ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VIPERFAV, concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Equine immunoglobulin F(ab')$_2$ fragment antivenom for European vipers, which neutralises:

Vipera aspis venom ..... ≥ 1000 EL.U*

Vipera berus venom..... ≥ 500 EL.U*

Vipera ammodytes venom ..... ≥ 1000 EL.U*

per 4 ml

* EL.U: ELISA unit

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of envenomation (grade II or III) by European vipers (*Vipera aspis*, *Vipera berus*, *Vipera ammodytes*) in patients with rapidly spreading oedema and/or systemic signs: vomiting, diarrhoea, abdominal pain and hypotension.

Prognostic clinical severity criteria

Grade II: Extensive localised oedema in the bitten limb, with or without systemic signs (vomiting, diarrhoea, hypotension).

Grade III : Oedema that has spread beyond the bitten limb, affecting the trunk, and associated with severe systemic signs (prolonged collapse, shock, vomiting, diarrhoea, bleeding).

Prognostic laboratory severity criteria

Leucocytosis above 15,000/mm^3, thrombocytopenia below 150,000/mm^3, blood fibrinogen levels below 2 g/l, and a prothrombin time (%) below 60% are all severity factors.

The prognostic clinical (local and systemic) and laboratory signs of severity can appear separately within the first few hours of envenomation and it is therefore necessary to conduct repeat evaluations every 5 to 6 hours during the first day.

4.2. Posology and method of administration

Treatment with the equine immunoglobulin F(ab')$_2$ fragment antivenom for European vipers should be initiated early, i.e. as soon as the signs of severity appear and optimally within the first 6 hours. There is a risk that the expected therapeutic benefit may be less pronounced if treatment is initiated at a later time.

It is important that the treatment with equine immunoglobulin F(ab')$_2$ fragment antivenom for European vipers is combined with symptomatic treatment.

The use of equine immunoglobulin antivenom for European vipers is particularly recommended in children (as the venom/body-weight ratio is an essential severity factor), in adults who suffer from chronic disease (diabetes, haemophilia, history of cardiovascular disease), and in pregnant women.

Posology

The wound and the surrounding area must be carefully disinfected.

The initial recommended total dose is an infusion of 4 ml of equine immunoglobulin $F(ab')_2$ fragment antivenom for European vipers.

Paediatric population

It is recommended that the same dose be used as for adults, irrespective of age and weight.

This infusion can be repeated 2 more times at intervals of 5 hours according to clinical progress.

Method of administration

Precautions to be taken before handling or administering the medicinal product:

The 4 ml of solution must be diluted in 100 ml of sodium chloride 0.9% and administered as a slow intravenous infusion under medical supervision. To begin with, the rate of infusion must be reduced to 15 drops/min or 50 ml/hour.

The total duration of the infusion is one hour.

For instructions on diluting the medicinal product before administration, see section 6.6.

4.3. Contraindications

Relative contraindication in cases of known hypersensitivity to heterologous proteins of equine origin (see section 4.4) or to any of the excipients listed in section 6.1.

The risk to life associated with envenomation outweighs any potential contraindication.

4.4. Special warnings and precautions for use

The treatment must be administered in a hospital setting in order to be able to manage any immediate hypersensitivity reactions as soon as they occur.

Given that the equine immunoglobulin antivenom for European vipers is heterologous in nature, the risk of anaphylactic adverse reactions must always be evaluated:

in order to detect prior sensitisation to heterologous proteins, the patient must be questioned systematically and in detail regarding their history of allergies, with a particular focus on previous injections of heterologous proteins that may (or may not) have triggered possible reactions.

hypersensitivity to contact with animals – particularly horses – and even food allergies must also be determined.

In the event of signs of intolerance, reduce the rate of infusion or stop it if necessary.

The clinical signs of allergic or anaphylactic reaction can be mistaken for those of envenomation. If allergic or anaphylactic reactions occur, the infusion must be stopped immediately.

In the event of shock, treatment of the shock symptoms must be initiated immediately.

The infusion must always be started under close medical supervision, at a slow rate of 15 drops/min or 50 ml/hour.

