection containing a purified recombinant p45 protein derived from the gp70 surface glycoprotein of the feline leukaemia virus (FeLV) subgroup A, expressed in *Escherichia coli*. Each dose of 1 ml contains at least 102 µg of purified p45 recombinant product. The antigenic suspension is adjuvanted with an aluminium hydroxide gel and a purified extract of saponin (*Quillaja saponaria*).

Container

3-ml-insulin type vials are used. These are made of type I glass which conforms to the current edition of the European Pharmacopoeia. The vials are closed with butyl elastomer stoppers and sealed with perforated aluminium capsules conforming to the current Ph. Eur requirements. Sterilisation of the container components is performed. Stoppers are autoclaved. The method of sterilisation described was satisfactory. Filling and capping were described.

Development Pharmaceutics

The feline leukaemia virus (FeLV) antigen is a naturally occurring pathogenic retrovirus contagious for pet cats. The FeLV genome contains amongst the *gag* and *pol* genes the *env* gene that encodes the envelope protein composed of a glycoprotein of 70,000 dalton (gp 70) and a 15,000 dalton protein (p15E). Gp 70 is essential for binding of the virus to the cellular receptors for FeLV.

Due to the importance of the gp 70 in protection, gp 70-vaccines were developed. These predecessor vaccines were either not associated with the production of virus neutralising antibodies, or did not protect against FeLV challenge. In contrast, promising results were anticipated using a recombinant antigen that derived from the entire gp 70 gene supplemented by an effective adjuvant to increase the immune response, especially against FeLV-subgroup A.. Consequently, a vaccine was developed containing purified recombinant p45 protein that was derived from the gp70 surface glycoprotein of the FeLV subgroup A and is expressed in *Escherichia coli*. The p45 structure is adsorbed on to aluminium hydroxide gel and a highly purified extract of *Quillaja saponaria*, both acting as adjuvant. They allow for a correct presentation of the p45 in space and improve the immunological response.

The process implementation was described.

Clinical trial formulations

The composition of batches used in the clinical trials was described and Virbac S.A. confirmed that they were produced according to the described outline of production.

METHOD OF MANUFACTURE

The manufacturing process with regard to production steps and the manufacturing process for the p45 envelope antigen were described.

Flow charts of the production steps were provided, detailing formulation, the blending and filling of the finished product including bulk preparation, preparation of vials and stoppers, and filling as well as packaging.

A detailed description of these production processes was provided. Preparation and control of the recombinant *E. coli* and of the p45 FeLV envelope antigen including the genetic engineering steps were also described.

A detailed description was provided for the preparation of the vials and stoppers as well as of the filling, crimping, and coding. The method of preparation was clearly described beginning with the decitraconylation process and ending with the final product. Further information on controls and results were presented. Relevant in-process stability data were provided along with information on the storage period and relating stability data.

Validation studies

Information on validation studies were provided concerning critical steps of the process. Information was also provided for the validation of the sterilisation of the vials as well as for the validation of the filling process. The data provided were satisfactory.

CONTROL OF STARTING MATERIALS

Information was provided concerning starting materials listed in a Pharmacopoeia. Satisfactory certificates were provided showing that the specifications are as per current edition of Ph. Eur. monograph.

Starting materials of biological origin not listed in a Pharmacopoeia include recombinant *E. coli* and p45 FeLV Envelope Antigen Active Ingredient as well as starting materials of biological origin that are used for the composition of the media:

Information was provided on description, preparation and control of the Recombinant *E. Coli* seed lot. The following controls are carried out on Master and Working Seed Lots: Cell viability, Auxotrophic markers, Contamination with other microorganisms, Restriction mapping of isolated plasmid, Western blot analysis of induced proteins and DNA sequencing. These controls were described in detail.

The validation of Master and Working Seeds following fermentation was also described. A satisfactory certificate of analysis of the Working Seed Lot was provided.

Genetic engineering

The gene of interest is the DNA which encodes the FeLV envelope antigen. Sourcing and preparation of the genomic DNA were described. The starting *E. Coli* strain used as the host strain for expression of the FeLV envelope recombinant antigen is detailed. Its origin, history, identification and characteristics as well as relevant tests and results of the master and seed lots were described.

The preparation of the production strain includes the following steps: cloning DNA which encodes FeLV envelope antigen, construction of the expression vector, cloning for expression, modification for selection and introduction into the starting strain.

A flow chart was provided detailing each step.

Genetic stability

Data on stability are available with regard to constructional stability, segregational stability, stability up to and beyond the maximum passage level encompassing plasmid stability and stability of auxotrophic mutations.

P45 FELV ENVELOPE ANTIGEN ACTIVE INGREDIENT (PRODUCTION AND CONTROL)

Details were provided on description and control of the p45 FeLV envelope antigen as well as process, including description of *in-process* controls and the relevant validations plus certificates of analysis. Detailed information was provided with regard to the analytical reagents used. Relevant certificates of analysis were included. The tests performed were also explained in detail.

Process with description of in-process controls and description of validation (Description and control of the p45 FeLV envelope antigen)

Description of the production process

In this section, flow charts were presented which relate to the different production steps of amplification respectively culturing of the active ingredient, purification and preparation of the purified p45 envelope antigen.

The stability data on batches at T0 and after 48 months of storage indicated that there is no change in the specification of the product. Therefore, the claimed period of storage was fully justified.

Result of relevant validation studies

Batch-to-batch-consistency

Data showing the yields from each key stage of the production process for batches of purified antigen was presented.

Control test during production

The tests conducted during the production process of the p45 FeLV envelope antigen are detailed. Norms are mentioned whenever applicable.

A high level of batch reproducibility underlining the batch to batch consistency of the process was demonstrated. The production and control of the p45 active ingredient was described in detail. Relevant validation data were included and consistency of the p45 envelope antigen was demonstrated.

Starting material included in the composition of the media

A comprehensive list of the starting materials was provided which specifies the internal codification of each product. Each starting material was described and specification sheets were supplied. Certificates of analysis and supplier's documentation were provided.

The starting materials of non-biological origin were listed. Suppliers' documentation was provided. Information on function, methods of identification, purity, storage conditions and storage life were all provided, as well as controls and tests carried out.

SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

Assessment of starting materials has been conducted in compliance with Commission Directive 1999/104/EC and in accordance with Guideline EMEA/CVMP/410/01 Rev. 2 OCT 2003 (2004/C 24/03): "Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products", Eur. Ph. monograph 01/2005:1483: "Products with risk of transmitting agents of animal spongiform encephalopathy " and related chapter 01/2005:50208 and Position paper EMEA/CVMP/019/01: "Assessment of the risk of transmission of animal spongiform encephalopathy agents by master seed materials used in the production of veterinary vaccines".

For the starting materials of animal origin or including an animal origin component it was shown that they comply with the current guidelines and regulatory texts related to the TSE Guideline EMEA/CVMP/410/01 Rev. 2.

CONTROL TESTS DURING PRODUCTION

Control tests relating to the manufacturing of the active ingredient and other manufacturing steps were described. Each test was shortly described and a limit of acceptance provided, if applicable. If relevant, the corresponding SOP was mentioned. Batch to batch consistency related to these steps could be observed. Results of a number of consecutive batches were systematically presented.

CONTROL TESTS ON THE FINISHED PRODUCT

The control tests performed on the finished product were detailed, including the corresponding SOPs: Physico-chemical character: aspect, pH, volume, sterility, bacterial and fungal sterility controls, adjuvant, dosage of Alhydrogel, control of the identity and purity of the vaccine, titration, potency, endotoxins and safety.

Timing and frequency of each testing were indicated. The tests were described and details of related SOPs and associated validations were presented.

STABILITY

Stability of the bulk antigen

Stability data regarding the respective manufacturing steps were provided. Stability data on the FeLV p45 antigen for up to 48 months were also included.

Stability of the finished product

The stability of the finished product was documented demonstrating stability of four industrial batches of Leucogen stored for 27 months at + 4°C. The following tests were performed: Physico-chemical parameters (aspect, volume, pH), identity/purity, sterility, protein titration, potency, and safety.

The relevant SOPs were mentioned. Brief test descriptions were provided including limits of acceptance. Based on the data provided, a shelf life of 24 months was fully justified.

DATA RELATED TO THE ENVIRONMENTAL RISK ASSESSMENT FOR PRODUCTS CONTAINING OR CONSISTING OF GENETICALLY MODIFIED ORGANISMS

As this vaccine does not contain a GMO capable of replicating in the environment but a properly defined not viable recombinant protein, this part is not applicable for the evaluation of the product in question.

OVERALL CONCLUSION ON QUALITY

Leucogen is a genetically engineered vaccine containing as active ingredient the highly purified protein p45 envelope antigen which is expressed by an appropriate *E. coli*. Efficient adjuvants are added (aluminium hydroxide gel and purified extract of *Quillaja saponaria*). All relevant directives, guidelines and monographs as well as related EMEA position papers and VICH guidelines were taken into account.

The description of the plasmid construction and its insertion into the *E. coli* host strain was comprehensible. Identity, purity and stability were well documented. Results of *in-process* controls demonstrate consistency of the production process and the final product testing results indicated consistency. The methods used for final batch testing are properly validated.

All starting materials used are well documented and tested before their use. Any potential TSE risk is considered to be nil. The stability of the product is demonstrated for several production steps and for the final product. A shelf life of 24 months is fully justified. The production of a consistent vaccine of high quality is ensured under the conditions documented.

3. SAFETY ASSESSMENT

Introduction

The vaccine is a liquid adjuvanted vaccine, containing the purified recombinant p45 protein derived from the gp70 surface glycoprotein of the FeLV subgroup A, expressed in *Escherichia coli*. One dose of Leucogen contains not less than 102 µg of purified p45 recombinant protein. The monovalent vaccine is intended for the immunisation of kittens against Feline Leukaemia. The regimen of vaccination recommends two subcutaneous injections of one dose at a three-week interval in kittens from eight weeks of age corresponding to the basic vaccination scheme. An annual booster immunisation with one dose of the vaccine is recommended (re-vaccination scheme).

GENERAL REQUIREMENTS

As regards the target species, the vaccine is intended for cats only. Therefore, the safety tests have been carried out in the feline species. The laboratory trials were conducted using Specific Pathogen Free (SPF) cats. Leucogen is aimed for kittens from eight weeks of age. For animal welfare reasons the animals used in the laboratory studies were not vaccinated at the minimum recommended age but slightly older. Nevertheless, the minimum age of 8 weeks recommended for this vaccination was supported by data from the field safety study, in which kittens were exactly 56 to 63 days old. An overdose study provided results on cats at the minimum recommended age for the primary vaccination, as mentioned in the SPC ("from eight weeks of age"). It was concluded that the data presented were sufficient to claim a minimum age for primary vaccination "from eight weeks of age".

Vaccine administration is recommended via the subcutaneous route. Therefore, this route of administration was used in all of the laboratory and field safety studies. One dose is given twice at a three-week interval to kittens from eight weeks of age (basic vaccination scheme). An annual booster immunisation using one dose recommended (revaccination scheme). The vaccinations performed during the laboratory and field studies thus followed this vaccination scheme.

All the doses of Leucogen used for the safety studies originated from batches produced in accordance with the manufacturing process described by the manufacturer in the dossier (Analytical tests) of application for marketing authorisation. The batch protocols or certificates of analysis for all the products used in these safety studies were provided in the final report of each trial.

The batches used were detailed. Each dose of the vaccine used in the laboratory and field studies contained not less than 102 µg of purified p45 recombinant protein. The laboratory tests were carried out in compliance with the principles of Good Laboratory Practices and the European Pharmacopoeia Monographs. The field study was carried out in compliance with the principles of Good Clinical Practices.

LABORATORY TESTS

In compliance with the Note for Guidance CVMP/IWP/52/97, the safety studies performed with Leucogen associated with the Feligen CRP vaccine (i.e. Leucofeligen FeLV/RCP vaccine) are sufficient to demonstrate the safety of the Leucogen vaccine alone.

Safety of the administration of one dose and the repeated administration of one dose

A detailed description of the study was provided, where cats received one dose of Leucofeligen FeLV/RCP (i.e. one dose of Feligen CRP reconstituted with one dose of Leucogen) subcutaneously Two additional single dose administrations of this vaccine were performed at a three-week interval.

