Rapporteur’s
Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as amended

Favirab

F(ab’)2 fragments of equine antirabies immunoglobulin

RO/W/0002/pdWS/001

Marketing Authorisation Holder:
SanofiPasteur

<table>
<thead>
<tr>
<th>Rapporteur:</th>
<th>Romania</th>
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<tbody>
<tr>
<td>Finalisation procedure (day 120):</td>
<td>30.12.2011</td>
</tr>
<tr>
<td>Date of finalisation of PAR</td>
<td>07.08.2012</td>
</tr>
</tbody>
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# ADMINISTRATIVE INFORMATION

<table>
<thead>
<tr>
<th>Invented name of the medicinal product:</th>
<th>Favirab</th>
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<tbody>
<tr>
<td>INN (or common name) of the active substance(s):</td>
<td>Purified Equine Rabies Immunoglobulin</td>
</tr>
<tr>
<td>MAH:</td>
<td>Sanofi Pasteur</td>
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<tr>
<td>Currently approved Indication(s):</td>
<td>Seroprophylaxis in individuals exposed to rabies virus</td>
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<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>J06BB05</td>
</tr>
<tr>
<td>Pharmaceutical form(s) and strength(s):</td>
<td>200-400UI/ml</td>
</tr>
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</table>
I. EXECUTIVE SUMMARY

This is an assessment of data for Favirab, as part of the Article 46 EU work-sharing procedure. The RO has been appointed as Rapporteur for this product and the initial assessment report (day 70) has been circulated to concerned Member States on 24th April 2011. The MAH’s responses to the Request for Supplementary Information (issued on 27th April 2011), submitted in July 2011, are summarized and assessed in this report.

The studies investigated primarily the safety of this product. Since studies were uncontrolled, efficacy was assessed descriptively only.

The current therapeutic indication for Favirab is the following:
- Seroprophylaxis of rabies in subjects suspected to be exposed to the rabies virus, particularly in the event of severe exposure (e.g., multiple severe bites located on the face, head, neck, hands when the domestic or wild animal responsible either cannot be examined, or is infected or suspected to be infected by the rabies virus or bites to young children).

The Company’s view is that no SmPC and PL changes are necessary as a consequence of the data presented.

However, based on the submitted paediatric data the Rapporteur considers that the amendments proposed in section VI of this report should be implemented in the SmPC and PL.

Thus, SmPC and PL changes are proposed in sections 4.1, 4.2 and 5.1, according with the outcome of this worksharing procedure.

II. RECOMMENDATION

It is the Rapporteur’s opinion that some changes to the SmPC might be advisable. The rapporteur considered that the SmPC/PIL in sections 4.1, 4.2 and 5.1 should be updated with specific wording regarding the use in paediatric population.

In general, based on the review of the submitted paediatric data it is agreed with the MAH that the results of these studies do not change the favorable benefit-risk profile of Favirab in children when used in accordance with the approved product labeling.

However, it is the Rapporteur’s opinion that it may be considers necessary an update of the SmPC and PIL regarding the stratification of paediatric population with respect of age for this product, in order to be in line with the revised SPC guideline (September 2009) and QRD template.

The SmPC and the corresponding section in PIL should be amended including the age group in which the product is indicated, specifying the age limits.

The authorized indication in paediatric population or paediatric subsets should be made clear.

Although the recommended indication of Favirab F(ab')2 fragments of equine antirabies immunoglobulin covers both adults and paediatrics, the age range limits are not explicitly mentioned in paediatric population.

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1 The recommendation from section V can be copied in this section
Thus, an explicit wording in section 4.1, respective 4.2 for paediatric population subsets is considered necessary.

Also, the results of FAV04 study may be considered to be included in section 5.1 of Favirab SmPC, stressing the expected effect of F(ab')2 fragments of equine antirabies immunoglobulin in the recruited population (paediatric population and adults). (see section VIII “Overall conclusion and benefit-risk assessment”).

According to Rapporteur's recommendations the Company has submitted a proposal and it was agreed that following amendments would be implemented in the SmPC/PIL, using a type IB variation.

PROPOSED CHANGES IN SmPC:
“Section 4.1 Therapeutic indications
FAVIRAB is indicated in rabies post-exposure prophylaxis in all paediatric population subsets and adults suspected to have been exposed to the rabies virus, particularly in case of severe exposure (see Section 4.2).

According to the recommendations of the WHO expert consultation on rabies, FAVIRAB must always be used in association with a rabies vaccine. The only exception is for patients already immunised with a rabies vaccine and who are able to produce documentation confirming vaccination with a cell-culture vaccine (i.e. full pre-exposure vaccination within the previous year, subsequent booster injection within the 5 previous years or full post-exposure prophylaxis). These people may receive the vaccine alone.

Administration must always be performed under medical supervision (according to local recommendations) in a rabies centre.”

“Section 4.2:
Treatment must be adapted according to the type of contact (see Table 1) and the subject's immune status.

Table 1 below is a guide for post-exposure prophylaxis based on WHO report TRS 931, 2004.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Type of contact</th>
<th>Type of exposure</th>
<th>Treatment recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Touching or feeding of animals. Licks on intact skin.</td>
<td>None</td>
<td>None if reliable case history is available</td>
</tr>
<tr>
<td>II</td>
<td>Nibbling of uncovered skin. Minor scratches or abrasions without bleeding.</td>
<td>Minor</td>
<td>Administer vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques.</td>
</tr>
<tr>
<td>III</td>
<td>Single or multiple transdermal bite(s) or scratch(es). Licks on broken skin.</td>
<td>Severe</td>
<td>Administer rabies immunoglobulin and vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques.</td>
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</table>

Immunoglobulins must be injected by infiltration. In cases of multiple severe exposures, the human rabies immunoglobulin should be used when possible (WHO recommendations TRS 931, 2004).
For post-exposure prevention of rabies, treatment associating the equine rabies immunoglobulin with the rabies vaccine is recommended, although experience indicates that vaccine alone could be sufficient for minor exposure (category II).

Prompt and local treatment of all bite or scratch wounds is very important and must be performed immediately following the bite or the scratch.

**Posology**

FAVIRAB should be injected as soon as possible after exposure.

The recommended dose for all age groups is 40 IU/kg of body weight.