This medicinal product contains sodium. The level of sodium is less than 1 mmol per dosage unit, i.e. "sodium-free".

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

No interaction of equine immunoglobulin $F(ab')_2$ fragment antivenom for European vipers with other medicinal products has been reported.

4.6. Fertility, pregnancy and lactation

Pregnancy

The safety of the product during pregnancy has not been established in clinical trials in humans. Given the risk to life associated with envenomation, pregnancy is not a contraindication for the initiation of antivenom treatment post-exposure.

4.7. Effects on ability to drive and use machines

There is nothing to suggest that this medicinal product has an influence on the ability to drive and use machines.

4.8. Undesirable effects

As with other products that contain equine $F(ab')_2$ fragments, it is possible that immediate or delayed allergic reactions may occur.

Anaphylactoid reactions involving urticaria, angioedema, hypertension, dyspnoea, cough, erythema of the face, or anaphylactic shock can occur. However, true anaphylactic shock is rare.

Delayed reactions similar to serum sickness can occur around six days after the start of treatment. These involve an inflammatory reaction caused by complement activation and the formation of immune complexes (type III hypersensitivity reaction) and are sometimes accompanied by clinical symptoms such as fever, pruritus, erythema or urticaria, adenopathy, and arthralgia. These reactions are observed in approximately 1% of subjects following administration of equine $F(ab')_2$ fragments.

The following adverse reactions have been reported following the administration of VIPERFAV:

Immune system disorders

Anaphylactoid reactions

Anaphylactic shock

Skin and subcutaneous tissue disorders

Immediate reactions:

Sweating

Skin rash

Delayed reactions:

Urticaria

Gastrointestinal disorders

Nausea

Musculoskeletal and connective tissue disorders

Arthralgia

General disorders and administration site conditions

Fever

Investigations

Moderate drop in blood pressure

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: French National Agency for Medicines and Health Products Safety (*Agence nationale de sécurité du médicament et des produits de santé,* ANSM) and the network of Regional Pharmacovigilance Centres - website: www.ansm.sante.fr.

4.9. Overdose

No known risk of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Specific immunoglobulins, ATC code: J06BB.

VIPERFAV is a preparation of equine immunoglobulin $F(ab')_2$ fragments which has the property of neutralising the venom of three species of viper: *Vipera aspis*, *Vipera berus*, and *Vipera ammodytes.*

These equine immunoglobulin $F(ab')_2$ fragments bind to the venom antigens present in the circulation to form inactive $F(ab')_2$-antigen complexes, thereby reducing the concentration of free venom.

Experimental testing has shown that they are responsible for redistributing the venom antigens from peripheral tissue sites to the vascular compartment, where they are bound and inactivated.

5.2. Pharmacokinetic properties

An analysis of the results of 13 envenomated patients highlighted a linear relationship between the administered dose and the initial concentrations, with an estimated elimination half-life of equine immunoglobulin $F(ab')_2$ of 40 to 105 hours. These data should be viewed with great caution given the limited experimental testing and the lack of reliable data in the literature.

5.3. Preclinical safety data

VIPERFAV has not been shown to have any mutagenic effects in the non-clinical studies.

No studies of reproduction, repeated administration, or local or general tolerance have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride, polysorbate 80 and water for injections.

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

2 years

6.4. Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

6.5. Nature and contents of container

4 ml of solution in a type I glass vial with a chlorobutyl stopper – carton of 1.

6.6. Special precautions for disposal and other handling

The 4 ml of solution must be diluted in 100 ml sodium chloride 0.9% solution before administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MICROPHARM LTD
UNITS F&G STATION ROAD INDUSTRIAL ESTATE
STATION ROAD
NEWCASTLE EMLYN
SA38 9BY
UNITED KINGDOM

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 562 154 0 9: 4 ml of solution in a type I glass vial with a chlorobutyl stopper – carton of 1.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed at a later stage by the marketing authorisation holder]

10. DATE OF REVISION OF THE TEXT

[to be completed at a later stage by the marketing authorisation holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I

Medicinal product reserved for hospital use.