Details were provided on the vaccines used and the relevant batch protocols were presented. For each cat, daily general and local clinical examinations were carried out for 14 days after the last administration, or until reaction(s) had disappeared. The rectal temperature was measured the day before the first injection, 4 hours after each injection and during each clinical examination. The cats were weighed once a week. Blood sampling was performed prior to vaccination to confirm that cats were seronegative towards the four vaccine valences.

The serological analyses confirmed that all the kittens were free from antibodies against Feline Calicivirus, Feline Rhinotracheitis virus, Feline Panleucopenia virus and Feline Leukemia virus before the first vaccination.

After the first vaccine administration, all cats remained in perfect health and showed a regular bodyweight increase during the follow-up. No general reaction or significant variation of the rectal temperature was observed.

This study demonstrates the safety of the administration of one dose as well as of the repeated administration of one dose of Leucofeligen RCP/FeLV as required by the current Ph. Eur. Monographs 0062 and 50206. At the injection site, a moderate oedema occurred in some cases, followed by a swelling which could turn into a nodule. All these reactions were $\leq$2cm and disappeared within 3 to 4 weeks at the latest.
Local reactions observed after the second and third injections were weaker than those seen after the first vaccination.

Safety of the administration of an overdose.

Cats received by the subcutaneous route one injection of an overdose of the vaccine corresponding to ten doses of the Feligen CRP fraction reconstituted with two doses of Leucogen and two doses of diluent.

For each kitten, general and local clinical examinations were carried out daily during 14 days after the vaccination, or until reaction(s) had disappeared. The rectal temperature was measured the day before the injection, 4 hours after the injection and during each clinical examination. The cats were weighed once a week until the end of the follow-up (from D0 to D14, or until disappearance of the local signs). Blood sampling was performed prior to vaccination to check the serological status of the cats towards the four vaccine valences.

The serological analyses confirmed that all the kittens were free from antibodies against Feline Calicivirus, Feline Rhinotracheitis virus, Feline Panleucopenia virus, and Feline Leukemia virus before the first vaccination.

This overdose administration did not induce systemic reactions except for transient hyperthermia for two days at the most. No local reactions other than those observed after injection of a single dose were noticed but they lasted longer (five to six weeks at the most). This study thus demonstrates the safety of an overdose administration of Leucofeligen FeLV/RCP (i.e. ten doses of Feligen CRP reconstituted with two doses of Leucogen and two doses of diluent).

Examination of reproductive performance

As Leucogen is not intended for use in pregnant animals, no study on reproductive performance was conducted. Corresponding information is provided in the relevant point of the SPC and package insert.

Examination of immunological functions

The vaccine contains a purified p45 recombinant protein which is derived from the gp70 surface glycoprotein of the FeLV. As the Feline Leukaemia wild virus is known to induce

immunosuppression, the effect of the recombinant protein of the vaccine has been assessed. It was shown that the peptide responsible for this is not contained in Leucogen.

Special requirements for live vaccines

Not applicable.

Study of residues

As the vaccine is an immunological product and is not intended for immunisation of food producing animals, no investigation regarding the residues was undertaken.

Interactions

The use of immunosuppressive drugs (e.g. corticosteroids) close to vaccination with Leucogen® should be avoided since it may interfere with the induction of immunity.

No information is available on the safety of the association of this vaccine with any other except for the Feligen CRP vaccine. Two studies presented showed that the association of the Leucogen with the Feligen CRP vaccine is safe. Other studies were undertaken for the assessment of the efficacy of this association. They are presented in the dossier. Moreover, an application for marketing authorisation is has been submitted by VIRBAC Laboratories and processed for this association under the name of Leucofeligen FeLV/RCP.

FIELD STUDIES

A field safety study of Feligen CRP / Leucogen vaccine in 8/9 week old kittens was presented. Each cat was administered subcutaneously:
-One dose of Leucofeligen FeLV/RCP vaccine (i.e. one dose of Feligen CRP reconstituted with one dose of Leucogen at 8 to 9 weeks of age, first vaccination on D0),
-One dose of Leucofeligen FeLV/RCP vaccine, at 11 to 12 weeks of age, on a different injection site (second vaccination, on D21).

Two cats out of sixty were excluded during the second vaccine period. Sixty cats were thus followed after the first injection, and fifty-eight after the second.

Each animal was followed for 35 days. During each vaccine period (first vaccine period from D0 to D21 and second vaccine period from D21 to D35), four or eight veterinary examinations were performed by the investigator, including rectal temperature and body weight measurements. Between each visit, owners carried out a daily clinical observation. The cats were thus examined or observed daily for signs of abnormal local and systemic reactions for each vaccine period. Blood was collected on the day of the first injection to determine the serological status of the kittens prior to vaccination.

Before vaccination (on D0), all kittens were seronegative to FeLV. 19, 48 and 22 % of them were seropositive to Feline Rhinotracheitis virus, Calicivirus and Feline Panleucopenia virus respectively.

This study demonstrates the safety of the vaccination with Leucofeligen FeLV/RCP, and thus of Leucogen, under field conditions, because:
(1) the cats remained in good health after each injection;
(2) only slight and transient systemic reactions, commonly reported with the parenteral vaccination, were observed (mainly weakness and diarrhoea);
(3) no abnormal local reaction was observed at the injection site compared to the results of laboratory studies (transient and moderate oedema, swelling and/or nodule). The pain at palpation noted in field animals did not occur in the laboratory animals.

Since the cats were aged from eight weeks on the day of the first injection, this data also supported the minimum age recommended for this vaccination.

As the observed local and systemic reactions are described in the SPC, the study was acceptable. Sneezing and conjunctivitis presumably caused by the attenuated viral components are to be mentioned in the SPC of the combined product.

Pharmacovigilance data

Marketing authorisations for Leucogen have been granted in several Member States of the European Community since 1988. A pharmacovigilance survey has then been conducted in these European countries for many years. Additional information relating to the potential risk of the use of this vaccine under practical conditions has been summarised in a Periodic Safety Update Report.

Reports of suspected adverse drug reactions (SADRs) relating to its use were divided into different categories of post-vaccinal complications: local reaction at injection site, systemic reaction and immunologic reaction.

As a final conclusion, most of the reactions reported were considered as possibly associated with the use of Leucogen. Nevertheless, the incidence was extremely low.