The dose calculation is based on a product concentration of 200 IU/mL in the vial.

In the case of multiple wounds, the volume of the calculated dose of the equine rabies immunoglobulin may not be sufficient to infiltrate all wounds. In these circumstances, the recommended dose of FAVIRAB may be diluted to 1/2 or 1/3 in a 0.9 % NaCl solution to obtain a sufficient volume to be able to infiltrate all wounds.

Because of the risk of interference with antibody production related to vaccination, neither the dose should be increased nor repeated rabies immunoglobulin doses be given (even if the onset of the simultaneous prophylaxis is delayed).

**Paediatric population**

The dosage in paediatric population is the same as indicated above, in the "Posology" subsection.

**Method of administration**

Infiltration around and into the wounds. Any remainder of the dose should be administered slowly by intramuscular route.

First-aid recommendations include immediate and thorough flushing out and washing of the wound for 15 minutes with water and soap, detergent, povidone iodine or any other substance with a proven destructive action on the rabies virus. If no soap or antiviral agents are available, the wound should be thoroughly and extensively washed with water.

As much as possible of the dose should be infiltrated around and into the wounds if anatomically feasible. Any remainder of the dose should be administered slowly by intramuscular route in a single injection at a site distant from the rabies vaccine injection site. If possible, the vaccine should be injected contra-laterally to the immunoglobulin administration sites.

Infiltration of wounds in some anatomical sites (fingertips) must be carried out with caution in order to prevent increased pressure in the tissue compartment (compartment syndrome).

The first dose of vaccine should be injected at the same time as the equine rabies immunoglobulin. If equine rabies immunoglobulins are not available when the rabies vaccine is administered, they can be administered up to the 7th or 8th day after the first dose of vaccine. After this period, the active response produced by the vaccine is considered to have taken place.”

“Section 5.1:

5.1 Pharmacodynamic properties

**Pharmacotherapeutic category**

Immune globulins – Specific immune globulins.

ATC Code: J06BB

FAVIRAB contains F(ab’); fragments of equine antirabies immune globulin which are capable of neutralising the rabies virus.

In one prospective study, open-label and un-controlled study design (not randomized), one-year follow-up, carried out in 193 persons with confirmed category III rabies exposure shows that post-exposure prophylaxis (PEP) using pERIG Favirab™ is well tolerated and highly effective.
Children under 15 years represented 40.9% of the subjects of this study, with 20.2% of subjects between the age of 5 and 9 years old. The mean age was 24.9 years (range 16 months-79 years).

There were no immediate reactions and serious adverse events related to administration of pERIG Favirab™ or other products administered.

The survival of 99% of patients with laboratory-confirmed rabies exposure confirms the efficacy of pERIG Favirab™ in PEP. The single PEP intervention failure demonstrated the importance of ensuring immediate and complete application of recommended PEP protocol, sustained education and training in rabies management.”

PROPOSED CHANGES IN PIL:

“WHAT FAVIRAB, solution for injection, F(ab’)2 fragments of equine rabies immune globulin IS AND WHAT IT IS USED FOR

<table>
<thead>
<tr>
<th>Pharmacotherapeutic group</th>
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<tbody>
<tr>
<td>Immunoglobulin specific to rabies.</td>
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<th>Therapeutic indications</th>
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</tr>
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</table>

“HOW TO USE FAVIRAB, solution for injection, F(ab’)2 fragments of equine rabies immune globulin

<table>
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<tr>
<th>Instructions for proper use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration should always be performed under medical supervision (according to local recommendations) in a rabies centre.</td>
</tr>
<tr>
<td>Treatment must be adapted according to the type of contact (see Table 1) and the subject’s immune status.</td>
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<td>Table 1 below is a guide for post-exposure prophylaxis based on WHO report TRS 931, 2004.</td>
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Table 1: Type of contact and exposure

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</tr>
<tr>
<td></td>
<td>Licks on broken skin.</td>
<td></td>
<td>* Immunoglobulins must be injected by infiltration. In cases of multiple severe exposures, the human rabies immunoglobulin should be used when possible (WHO recommendations TRS 931, 2004).</td>
</tr>
<tr>
<td></td>
<td>Contamination of mucous membrane with saliva (i.e. licks).</td>
<td></td>
<td>For post-exposure prevention of rabies, treatment associating the equine rabies immunoglobulin with the rabies vaccine is recommended, although experience indicates that vaccine alone could be sufficient for minor exposure (category II).</td>
</tr>
<tr>
<td></td>
<td>Exposure to bats.</td>
<td></td>
<td>Prompt and local treatment of all bite or scratch wounds is very important and must be performed immediately following the bite or the scratch.</td>
</tr>
</tbody>
</table>

* Dosage/ Method and/or route(s) of administration/ Frequency of administration/ Duration of treatment

Posology

FAVIRAB should be injected as soon as possible after exposure.

The recommended dose for all age groups is 40 IU/kg of body weight.

The dose calculation is based on a product concentration of 200 IU/mL in the vial.

In the case of multiple wounds, the volume of the calculated dose of the equine rabies immunoglobulin may not be sufficient to infiltrate all wounds. In these circumstances, the recommended dose of FAVIRAB may be diluted to 1/2 or 1/3 in a 0.9 % NaCl solution to obtain a sufficient volume to be able to infiltrate all wounds.

Because of the risk of interference with antibody production related to vaccination, neither the dose should be increased nor repeated rabies immunoglobulin doses be given (even if the onset of the simultaneous prophylaxis is delayed).

Always use FAVIRAB exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Use in children and adolescents

The recommended dose in children and adolescents is the same as indicated above, in the "Posology" subsection.
**Method of administration**

Infiltration around and into the wounds. Any remainder of the dose should be administered slowly by intramuscular route.

First-aid recommendations include immediate and thorough flushing out and washing of the wound for 15 minutes with water and soap, detergent, povidone iodine or any other substance with a proven destructive action on the rabies virus. If no soap or antiviral agents are available, the wound should be thoroughly and extensively washed with water.

As much as possible of the dose should be infiltrated around and into the wounds if anatomically feasible. Any remainder of the dose should be administered slowly by intramuscular route in a single injection at a site distant from the rabies vaccine injection site. If possible, the vaccine should be injected contra-laterally to the immunoglobulin administration sites.

Infiltration of wounds in some anatomical sites (fingertips) must be carried out with caution in order to prevent increased pressure in the tissue compartment (compartment syndrome).

The first dose of vaccine should be injected at the same time as the equine rabies immunoglobulin. If equine rabies immunoglobulins are not available when the vaccine is administered, they can be administered up to the 7th or 8th day after the first dose of vaccine. After this period, the active response produced by the vaccine is considered to have taken place."

**Scope of the variation**

None proposed by the MAH.

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**III. INTRODUCTION**

On 4.11.2011, the MAH submitted two completed paediatric studies for Favirab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

Short critical expert overviews have also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Favirab and that there is no consequential regulatory action.

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**IV. SCIENTIFIC DISCUSSION**

**IV.1 Information on the pharmaceutical formulation used in the studies**

The studies were performed with commercial batches.

Active ingredients (per ml)

F (ab')\(_2\) fragments of equine antirabies immune globulin: 200 – 400 IU/mL

One 5-mL vial contains 1000 to 2000 IU of F (ab')\(_2\) fragments.

Other ingredients (per mL)

Polysorbate 80, sodium chloride, water for injection, hydrochloric acid or sodium hydroxide, to adjust the pH to between 6.0 and 7.0.

This medicinal product contains less than one millimole (or 23 mg) of sodium per dosage unit.
Dose: 40 IU/kg
Route: to be infiltrated around and into the wound(s) if anatomically feasible. Any remainder of the dose should be administered by single intramuscular injection at a site distant from the vaccine injection site.
A two to three fold dilution using normal saline may be done to allow the infiltration of multiple wounds.
However, in children, and particularly in the case of multiple wounds, the recommended dose may be diluted to ½ or 1/3 in a 9‰ NaCl solution, so that the quantity of equine antirabies immune globulin necessary for the satisfactory infiltration of all wounds is sufficient.

IV.2 Clinical aspects

1. Introduction

The MAH submitted two final reports for:
1. FAV03, Favirab Post Prescription Event Monitoring which is a monocentric prescription event monitoring study
2. FAV04, Favirab Post Prescription Event Monitoring, which is a monocentric prescription event monitoring study

2. Clinical studies

FAV03, Favirab Post Prescription Event Monitoring

➢ Description

FAV03, a prescription event monitoring study, was carried out in Thailand, a rabies enzootic country, and it was designated to determine health status of patients who received post-exposure prophylaxis (PEP) using purified equine rabies immunoglobulin (pERIG) Favirab for category III exposures to a laboratory-proven rabid animal.

➢ Methods

- Objectives
  - Primary Objective: to evaluate the efficacy of the Equine Rabies Immune Globulin (Favirab) six (6) and twelve (12) months after administration when used in rabies post exposure treatment among patients with category III exposures to a proven rabid animal.
  - Secondary Objective: to monitor serious adverse events (SAEs) within 30 days following administration.

- Study design
  This was a monocentric Post Prescription Event Monitoring of patients with category III bites from a proven rabid animal.

- Study population /Sample size
  A sample size of 250 subjects was chosen. Actual sample size: 178. There is only one group in this study.
A potential subject had to meet all of the following criteria to be considered for trial enrollment:
1. Subject with Category III bites that were either:
   a) inflicted by proven rabid animals regardless of location or number of bites OR
   b) inflicted by suspected rabid animals where bite is on the head, neck, face or fingers, regardless of number of bites OR
   c) inflicted by suspected rabid animals where bite was multiple regardless of location or one bite with deep wound and bleeding
2. Subject of either sex without any age limitation
3. Subject had received Equine Rabies Immunoglobulin (Favirab) correctly as prescribed by attending physician
4. Subject had received the first dose of rabies vaccine correctly.
5. Written informed consent signed by the patient or a legally acceptable representative in case of age under 18 years.

• Treatments
40IU/kg to be infiltrated around the wound(s). The remaining product can be administered intramuscularly on the gluteal area (deltoid muscle or anterior surface to the thigh in children).
A two to three fold dilution using normal saline may be done to allow the infiltration of multiple wounds.

• Outcomes/endpoints
Primary endpoint: Survival rate of subject at 1 month in case of healthy animal and at 12 months in case of bitten by rabid suspected or proven rabid animal.
Secondary endpoint: To evaluate Serious Adverse Events within 30 days following administration of Favirab.

• Statistical Methods
Survival rate. The survival rate was determined by the number of survival cases divided by number of observational cases.

➢ Results

• Recruitment/ Number analysed
There were 178 recruited patients bitten by animals, who received Favirab and at least one dose of tissue culture derived rabies vaccine. However, 4 patients were with WHO category II exposure, thus these patients were excluded from efficacy evaluations.
Among 174 patients recruited, 164 patients completed the study and 10 patients were lost to follow up. The status of animals (14 days after the bite) related to those patients who completed the follow-up: 143 were healthy animals, and 21 were sick animals or animals disappeared. For those 10 patients with incomplete follow-up at one year, afterward all survival was confirmed as in details: 3 patients were reached by telephone call, 1 patient responded by the certified mail, and 6 patients were explored by official residence registration.
There were 10 patients that the dogs died and the brain specimens not sent for rabies proven. In Thailand the number of brain specimens of bitten animals sent for rabies proven has been reduced. In 2002 and 2006 there were 3039 and 1581 suspected animal's brains examined (dog's brain 78.8%, 77.1% and cat's brain 15.4%, 17.5%). According to Ministry of Public Health Guideline for Rabies Prophylaxis, all animal bite victims (mammal that can transmit rabies) in WHO Categories II and III have to receive rabies postexposure prophylaxis either rabies vaccine (Category II) or rabies vaccine plus rabies immunoglobulin (Category III). Exception: subjects who are bitten by dogs or
cats and fulfill all the following requirements: 1) 2 doses of rabies vaccine in the past 2 years 2) keep animal well in the house 3) non-provoke bite. Therefore, all study patients were immunized against rabies. And for 145 out of 174 patients (83.3%) after 14 days follow-up, the biting animals were still healthy.