Environmental Risk Assessment

A phase I environmental risk assessment was provided. The active ingredient is represented by the recombinant p45 FeLV protein expressed by *E. coli*. After intensive purification steps, only the antigenic fraction is included in the vaccine. Together with aluminium hydroxide (from mineral origin) and the purified saponin extract, the vaccine does not represent a risk for the environment. The recombinant p45 protein is considered to be an inert product. Consequently, the risks for the environment are nil, a phase II assessment and the thereof resulting impact assessment were not applicable.

OVERALL CONCLUSION ON SAFETY

All investigations show that the combined product Leucofeligen FeLV/RCP is well tolerated in cats. Clinical observations relevant for the safe use of the product are included in the package literature. Since no safety study has been performed using the monovalent vaccine only, identical SPC points for both Leucogen and Leucofeligen FeLV/RCP are generated.

After the first injection, a moderate and transient local reaction ($\leq$2 cm) could occur (oedema, swelling, nodule). This reaction resolves spontaneously within 3 to 4 weeks at the most. After the second injection, and subsequent administrations, this reaction is markedly reduced. In rare cases, pain at palpation, sneezing or conjunctivitis may be noted, that resolves without any treatment. The transient usual signs following vaccination may also be observed: fever (lasted 1-4 days), apathy, digestive disturbances.

In case of anaphylactic shock, appropriate symptomatic treatment should be administered.
An overdose administration of Leucofeligen FeLV/RCP showed no other reaction except local reactions that can last longer (5/6 weeks at the most).

As Leucogen is not intended for use in pregnant animals, no study on reproductive performance has been conducted. A specific contra-indication to that effect is included in the SPC. The studies carried out demonstrate the safety of this vaccine used at the requested minimum age of 8 weeks.

4. EFFICACY ASSESSMENT

The vaccine Leucogen is a liquid adjuvanted vaccine, containing the purified recombinant p45 protein derived from the gp70 surface glycoprotein of the FeLV subgroup A, expressed in *Escherichia coli*. One dose of Leucogen contains not less than 102 µg of purified p45 recombinant protein. The monovalent vaccine is intended for the immunisation of kittens against Feline Leukaemia.

The regimen of vaccination recommends two subcutaneous injections of one dose at a three to four week interval in kittens from eight weeks of age corresponding to the basic vaccination scheme. An annual booster immunisation with one dose of the vaccine is recommended (re-vaccination scheme). Leucogen is intended for the use in cats only. Therefore, the efficacy tests have been carried out in the feline species. The laboratory trials were conducted using Specific Pathogen Free (SPF) cats. Leucogen is intended for kittens from eight weeks of age via the subcutaneous route.
For animal welfare purposes, the kittens designated for the laboratory studies could not be sent by the breeder to Virbac at a too young age (i.e. before seven week of age). For this reason, and in order to respect a correct acclimatisation period, the animals used in most of the laboratory studies were not vaccinated at the youngest recommended age but slightly older. Nevertheless, the minimal age of 8 weeks recommended for this vaccination is supported by data from the field efficacy study, in which kittens were exactly 56 to 63 days old.

The vaccine was administered subcutaneously in all the laboratory and field efficacy studies. The vaccinations performed during the laboratory and field studies follow the recommended vaccination scheme. As maternally derived antibodies (MDA) may be observed at the minimum recommended age for the first injection, the possible interference between vaccination and these MDA has been assessed through field studies.

The onset and duration of immunity for Leucogen were demonstrated by virulent FeLV challenges after the primary vaccination. Efficacy has also been demonstrated in the combination with Feligen RCP for Leucofeligen FeLV/RCP.

LABORATORY TRIALS

The batches used were summarised.

Onset of protection

The onset of immunity was demonstrated after a virulent FeLV challenge three weeks after the basic vaccination scheme. The study was conducted in accordance with Ph. Eur. Monograph 1321.

Validation of the standard of the Leucogen activity test by a challenge infection in cats

In this study, 15 cats, 8-9 weeks old and seronegative, were administered subcutaneously two injections of Leucogen vaccine at a 3-week-interval. 10 cats, 8-9 weeks old and seronegative, served as control. The veterinary clinical examination, including the record of rectal temperature and body weight, was performed weekly throughout the vaccinal period (D0 to D42). Blood samples were taken at D0 (first vaccination) and at D42 (challenge day) in order to assess the serological status of the cats (ELISA). Three weeks after the second vaccination, all cats were challenged via the intraperitoneal route with a virulent FeLV strain. The veterinary clinical examination, including recording of rectal temperature and body weight, was performed weekly throughout the challenge period (15 weeks). Starting at the second week after challenge, the cats were weekly (until week 15) monitored for p27 antigenemia and p45 seroconversion.

Results:
During the vaccinal phase, the animals displayed a normal weight gain. All vaccinated cats displayed a seroconversion against FeLV three weeks after the second injection. High levels of antibodies were

seen at D42 except for one cat. The control group remained seronegative until D42. A transient enlargement of the lymph nodes (popliteal, prescapular, mandibular, mesenteric) was recorded in all control cats and in 6 vaccinated cats after the challenge. In both vaccinated and control groups, the cats were always in good health. Only liquid faeces were noted regularly in the pen of the controls and from time to time in the pen of the vaccinated. In the control group, 8/11 cats were persistently infected (infection = 73 %). In the vaccinated group, one cat became persistently infected, i.e. 14/15 cats showed no persistent infection (protection = 93 %).

Although efficacy of the Leucogen vaccine is demonstrated, it was not strictly in compliance with the requirements of Ph. Eur. Monograph 1321 because the infection rate of the control group is only 73 % instead of 80 %.

In order to assess the efficacy of the Leucogen vaccine, Virbac S.A. consulted the preventable fraction which is 75 % in the European Pharmacopoeia and 90 % in this study. The preventable fraction obtained for the vaccinates is superior to the preventable fraction required by Monograph 1321. Therefore, it is concluded that the virulence of the challenge is slightly below the monograph requirement. However, the preventable fraction allows this deviation and shows that the vaccine efficacy remains in conformity with the monograph.

Interactions: Efficacy of the association of Leucogen with Feligen CRP vaccine

The efficacy of Leucogen in the presence of Feligen CRP has been demonstrated by challenge.