- Baseline data
  The age of the 178 enrolled patients ranged from 6 months to 78 years with majority (71%) over 15 years. There were 87 males and 91 females. The biting animals were dogs (94.8%), rats (4.0%), and cats (1.1%). Majority of the site of animal bite was lower limb. The second and third common sites of animal bite were upper limb and head and neck respectively.

- Efficacy results
  164 patients completed follow-up and 10 patients were recorded with incomplete follow up at one year. Afterward all survival was confirmed as in details: 3 patients were reached by telephone call, 1 patient responded by the certified mail and 6 patients were explored by official residence registration.
  In this study all 174 recruited patients with WHO category III contacts, who received postexposure prophylaxis using Favirab, survived. Nevertheless, taking into account that most of the biting animals were healthy after 14 days follow up, none of the animals were proven to be rabid and only 21 patients bitten by sick animals or animals that disappeared were included into the follow-up, the efficacy of Favirab was unlikely determined.

- Safety results
  No SAE was observed during 30 days after Favirab administration. The investigators concluded that pERIG Favirab is safe when administered at the same time with tissue culture rabies vaccine.

FAV03 study revealed no relevant information regarding efficacy or safety profile not yet included in the Company’s Core Data Sheet; thus modifications of the pERIG Favirab Company Core Data Sheet and related documents – including the SmPC, Package Leaflet, and texts of outer or immediate packaging – are not needed.

In conclusion, FAV03 study did not reveal new or unexpected information on the product and results are considered comparable to results currently reflected in pERIG Favirab European licenses.

FAV04, Favirab Post Prescription Event Monitoring

- Description
  This prospective prescription event monitoring (PPEM) study, which was carried out in The Philippines, rabies enzootic country, was designated to determine a health status of patients who received PEP using pERIG Favirab for category III exposures to a laboratory-proven rabid animal.

- Methods
  - Objectives
    - Primary Objective: to evaluate the efficacy of the Equine Rabies Immune Globulin (Favirab) six (6) and twelve (12) months after administration when used in rabies post exposure treatment among patients with category III exposures to a proven rabid animal.
Secondary Objective: to monitor serious adverse events (SAEs) within 30 days following administration.

- Study design
  Monocentric, prospective post-prescription event monitoring, one-year follow-up

- Study population /Sample size
  The planned sample size was of 250 patients and factually 193 patients have been included. There is only one group in this study.

  The following inclusion criteria were applied:
  1. Subject with WHO category III exposure that is either:
     a) Inflicted by proven rabid animal regardless of location or number of bites OR
     b) Inflicted by suspected rabid animal with bites on the head, neck, face or fingers, regardless of number of bites OR
     c) Inflicted by suspected rabid animals with multiple bites regardless of location.
  2. Subject of either sex without any age limitation.
  3. Subject has received the right amount of pERIG FavirabTM as prescribed by attending physician, following the posology (40 IU/kg of body weight – 200 IU/mL of product).
  4. Subject has received the first dose of rabies vaccine correctly.

- Treatments
  In accordance with the manufacturer’s recommendation, a pERIG skin test was performed prior to pERIG infiltration around the wound. The test consisted of intradermal (ID) administration of 0.1 mL of 1:10 solution of pERIG, and read after 15 minutes. An induration > 6 mm was considered positive.

  40 IU/kg to be infiltrated around and into the wound(s) if anatomically feasible. Any remainder of the dose should be administered by single intramuscular injection at a site distant from the vaccine injection site.
  A two to three fold dilution using normal saline may be done to allow the infiltration of multiple wounds.

- Outcomes/endpoints
  Primary endpoint: Survival rate 180 and 365 days after the administration of pERIG Favirab.
  Secondary endpoint: To evaluate Serious Adverse Events within 30 days following administration of Favirab

- Statistical Methods
  For the primary objective: The statistical analysis was performed under the responsibility of the RITM’s Biostatistics platform using Epistat® software.
  Survival rate was measured using the following formula: number alive until time (T) / by number of subjects followed up.
  Survival rates were measured and curves were calculated and drawn at the time-points of 6 months and 12 months follow-up.
  For the secondary objective: Occurrence, nature (MedDRA terms), duration, seriousness criteria, relationship to vaccination, and outcome, of serious adverse events throughout the trial.

Results
Recruitment/ Number analysed
Between August 2004 and September 2006, a total of 1,370 subjects were seen at RITM (Research Institute for Tropical Medicine, Philippines); 193 subjects bitten by or exposed to laboratory-confirmed dFAT-positive animals were enrolled in the one-year surveillance study. These subjects met the inclusion criteria for the study. Other patients with a dFAT-positive exposure were not enrolled in the surveillance study as they did not meet the study inclusion criteria. The one-year health status surveillance was completed for 189 of these 193 subjects, a 98% completion rate. Twenty subjects exposed to animals where dFAT analysis (direct fluorescent antibody test) could not be performed received similar surveillance. A total of 138 dFAT-positive biting animals, all of which were dogs, inflicted wounds in the 193 subjects enrolled in the study. All subjects received at least two doses of rabies vaccine: 147 (76.2%) completed the 5 dose rabies vaccination series, 35 received 4 doses, 8 received 3 doses, and 3 received only 2 doses. Rabies vaccination was initiated via the ID route for 96.2% of subjects. Vast majority (99%) of subjects received purified Vero-cell rabies vaccine (PVRV) Verorab, Sanofi Pasteur, France.

Baseline data
Children under 15 years of age represented 40.9% of the subjects of this study, with 20.2% of subjects between the ages of 5 and 9 years old. The mean age was 24.9 years (range 16 months – 79 years). The study population was composed of 64.2% males and 35.8% females; a similar ratio to the overall population seen at RITM during the study period.

Efficacy results
Of the 193 enrolled victims of bites by laboratory-confirmed rabid dogs, 191 (99%) were alive and healthy one year after exposure. Two deaths occurred during the one-year surveillance period: a 73-year-old man died due to myocardial infection (unrelated to rabies) 291 days post-rabies exposure, and one child (six-year-old) died due to rabies infection 28 days postexposure. The single rabies fatality required detailed analysis to identify any deviation from the recommended protocol. Wound washing with soap and water was applied on the day of exposure; however some delay may have elapsed between the bite and the wound washing. Unfortunately, disinfection with ethanol or iodine after washing was not applied. The location of the bite, in the lip, meant that the administration of ERIG Favirab in the wound was not easy in the six-year-old patient. Also this patient received a first vaccine dose (at two sites) through intradermal route, but the second and third doses were administered on days 3 and 7 through intramuscular route (against WHO recommended practice of not changing the administration route). The single PEP intervention failure demonstrated the importance of ensuring immediate and complete application of recommended PEP protocol, sustained education and training in rabies management.

Safety results
No positive reaction to pERIG Favirab skin testing was observed. No immediate reaction (within 30 min) was observed following pERIG Favirab infiltration. Two episodes of hypersensitivity reaction manifesting as rash were considered to be possibly related to pERIG Favirab; the two other reactions (rash and fever) were considered to be unrelated to pERIG Favirab administration.

All participants were observed for serious adverse events and overall survival for a one-year period. All the patients were evaluated 30 days after the administration of Favirab.
evaluate the Serious Adverse Events via an interview and questioning. The result of these interviews is summarized for each patient in a data collection form. Throughout the surveillance period contacts were made consistently in over 95% of subjects.

During the one-year surveillance period a total of 13 cases, meeting the study evaluation criteria of a serious adverse event (SAE) have been reported in 11 subjects. The principal investigator considered the SAEs as unrelated to the administration of the products. No serious adverse events related to administration of pERIG Favirab or other products administered during postexposure prophylaxis were observed.

This prospective one-year follow-up in persons with confirmed category III rabies exposure shows that post-exposure prophylaxis (PEP) using pERIG Favirab is well tolerated and highly effective. There were no immediate reactions and serious adverse events related to administration of pERIG Favirab or other products administered. The survival of 99% of patients with laboratory-confirmed rabies exposure confirms the efficacy of pERIG Favirab in PEP.

The single PEP intervention failure demonstrated the importance of ensuring immediate and complete application of recommended PEP protocol, sustained education and training in rabies management.

V. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION ON DAY 89

➢ Overall conclusion
The submitted studies do not influence the benefit risk profile of Favirab in children. It is noted that section 5.1 of the SmPC does not contain efficacy data. Please refer to the recommendation.

➢ Recommendation
Based on the data submitted, the MAH should provide a proposal for wording of section 5.1 of the SPC, adding in the results from study FAV04 and clarifying the age range, as part of this worksharing procedure. Also, there were some additional points for consideration raised by another member state that should be addressed (see section VI “Request for Supplementary Information”).

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

List of questions at day 89

The following comments were received from UK and HU member states:

1. (UK) The submitted data does not impact on the favourable benefit: risk profile for Favirab in children. However, as section 5.1 of the SPC does not contain efficacy data the MAH should consider adding in the results from study FAV04 and clarifying the age range as this study demonstrated very high efficacy across a range of ages.

2. (HU) There is agreement with the overall conclusion of the Rapporteur. However, there are some additional points for consideration:
   2.1. In study FAV03, conducted in Thailand the biting animals were reported healthy after 14 days follow up and none of the animals were proven
Regarding the data, therefore, no conclusion with respect of efficacy can be drawn. The data could be evaluated with respect of safety in the pediatric population. Most of the participants were over 15 years of age. The limit of 15 years needs justification in light of ICH Topic E11. This NfG recommends 12 to 16-18 for the adolescent category. No information has been provided on the age stratification of the pediatric participants in this study. Such information would help in assessing the safety of Favirab in the various pediatric age categories.

2.2. Study FAV04 may be more informative. The patients enrolled were exposed to confirmed rabid animals. The pediatric population is stratified with respect of age. A statement in the SPC point 4.1 about indication in pediatric age groups may be considered.

VII. ASSESSMENT OF MAH’ RESPONSES TO THE PRELIMINARY PDAR DAY 89

Question 1: Rapporteur recommendation and UK comment:
The submitted data does not impact on the favourable benefit: risk profile for Favirab in children. However, as section 5.1 of the SPC does not contain efficacy data the MAH should consider adding in the results from study FAV04 and clarifying the age range as this study demonstrated very high efficacy across a range of ages.

Answer 1:
Indeed FAV04 clinical trial, a prospective one-year follow-up study in individuals (193 subjects, age range: 16 months – 79 years) with laboratory-confirmed rabies exposure (WHO’ category III contact), demonstrated that post-exposure prophylaxis including Favirab® is safe and effective. No immediate reaction or serious adverse events related to administration of Favirab® were observed. All patients, who received post-exposure prophylaxis in strict accordance with WHO recommended protocol, survived. Nevertheless, taking into account that current Favirab® SPC content is based on the data generated in several clinical trials and wide field experience since this product licensure (whereas in FAV04 study had a very limited number of subjects), it seems not appropriate to update the section 5.1 Pharmacodynamic properties of SPC using FAV04 study results. Indeed, FAV04 does not modify safety and efficacy profile of the Product.

Assessment of the Applicant’s response
The age range distribution for the population included in FAV04 study is presented in the following table 4.4

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
</tr>
<tr>
<td>0-4</td>
<td>12</td>
<td>9.7</td>
<td>10</td>
</tr>
<tr>
<td>5-9</td>
<td>23</td>
<td>18.6</td>
<td>16</td>
</tr>
<tr>
<td>10-14</td>
<td>15</td>
<td>12.1</td>
<td>3</td>
</tr>
<tr>
<td>15-19</td>
<td>9</td>
<td>7.3</td>
<td>4</td>
</tr>
<tr>
<td>Age Group</td>
<td>Favirab</td>
<td>RO</td>
<td>W0002</td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td>----</td>
<td>--------</td>
</tr>
<tr>
<td>20-24</td>
<td>14</td>
<td>11.3</td>
<td>8</td>
</tr>
<tr>
<td>25-29</td>
<td>5</td>
<td>4.0</td>
<td>5</td>
</tr>
<tr>
<td>30-34</td>
<td>5</td>
<td>4.0</td>
<td>2</td>
</tr>
<tr>
<td>35-39</td>
<td>14</td>
<td>11.3</td>
<td>6</td>
</tr>
<tr>
<td>40-44</td>
<td>6</td>
<td>4.8</td>
<td>5</td>
</tr>
<tr>
<td>45-49</td>
<td>8</td>
<td>6.4</td>
<td>4</td>
</tr>
<tr>
<td>50-54</td>
<td>3</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>55-59</td>
<td>7</td>
<td>5.6</td>
<td>1</td>
</tr>
<tr>
<td>60-64</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>65-69</td>
<td>1</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>70-74</td>
<td>1</td>
<td>0.8</td>
<td>2</td>
</tr>
<tr>
<td>75-79</td>
<td>1</td>
<td>0.8</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>124 (100)</td>
<td></td>
<td>69 (100)</td>
</tr>
<tr>
<td>Mean¹</td>
<td>24.9 ± 18.2</td>
<td></td>
<td>24.8 ± 20.7</td>
</tr>
<tr>
<td>Median (range)</td>
<td>20.4 [2.9,79.3]</td>
<td></td>
<td>20.5 [1.4,79.2]</td>
</tr>
</tbody>
</table>