Study on the association of the Feligen CRP and Leucogen vaccines

The kittens were monitored for the presence of FeLV p27 antigen and antibodies against the p45 vaccine protein before vaccination and three weeks after the second vaccine injection, using specific ELISA tests. A veterinary clinical examination, including the body weight, was performed once weekly throughout the vaccination period (D1 to D42). The serological examination for FCV, FVR and FPV was undertaken on D0, 21, 36 and 42.

Three weeks after the second vaccination, all cats were challenged via the oronasal route with a virulent FeLV strain. On the challenge day, all the cats were of the same age since the controls were 13/15 weeks old (94 to 109 days) and the vaccinates were 14/15 weeks old (99 to 104 days). A table containing the birth dates of the cats is presented. Weekly clinical and antigenaemia (dosage of p27 blood circulating protein) follow-ups were performed for fifteen weeks. The cats were weighed once a week. The observation period thus complies with requirements of the Eur. Ph. Monograph 1321.

No abnormal local or general reaction attributable to the vaccine was recorded after Leucogen administration. All cats were free from antibodies against p45 protein and p27 antigen before vaccination (D0) and were still negative for p27 antigen on the challenge day (D42). Three weeks after the second injection, all cats vaccinated with Leucogen had seroconverted to FeLV p45 protein.

These results demonstrate the efficacy of the FeLV component of Leucofeligen FeLV/RCP according to Ph. Eur. Monograph 1321, since 80 % of the control cats were infected whereas more than 80 % of the vaccinates were protected. This study shows that Leucofeligen FeLV/RCP vaccine allows preventing the persistent viraemia associated with a feline Leukaemia infection.

Although the Ph. Eur. monograph requires cats to be free from antibodies against the antigens of feline leukaemia virus and against feline oncogene membrane antigen (FOCMA), no analysis was performed to detect anti-FOCMA antibodies before the vaccination. Indeed, even if the protective role of antibodies to FOCMA in the development of FeLV related neoplastic disease is well-documented, their role in the protection against persistent viraemia remains unclear. There is no correlation between the presence of such antibodies and the protection: cats that presented anti-FOCMA antibodies could become persistently infected and cats that did not become persistently infected would not necessarily

present antibodies to FOCMA (Harbour D.A et al, 2002). Consequently; this test does not reflect the sensitivity of the cats to a FeLV challenge.

The efficacy of Feligen CRP in the presence of Leucogen has been demonstrated by serological follow-ups several weeks after combined or separate administration of both vaccines. The serological data of two efficacy studies undertaken to demonstrate protection against FCV (F-912.030000-58032) and FVR (F-912.030000-58028) challenges were used for a statistical analysis (F-134.160000-58009) to demonstrate any potential impact on the development of the immunoresponse.

Efficacy study of Feligen CRP vaccine associated or not with Leucogen: Calici valence activity according to monograph 1102

Thirty 9-10-week-old (63-68 days) SPF kittens (seronegative concerning FCV, FVR, FPV and FeLV) were used in this study: ten non-vaccinated control cats, ten cats vaccinated with Leucofeligen FeLV/RCP (i.e. one dose of Feligen CRP reconstituted with one dose of Leucogen) and ten cats vaccinated with Feligen CRP. Each vaccinated cat received two doses of the respective vaccine at a three-week interval (on D0 and D21) by the subcutaneous route.

Four weeks after the last vaccination, all cats were challenged intranasally with a heterologous virulent Feline Calicivirus, and were observed daily for 21 days.

During the vaccinal phase, daily clinical observation was performed, clinical examination and weighing were undertaken once a week and blood samples were taken on D0, 21, 35 and 49 for serological examination.

During the challenge period (T0 to T21) daily clinical examinations were performed. Animals were weighed once a week. Clinical signs of Feline Calicivirosis (hyperthermia, nasal and buccal ulcerations, nasal and ocular discharge) were assessed using a scoring system according to Monograph 1102. Blood samples were collected on T7, 14 and 21 for serological examination. Nasal washings were carried out daily from T2 to T21 for evaluation of virus excretion (isolation of Calicivirus on permissive cells).

Results:
During the vaccination phase, all animals remained in excellent health and no abnormal clinical sign was noted. At the beginning of the study (D0), all cats were free from antibodies against FCV, FVR, FPV and FeLV and the controls remained seronegative during the vaccination period. All cats vaccinated with Feligen CRP or Leucofeligen FeLV/RCP presented a good seroconversion against Calicivirus and Panleucopenia virus after vaccination. During this period, the seroconversion to Rhinotracheitis virus was registered in six out of ten cats vaccinated with Feligen CRP and in the ten cats vaccinated with Leucofeligen FeLV/RCP.

After inoculation of the heterologous Calicivirus challenge strain, the vaccinated cats showed a rapid boost of their serological response whereas this seroneutralising response remained very low for the controls. The clinical examinations showed that vaccinated cats presented only a superficial Calicivirus infection (ulcers) and were protected against a systemic affection (hyperthermia, weight loss).

The data recorded for clinical signs and viral excration were transposed into the scoring system of Ph. Eur. Monograph 1102. The scores obtained for the cats vaccinated with Feligen CRP or Leucofeligen FeLV/RCP were significantly lower than those for the controls, demonstrating that Leucofeligen FeLV/RCP reduces clinical signs of Calicivirosis induced by a virulent heterologous experimental challenge performed four weeks after the primry vaccination..

This challenge test also demonstrates that the cats vaccinated with the F9 Calicivirus vaccine strain of Feligen CRP and Leucofeligen FeLV/RCP were protected to an exposure against the virulent heterologous Calicivirus strain FPV-255.

One point has to be discussed regarding Ph. Eur. Monograph 1102:

- Kittens were not at the youngest recommended age for the first vaccination due to the date of their arrival at the Virbac animal unit, which does not interfere with the validity of the test.

Efficacy study of Feligen CRP vaccine associated or not with Leucogen: FVR valence activity according to monograph 1206,

Thirty 9-10-week-old (63-67 days) SPF kittens (seronegative concerning FCV, FVR, FPV and FeLV) were used in this study: ten cats vaccinated with Feligen CRP, ten cats vaccinated with Leucofeligen FeLV/RCP (i.e. one dose of Feligen CRP reconstituted with one dose of Leucogen) and ten non-vaccinated control cats. Each vaccinated cat received two doses of the respective vaccine at a three-week interval by the subcutaneous route.