(¹) mean ± standard deviation (in years)

Children under 15 years represented 40.9% of the subjects of this study, with 20.2% of subjects between the age of 5 and 9 years old. The mean age was 24.9 years (range 16 months-79 years).

The submitted FAV04 study has several shortcomings which reduce its informative value, mainly the open-label and un-controlled study design, not randomized.

This trial involved 1 center the Research Institute for Tropical Medicine (RITM).

The primary objective was to evaluate the efficacy of purified equine rabies immunoglobulin (pERIG) Favirab in terms of survival rate six (06) and twelve (12) months administration when used in rabies post/exposure treatment among patients with category III exposures to a proven rabid animal.

The primary endpoint was survival rate at Day180 and Day 365 after the administration of Favirab™. However no hypotheses were tested for primary endpoint. Thus, the interpretation of the study results is hampered by the chosen design.

Since the study was small and un-controlled, efficacy was assessed exploratory only.

Taking into account the fact that the section 5.1 does not contain any efficacy data, the inclusion of this information may be considered.

The results can be used to emphasis the effect of F(ab')2 fragments of equine antirabies immunoglobulin that should have been expected in the recruited population (paediatric population and adults).

**Question 2: request for supplementary information by HU.**

There is agreement with the overall conclusion of the Rapporteur.

However, there are some additional points for consideration:

2.1 In study FAV03, conducted in Thailand the biting animals were reported healthy after 14 days follow up and none of the animals were proven rabid.

Regarding the data, therefore, no conclusion with respect of efficacy can be drawn. The data could be evaluated with respect of safety in the pediatric population. Most of the participants were over 15 years of age. The limit of 15 years needs justification in light of ICH Topic E11. This NfG recommends 12 to 16-18 for the adolescent category. No information has been provided on the age stratification of the pediatric participants in this study. Such information would help in assessing the safety of Favirab in the various pediatric age categories.
Answer 2.1:

FAV03 clinical trial was a prospective prescription event monitoring (PPEM) study. Subjects have been screened for the inclusion/exclusion criteria after they have been evaluated by the physician on duty at the emergency room of the hospital and have received Favirab® and the first dose of rabies vaccine following the routine medical practice of post-exposure health care. There were 178 recruited patients bitten by animals who received Favirab® and at least one dose of tissue culture derived rabies vaccine. Four patients were with WHO category II exposure, thus these patients were excluded from efficacy evaluations. The age of the 178 enrolled patients ranged from 6 months to 78 years with majority (71%) over 15 years. Children aged below 15 years represented 29% (n=51) of patients (The details of patients’ age distribution are presented in the table 4.3.1 of the Final Report, see an extract below). Thus, taking into account that current Favirab® SPC content is based on the data generated in several clinical trials and wide field experience since this product licensure (whereas in FAV03 study had a very limited number of pediatric age subjects), it seems not appropriate to update SPC using FAV03 ‘pediatric population’ results. Indeed, FAV04 does not modify safety and efficacy profile of the Product.

**Table 4.3.1: Patients Baseline Data (N=178)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Gender</th>
<th>Previous vaccination</th>
<th>Number fulfill criteria</th>
<th>SN* not fulfill criteria</th>
<th>Reason of protocol violations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-&lt;1 yr</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>inclusion 1 exclusion 1</td>
</tr>
<tr>
<td>1-&lt;5 yr</td>
<td>21</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>20</td>
<td>“168”</td>
</tr>
<tr>
<td>5-&lt;10 yr</td>
<td>20</td>
<td>12</td>
<td>8</td>
<td>1</td>
<td>19</td>
<td>“65” inclusion 1 exclusion 1</td>
</tr>
<tr>
<td>10-&lt;15 yr</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>8</td>
<td>inclusion 1 exclusion 1</td>
</tr>
<tr>
<td>15-&lt;20 yr</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>“48” inclusion 1 exclusion 1</td>
</tr>
<tr>
<td>20-&lt;30 yr</td>
<td>34</td>
<td>17</td>
<td>17</td>
<td>3</td>
<td>34</td>
<td>inclusion 1 exclusion 1</td>
</tr>
<tr>
<td>30-&lt;40 yr</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>16</td>
<td>inclusion 1 exclusion 1</td>
</tr>
<tr>
<td>40-&lt;50 yr</td>
<td>26</td>
<td>8</td>
<td>18</td>
<td>3</td>
<td>25</td>
<td>“4” inclusion 1 exclusion 1</td>
</tr>
<tr>
<td>50-&lt;60 yr</td>
<td>24</td>
<td>8</td>
<td>16</td>
<td>4</td>
<td>24</td>
<td>inclusion 1 exclusion 1</td>
</tr>
<tr>
<td>≥60 yr</td>
<td>20</td>
<td>12</td>
<td>8</td>
<td>5</td>
<td>20</td>
<td>inclusion 1 exclusion 1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>178</td>
<td>87</td>
<td>91</td>
<td>19</td>
<td>174</td>
<td></td>
</tr>
</tbody>
</table>

*SN = subject number

**Assessment of the Applicant’s response**
The requested data has been submitted. However the justification of the limit 15 years for the paediatric population was not given.

2.2 Study FAV04 may be more informative. The patients enrolled were exposed
to confirmed rabid animals. The pediatric population is stratified with respect of age. A statement in the SPC point 4.1 about indication in pediatric age groups may be considered.

**Answer 2.2:**
Indeed the results of FAV04 study in pediatric age subjects are quite informative. However, since rabies is 100% fatal disease and consequently rabies immunobiologics for post-exposure prophylaxis are indicated for all patients without any age restrictions, it seems that it will be not appropriate to define the target population age in 4.1 Therapeutic indications section of SmPC.

**Assessment of the Applicant's response**
The requested data has been submitted. The Company’s view is that no change is necessary as a consequence of the data presented.

**VIII. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

As a result of the submitted paediatric studies, the MAH did not propose any change to the approved SmPC of Favirab. The MAH stated that the submitted paediatric studies do not influence the benefit risk balance for Favirab and thus there is no consequential regulatory action.

No additional documentation has been included.

The MAH stated that based on the review of the available data, no amendment to the existing Core Data Sheets is warranted.

The current therapeutic indication for Favirab is the following:

- Seroprophylaxis of rabies in subjects suspected to be exposed to the rabies virus, particularly in the event of severe exposure (e.g., multiple severe bites located on the face, head, neck, hands when the domestic or wild animal responsible either cannot be examined, or is infected or suspected to be infected by the rabies virus or bites to young children).

The Sanofi Pasteur has reviewed the results of 2 own clinical studies and has concluded that no changes of the Favirab (F(ab’2) fragments of equine antirabies immunoglobulin) SmPC are required. A short clinical expert overview has been provided.

Although Favirab is already recommended by WHO for use among Category III exposed patients, there is little data on efficacy in humans since conducting such a study is not considered ethical.

In order to improve the quality of its previous Equine Rabies Immunoglobulin, Sanofi Pasteur introduced new steps in the manufacturing process. The most important modification was the introduction of a chromatography purification step which allows the removal of the majority of reactogenic proteins.

WHO has suggested Sanofi Pasteur to set up a post marketing surveillance, in countries where the product is available.

Thus, the performed studies submitting by Sanofi Pasteur are mostly observational studies (non-interventional trial), phase IV, non-randomized, single arm relating to safety data of Favirab in the licensed indications. Efficacy was assessed exploratory only.

Although the recommended indication of Favirab F(ab’)2 fragments of equine antirabies immunoglobulin covers both adults and paediatrics the age range limits are not explicitly mentioned in paediatric population. Thus, an explicit wording in section 4.1, respective 4.2 for paediatric population is considered necessary.
The specific sub-section of “paediatric population” should always be included and the information given should cover the subsets of the paediatric population according with the stratification of paediatric population of ICH Topic E11.

Based on the review of the presented paediatric data it is agreed with the MAH that the data from the submitted studies do not influence the benefit risk profile of Favirab in children.

However, it is the Rapporteur’s opinion that it may be considers necessary an update of the SmPC and PIL regarding the stratification of paediatric population with respect of age for this product in order to be in line with the revised SPC guideline (September 2009) and QRD template.

Also, the results of FAV04 study may be considered to be included in section 5.1 of Favirab SmPC, stressing the expected effect of F(ab’2 fragments of equine antirabies immunoglobulin in the recruited population (paediatric population and adults).

According to Rapporteur’s recommendations the Company has submitted a proposal and it was agreed that following amendments would be implemented in the SmPC/PIL, using a type IB variation.

PROPOSED CHANGES IN SmPC:

“Section 4.1 Therapeutic indications
FAVIRAB is indicated in rabies post-exposure prophylaxis in all paediatric population subsets and adults suspected to have been exposed to the rabies virus, particularly in case of severe exposure (see Section 4.2).

According to the recommendations of the WHO expert consultation on rabies, FAVIRAB must always be used in association with a rabies vaccine. The only exception is for patients already immunised with a rabies vaccine and who are able to produce documentation confirming vaccination with a cell-culture vaccine (i.e. full pre-exposure vaccination within the previous year, subsequent booster injection within the 5 previous years or full post-exposure prophylaxis). These people may receive the vaccine alone.

Administration must always be performed under medical supervision (according to local recommendations) in a rabies centre.”

“Section 4.2:
Treatment must be adapted according to the type of contact (see Table 1) and the subject’s immune status.

Table 1 below is a guide for post-exposure prophylaxis based on WHO report TRS 931, 2004.

Table 1: Type of contact and exposure
<table>
<thead>
<tr>
<th>Categories</th>
<th>Type of contact</th>
<th>Type of exposure</th>
<th>Treatment recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Touching or feeding of animals. Licks on intact skin.</td>
<td>None</td>
<td>None if reliable case history is available</td>
</tr>
<tr>
<td>II</td>
<td>Nibbling of uncovered skin. Minor scratches or abrasions without bleeding.</td>
<td>Minor</td>
<td>Administer vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques.</td>
</tr>
<tr>
<td>III</td>
<td>Single or multiple transdermal bite(s) or scratch(es). Licks on broken skin. Contamination of mucous membrane with saliva (i.e. licks). Exposure to bats.</td>
<td>Severe</td>
<td>Administer rabies immunoglobulin and vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques.</td>
</tr>
</tbody>
</table>

Immunoglobulins must be injected by infiltration. In cases of multiple severe exposures, the human rabies immunoglobulin should be used when possible (WHO recommendations TRS 931, 2004).

For post-exposure prevention of rabies, treatment associating the equine rabies immunoglobulin with the rabies vaccine is recommended, although experience indicates that vaccine alone could be sufficient for minor exposure (category II).

Prompt and local treatment of all bite or scratch wounds is very important and must be performed immediately following the bite or the scratch.

**Posology**

FAVIRAB should be injected as soon as possible after exposure.

The recommended dose for all age groups is 40 IU/kg of body weight.

The dose calculation is based on a product concentration of 200 IU/mL in the vial.

In the case of multiple wounds, the volume of the calculated dose of the equine rabies immunoglobulin may not be sufficient to infiltrate all wounds. In these circumstances, the recommended dose of FAVIRAB may be diluted to 1/2 or 1/3 in a 0.9 % NaCl solution to obtain a sufficient volume to be able to infiltrate all wounds.

Because of the risk of interference with antibody production related to vaccination, neither the dose should be increased nor repeated rabies immunoglobulin doses be given (even if the onset of the simultaneous prophylaxis is delayed).

**Paediatric population**

The dosage in paediatric population is the same as indicated above, in the “Posology” subsection.