Four weeks after the last vaccination, all cats were challenged intranasally with a virulent Feline Rhinotracheitis virus strain and were observed daily for 21 days.

During the vaccinal phase, daily clinical observation was performed, clinical examination and weighing were undertaken once a week and blood samples were taken on D0, 7, 10, 14, 35 and 49 for serological examination.

During the challenge period (T0 to T21) daily clinical examinations were performed. Animals were weighed once a week. Clinical signs of Feline Rhinotracheitis (hyperthermia, glossitis, nasal and ocular discharge, cough, sneezing and conjunctivits) were assessed using a scoring system according to monograph 1206. Blood samples were collected on T7, 14 and 21 for serological examination. Nasal washings were carried out daily from T2 to T21 for evaluation of virus excretion (isolation of FVR on permissive cells).

During the vaccination phase, all animals remained in excellent health and no abnormal clinical sign was noted. At the beginning of the study (D0), all cats were free from antibodies against FCV, FVR and FPV. All controls remained seronegative during the vaccination period, whereas a seroconversion to these three valences was observed in both vaccinated groups (Feligen CRP or Leucofeligen FeLV/RCP). The obtained serological responses were lower than those usually induced by Feligen CRP alone or combined with Leucogen. The reason for this unusual response could be the depressed state of the kittens due to handling and repeated blood samplings in very young animals during the vaccination period.

After the inoculation of the challenge strain, the vaccinated cats showed a rapid boost of their serological response which remained on a high level until the end of the study whereas this seroneutralising response was delayed for the controls. In the three groups, some or all the clinical signs of Feline Rhinotracheitis were observed (hyperthermia, nasal and ocular discharges, sneezing, cough, conjunctivitis, glossitis); but the vaccinates presented fewer signs and for less time than the controls.

During the first week following challenge, the control group exhibited a longer and higher excretion of the FVR and a more significant loss of weight (≥ 5 %) compared to the cats vaccinated with Feligen CRP or Leucofeligen FeLV/RCP.

As required by Ph. Eur. Monograph 1206, the data collected during the fourteen days following challenge were transposed to a scoring system. The scores obtained for the cats vaccinated with Feligen CRP or Leucofeligen FeLV/RCP were significantly lower than those for the controls, demonstrating the efficacy of Rhinotracheitis component contained in both vaccines.

This study shows that Leucofeligen FeLV/RCP reduces clinical signs of Feline Rhinotracheitis and viral excretion induced by a virulent experimental challenge performed four weeks after the primo-vaccination.

Due to the arrival date of the animals at the Virbac facilities, the cats could not be vaccinated at the youngest recommended age, as specified in Ph. Eur. Monograph 1206. This deviation from the monograph does not affect the test validity.

Comparison of the serological responses toward the Feligen CRP vaccine associated or not with the Leucogen vaccine.

In this statistical study, the results of the serological follow-ups performed during two efficacy studies conducted within the framework of the Leucofeligen FeLV/RCP vaccine dossier were used. This data allowed to compare the immune responses to FCV, FVR and FPV antibody titres obtained in the cats vaccinated with Feligen CRP alone to those in the cats vaccinated with Feligen CRP combined with Leucogen. The time course of the mean antibody titres against each valence observed in both studies is as follows:

The statistical comparison of the area under the curves for each study showed that:

- the seroneutralising antibodies against feline Rhinotracheitis virus detected after the vaccination in both studies were significantly higher when Feligen CRP was combined with Leucogen (i.e. in Leucofeligen FeLV/RCP) than when it was used alone.
- the level of total IgG against Calicivirus was significantly higher in cats vaccinated with Leucofeligen FeLV/RCP compared to cats vaccinated with Feligen CRP in one study, whereas these titres were not statistically different in the other study.
- no significant difference was found on the titres of seroneutralising antibodies against Calicivirus in both studies.
- the seroneutralising antibodies to feline Panleucopenia virus titres were significantly higher in the group of cats vaccinated with Leucofeligen FeLV/RCP compared to the group of cats vaccinated with Feligen CRP alone in one study were similar in another study. This could be due to the fact that most of the titres reached a plateau corresponding to the maximum threshold of the technique, thus impeding to see any difference between both groups.

These results demonstrate that, when Feligen CRP is combined with Leucogen (i.e. in Leucofeligen FeLV/RCP), the humoral immunological response to FCV, FVR and FPV is similar to or higher than when Feligen CRP is administered alone. This boost of the serological response is probably due to the presence of the adjuvant in the Leucogen fraction of Leucofeligen FeLV/RCP vaccine which allows increasing the immune response.
These data confirm that the results of challenge studies obtained with Feligen CRP are relevant to assess the efficacy of FCV, FVR and FPV of Leucofeligen FeLV/RCP vaccine.

The onset of immunity of the feline Panleucopenia virus component was therefore shown in two studies according to Ph. Eur. Monograph 0251 (virulent challenge 20 to 22 days after the last vaccination). These studies used Feligen CRP vaccine alone and are thus valid to demonstrate the efficacy of the same component of Feligen CRP combined to Leucogen.

The Influence of Maternal Antibody on the Efficacy of the Vaccine

As maternally derived antibodies (MDA) may be observed at the minimum recommended age for the first injection, the possible interference between vaccination and these MDA has been assessed through field studies. In addition, a laboratory study using the combined product has also been performed to address this specific issue. This issue has been considered in the assessment of the Leucofeligen RCP application since the impact of MDA is of minor relevance as regards the FeLV component.

Duration of Immunity

The duration of immunity for Leucogen is supported by a virulent challenge performed one year after the basic vaccination with the monovalent product or in combination with Feligen CRP.

Efficacy study of Leucogen associated or not to Feligen CRP after a one year immunity

Forty-nine cats, 8 to 9 weeks old, seronegative against FCV, FVR, FPV and FeLV were involved in this study. Eighteen cats received two injections of Leucogen, eighteen cats received two injections of Leucofeligen FeLV/RCP (i.e. one dose of Feligen CRP reconstituted with one dose of Leucogen) and thirteen cats received two injections of Feligen CRP. The vaccines were administered by the subcutaneous route; the interval between the two injections was 24 days (between 3 and 4 weeks).

The animals were observed for one year (clinical examinations and serology).
Serological analyses were performed to follow the serological response towards FCV, FVR, FPV and FeLV for one year after the basic vaccination scheme.

One year after the last injection of the primary vaccination, all the remaining cats were challenged intraperitoneally with a FeLV virulent strain and the antigenaemia (dosage of p27 blood circulating protein) was followed for fifteen weeks. During this challenge period, one cat had to be sacrificed because of an acute urethral blockage independent of the challenge, and was thus not considered for the analysis. As described in Ph. Eur. Monograph 1321, a cat was considered as persistently infected when it showed a positive antigenaemia during three consecutive weeks or on five occasions, consecutively or not, between the third and the fifteenth week.

No abnormal reaction was observed after the vaccination. Three vaccinated cats died during the vaccination period for reasons unrelated to the vaccinations. The cats vaccinated with Leucofeligen FeLV/RCP seroconverted to Calicivirus, Rhinotracheitis virus and Panleucopenia virus valences, except for one kitten that remained seronegative against Calicivirus.
A good serological response to the Leukaemia component was obtained in the groups of cats vaccinated with Leucogen and Leucofeligen FeLV/RCP. As the level of antibodies decreased in most cats, a challenge was performed at the end of the duration of immunity period.

In the vaccinated groups, a persistent infection was detected in three out of sixteen cats vaccinated with Leucofeligen FeLV/RCP (protection = 81 %) and in two out of seventeen cats vaccinated with Leucogen.
The antigenaemia follow-up showed a persistent infection in eleven out of thirteen control cats (infection = 85 %) indicating the validity of the test.

These results demonstrate the efficacy of the Leucogen component of Leucofeligen FeLV/RCP vaccine in compliance with the requirements of Ph. Eur. Monograph 1321 since 80 % of the control cats were infected whereas more than 80 % of the vaccinates were protected. Therefore, this study shows that Leucofeligen FeLV/RCP vaccine allows prevention of persistent viraemia associated with Feline Leukaemia infection one year after the basic vaccination scheme.

FIELD TRIALS

Clinical efficacy of the feline vaccine Leucogen administered to 8-9 week old kittens

8-9-week-old kittens (55 to 65 days) were selected from 14 geographically distinct clinical sites. Each cat received by the subcutaneous route two injections of one dose of Leucogen at a three-week interval (primary vaccination) and a third injection of the same vaccine one year later (annual booster injection). All kittens were also vaccinated with Feligen CRP at the same time but at different injection sites.

A clinical examination and blood sampling were carried out at the vaccination times, three and four weeks after the primary vaccination and three weeks after the annual booster. The serum was tested for the presence of anti-p45 antibodies. The body weight was measured on three occasions. The serum was not tested for FCV, FVR and FPV, but the fact that the vaccine had been administered allowed to evaluate the impact of the said antigens on the immune response to the FeLV component of Leucogen.

Results:
No abnormal reaction was observed after the primary vaccination.
Kittens were chosen for analyses after the primary vaccination. Seroconversion against FeLV was seen in 69 % of the cats after the first injection and in 100 % after the second injection. Only one kitten presented maternally derived antibodies to FeLV prior to the vaccination. After vaccination, this cat seroconverted similarly to the others, thus indicating that the presence of maternally derived antibodies did not interact with the serological response to Leucogen.

Cats were also chosen for analyses after the annual vaccination. None of the cats showed local or abnormal general reactions after this last injection. 64 % still showed anti-p45 antibodies before the annual booster injection. Three weeks after the booster injection (W58), all cats showed high level of antibodies against p45.

This study demonstrates that Leucogen vaccine induces high and long-lasting antibody titres to FeLV, which were not affected by Feligen CRP administered at the same time. The strong and rapid enhancement of the serological response to the annual booster vaccination revealed the presence of a memory response one year after the primary vaccination. These results therefore confirm the one-year duration of immunity of Leucogen and of the FeLV component of the Leucofeligen FeLV/RCP.

Clinical efficacy of the Feligen CRP/ Leucogen vaccine administered at 8/9 weeks of age

Cats, 8 to 9 weeks old (56 to 63 days), were selected in France from eleven geographically distinct clinical sites. Each kitten was administered by the subcutaneous route two doses of Leucofeligen FeLV/RCP (i.e. one dose of Feligen CRP reconstituted with one dose of Leucogen) at a three-week interval (at 8/9 and 11/12 weeks of age). Clinical examinations, including weighing and rectal temperature measurement, and serological analysis were carried out on the first and the second vaccination day, and then two, three and four weeks after the second injection. Information on type of breed was also presented.

The efficacy of Leucofeligen FeLV/RCP was evaluated by a seven-week serological follow-up. The sera were tested for antibodies against FCV, FVR, FPV and FeLV and the serological response was assessed by the percentages of seroconversion observed two, three and four weeks after the second vaccination. The results were analysed according to the serological status of the animals on the day of the first injection, i.e. the presence or absence of maternally derived antibodies before the vaccination.

No abnormal general or local reaction was registered after injection of Leucofeligen FeLV/RCP vaccine. Most of the kittens were seronegative to FCV (62 %), FVR (88 %), FPV (64 %) and FeLV (96 %) prior to vaccination. High seroconversion rates were observed in these seronegative cats after the primary vaccination.

Prior to vaccination, 38 % were seropositive for FCV, 12 % for FVR, 36 % for FPV and 4 % for FeLV. These antibodies were probably of maternal origin and could interfere with the vaccination because the seroconversion rates were lower in the seropositive animals than in the seronegative cats after the primary vaccination. The presence of maternally derived antibodies had no effect on the seroconversion to the leukaemia valence, a moderate effect on the seroconversion to FCV, and interfered with the seroconversion to FPV and FVR.

Considering the whole population of the vaccinated cats, the maximum seroconversion rates observed after the primo-vaccination with Leucofeligen FeLV/RCP were 82 % three weeks after the second

injection for FCV, 84 % three and four weeks after the second injection for FVR, 68 % four weeks after the second injection for FPV and 100 % two weeks after the second injection for FeLV.

This study demonstrates that two injections of Leucofeligen FeLV/RCP vaccine induce high seroconversion rates for the four components and that a high level of maternal antibodies can reduce this seroconversion, except for the FeLV valence.

Pharmacovigilance data have been provided as supportive data for efficacy. Data from July 2002 until June 2007 were collected and analysed with regard to efficacy breakdowns in the field. It could be shown that there is a very low incidence of a vaccine breakdown in the field (incidence ranging from 0.00005% to 0.0004%).