**Method of administration**

Infiltration around and into the wounds. Any remainder of the dose should be administered slowly by intramuscular route.

First-aid recommendations include immediate and thorough flushing out and washing of the wound for 15 minutes with water and soap, detergent, povidone iodine or any other substance with a proven destructive action on the rabies virus. If no soap or antiviral agents are available, the wound should be thoroughly and extensively washed with water.

As much as possible of the dose should be infiltrated around and into the wounds if anatomically feasible. Any remainder of the dose should be administered slowly by intramuscular route in a single injection at a
site distant from the rabies vaccine injection site. If possible, the vaccine should be injected contra-laterally to the immunoglobulin administration sites.

Infiltration of wounds in some anatomical sites (fingertips) must be carried out with caution in order to prevent increased pressure in the tissue compartment (compartment syndrome).

The first dose of vaccine should be injected at the same time as the equine rabies immunoglobulin. If equine rabies immunoglobulins are not available when the rabies vaccine is administered, they can be administered up to the 7th or 8th day after the first dose of vaccine. After this period, the active response produced by the vaccine is considered to have taken place.”

“Section 5.1:

5.1 Pharmacodynamic properties

Pharmacotherapeutic category

Immune globulins – Specific immune globulins.
ATC Code: J06BB
FAVIRAB contains F(ab’)_2 fragments of equine antirabies immune globulin which are capable of neutralising the rabies virus.

In one prospective study, open-label and un-controlled study design (not randomized), one-year follow-up, carried out in 193 persons with confirmed category III rabies exposure shows that post-exposure prophylaxis (PEP) using pERIG Favirab™ is well tolerated and highly effective. Children under 15 years represented 40.9% of the subjects of this study, with 20.2% of subjects between the age of 5 and 9 years old. The mean age was 24.9 years (range 16 months-79 years).

There were no immediate reactions and serious adverse events related to administration of pERIG Favirab™ or other products administered.

The survival of 99% of patients with laboratory-confirmed rabies exposure confirms the efficacy of pERIG Favirab™ in PEP. The single PEP intervention failure demonstrated the importance of ensuring immediate and complete application of recommended PEP protocol, sustained education and training in rabies management.”

PROPOSED CHANGES IN PIL:

“WHAT FAVIRAB, solution for injection, F(ab’)2 fragments of equine rabies immune globulin IS AND WHAT IT IS USED FOR

Pharmacotherapeutic group

Immunoglobulin specific to rabies.

Therapeutic indications

FAVIRAB is indicated in rabies post-exposure prophylaxis in all paediatric population subsets and adults suspected to have been exposed to the rabies virus, particularly in case of severe exposure.

According to the recommendations of the WHO expert consultation on rabies, FAVIRAB must always be used in association with a rabies vaccine The only exception is for patients already immunised with a rabies vaccine and who are able to produce documentation confirming vaccination with a cell-culture vaccine (i.e. full pre-exposure vaccination within the previous year, subsequent booster injection within the 5 previous years or full post-exposure prophylaxis). These people may receive the vaccine alone.

Administration must always be performed under medical supervision (according to local recommendations) in a rabies centre.”
“HOW TO USE FAVIRAB, solution for injection, F(ab’)2 fragments of equine rabies immune globulin

<table>
<thead>
<tr>
<th>Instructions for proper use</th>
</tr>
</thead>
</table>

Administration should always be performed under medical supervision (according to local recommendations) in a rabies centre.

Treatment must be adapted according to the type of contact (see Table 1) and the subject’s immune status.

Table 1 below is a guide for post-exposure prophylaxis based on WHO report TRS 931, 2004.
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</tr>
</tbody>
</table>

*Immunoglobulins must be injected by infiltration. In cases of multiple severe exposures, the human rabies immunoglobulin should be used when possible (WHO recommendations TRS 931, 2004).*

For post-exposure prevention of rabies, treatment associating the equine rabies immunoglobulin with the rabies vaccine is recommended, although experience indicates that vaccine alone could be sufficient for minor exposure (category II).

Prompt and local treatment of all bite or scratch wounds is very important and must be performed immediately following the bite or the scratch.

**Dosage/ Method and/or route(s) of administration/ Frequency of administration/ Duration of treatment**

**Posology**

FAVIRAB should be injected as soon as possible after exposure.

The recommended dose for all age groups is 40 IU/kg of body weight.

The dose calculation is based on a product concentration of 200 IU/mL in the vial.

In the case of multiple wounds, the volume of the calculated dose of the equine rabies immunoglobulin may not be sufficient to infiltrate all wounds. In these circumstances, the recommended dose of FAVIRAB may be diluted to 1/2 or 1/3 in a 0.9 % NaCl solution to obtain a sufficient volume to be able to infiltrate all wounds.

Because of the risk of interference with antibody production related to vaccination, neither the dose should be increased nor repeated rabies immunoglobulin doses be given (even if the onset of the simultaneous prophylaxis is delayed).

Always use FAVIRAB exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

**Use in children and adolescents**

The recommended dose in children and adolescents is the same as indicated above, in the "Posology" subsection.
**Method of administration**

Infiltration around and into the wounds. Any remainder of the dose should be administered slowly by intramuscular route.

First-aid recommendations include immediate and thorough flushing out and washing of the wound for 15 minutes with water and soap, detergent, povidone iodine or any other substance with a proven destructive action on the rabies virus. If no soap or antiviral agents are available, the wound should be thoroughly and extensively washed with water.

As much as possible of the dose should be infiltrated around and into the wounds if anatomically feasible. Any remainder of the dose should be administered slowly by intramuscular route in a single injection at a site distant from the rabies vaccine injection site. If possible, the vaccine should be injected contra-laterally to the immunoglobulin administration sites.

Infiltration of wounds in some anatomical sites (fingertips) must be carried out with caution in order to prevent increased pressure in the tissue compartment (compartment syndrome).

The first dose of vaccine should be injected at the same time as the equine rabies immunoglobulin. If equine rabies immunoglobulins are not available when the vaccine is administered, they can be administered up to the 7th or 8th day after the first dose of vaccine. After this period, the active response produced by the vaccine is considered to have taken place.”

**IX. ADDITIONAL CLARIFICATIONS REQUESTED**

None