OVERALL CONCLUSION ON EFFICACY

In order to demonstrate efficacy of Leucogen several studies have been performed. The monovalent vaccine as well as the combined product Leucofeligen RCP was used.

Onset of immunity:
- FeLV- Challenge

Duration of immunity:
- FeLV-Challenge

Efficacy of the vaccine in the presence of maternally derived antibodies:
-One laboratory study (serology only)
-Serological data of the field study

Field study
Two field studies were conducted to verify the immunisation scheme of Leucogen.

Vaccination with Leucogen on two occasions at intervals of 3-4 weeks in kittens, aged 8 weeks or older, prevents persistent viraemia and clinical signs caused by FeLV infection.

The onset of immunity has been demonstrated by challenge to be three weeks after the primary vaccination for Leukaemia component.

The duration of immunity is one year after the primary vaccination.

The studies were carried out with cats of minimum age and with the minimum dose.

The experimental setup and the results of the studies performed by the Applicant are acceptable.

The issue of maternally derived antibodies has been discussed and a suitable warning inserted into the SPC.

The vaccination is not intended for pregnant cats.

Based on the data presented, the following indication for use of the vaccine is justified:

For active immunisation of cats from eight weeks of age against:

- Feline leukaemia to prevent persistent viraemia and clinical signs of the related disease.

Onset of immunity: 3 weeks after the primary vaccination.

The duration of immunity is one year after the primary vaccination.

The proposed vaccination scheme is as follows:

Primary vaccination :
- First injection in kittens from 8 weeks of age
- Second injection 3 or 4 weeks later.

Revaccination:
Annual

5. BENEFIT-RISK-BALANCE

Leucogen, already sold for many years world-wide, and especially in several countries of the European Union, is a highly purified vaccine against feline leukaemia produced by genetic engineering. Sequence of the envelope protein of FeLV was introduced via a plasmid in an appropriate Escherichia coli. FeLV envelope p45 protein is initially expressed in large quantities in inclusion bodies. These bodies are extracted and thoroughly purified. The final preparation includes the addition of aluminium hydroxide and purified extract of *Quillaja saponaria*. It is presented in vials containing one dose of 1ml as liquid preparation.

The description of the construction of the plasmid and its insertion into the *E. coli* vector is clear and comprehensive. Identity, purity and genetic stability of the seed are well demonstrated. The characteristics and the controls of the purified p45, also tested in accordance with the various pharmacopoeial and guideline requirements, are fully documented as well. Since the vaccine itself is highly purified and does not contain retraceable DNA, there are no concerns regarding potential recombination or reassortment. All other starting materials, including those of biological origin are extensively tested and have been shown to be of suitable quality.

With regard to the risk of transmission of spongiform encephalopathy the quality of starting materials of biological origin is in compliance with the current regulations on managing the TSE transmission risk. The overall TSE risk of the vaccine is therefore practically nullified.

The Leucogen production process is carefully controlled. Appropriate tests are applied throughout the procedure ensuring batch quality and consistency at every stage. Production process related consistency is documented convincingly. A rational update of the batch potency test taking into account the historical experience in the handling of the product is presented with a thorough validation. The data presented indicate a very high level of stability. The shelf-life of 24 months is justified. The products is manufactured and tested within a high level of GMP and Quality Assurance system, which ensures batch to batch consistency.

With regard to the safety and efficacy aspects of the product, the following is summarised. The regimen of vaccination recommends two subcutaneous injections of one dose of Leucogen at a three-week interval in kittens from eight weeks of age (basic vaccination scheme). An annual booster immunisation with one dose is recommended (re-vaccination scheme).

Leucogen was first commercialised in 1988 in France, supported by a national marketing authorisation presenting laboratory and field studies conducted in the 1980s. Since that time, many marketing authorisations have been granted in other European countries. In addition to the present dossier the documentation for Leucofeligen FeLV/RCP was submitted for a marketing authorisation in parallel. The liquid Leucogen vaccine must be reconstituted with the freeze-dried Feligen CRP vaccine. As proposed in the CVMP Note for Guidance “Requirements for combined veterinary vaccines” (CVMP/IWP/52/97), safety tests were carried out with the combined product. Within the scope of laboratory studies, the requirements of both Directive 2001/82/EC as amended by Directive

2004/28/EC and Monograph(s) (1102, 1206, 251) 1321 were fulfilled. All investigations demonstrate that the combined product Leucofeligen FeLV/RCP is well tolerable for cats. Clinical observations relevant for the safe use of the product are included in the package literature. Since no safety study has been performed using the monovalent vaccine only, identical SPC points for both Leucogen and Leucofeligen FeLV/RCP are generated.

Efficacy tests have been carried out in the feline species. The laboratory trials were conducted using Specific Pathogen Free (SPF) cats of minimum age. The vaccine was administered subcutaneously in all the laboratory and field efficacy studies. The vaccinations performed during the laboratory and field studies follow the recommended vaccination scheme. As maternally derived antibodies (MDA) may be observed at the minimum recommended age for the first injection, the possible interference between vaccination and these MDA has been assessed through field studies.

Onset and duration of immunity for Leucogen were demonstrated by virulent FeLV challenges after the primary vaccination. FeLV efficacy has also been demonstrated in combination with Feligen RCP.

In summary, the benefits of Leucogen are its prevention of persistent viraemia and clinical signs of the disease. The most common side effects are a moderate and transient local reaction (≤ 2cm) which can occur after the first injection but which resolves spontaneously within 3 to 4 weeks at the most. After the second injection, and subsequent administrations, this reaction is markedly reduced. In rare cases, pain at palpation, sneezing or conjunctivitis may occur which resolve without any treatment. Transient signs such as hyperthermia, apathy and digestive disturbances may also be observed following vaccination.

The approved indication is: “the active immunisation of cats from eight weeks of age against feline leukaemia for the prevention of persistent viraemia and clinical signs of the related disease”.

The CVMP, on the basis of quality, safety and efficacy data submitted, considers that there is a favourable benefit to risk balance for Leucogen and therefore recommends the granting of the marketing authorisation.

Based on the data presented, the Committee for Medicinal Products for Veterinary Use concluded that quality, safety as well as efficacy of the product were considered to be in accordance with Directive 2001/82/EC as amended.