ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
KT15 3LS
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

HYPERMUNE RE EQUINE PLASMA

PuAR correct as of 09/04/2019 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0298/001/MR
Name, strength and pharmaceutical form	Hypermune RE Equine Plasma
Applicant	Veterinary Immunogenics Ltd Carleton Hill Penrith Cumbria CA11 8TZ
Active substances	Frozen Equine Plasma Equine IgG ≥ 24 g/l Equine Total Protein ≥ 50 g/l Antibodies to *Rhodococcus equi* ≥ 40% VIL standard
ATC Vetcode	Q105AM
Target species	Horses
Indication for use	For foals with Failure of Passive Transfer To raise the level of circulating IgG in neonatal foals which have been shown to have low levels (less than 4g/l). The raised level has been demonstrated approximately 24 hours after administration but the duration of the effect is not known. For foals with Normal passive Transfer To raise the level of Rhodococcus equi antibodies. The raised level has been demonstrated approximately 24 hours after administration and raised levels though declining generally last for up to 21 days.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (**WWW.HMA.EU**).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	28 May 2008
Date product first authorised in the Reference Member State (MRP only)	03 April 2007
Concerned Member States for original procedure	Ireland

I. SCIENTIFIC OVERVIEW

Hypermune RE is an extension of the authorised product Hypermune.

Hypermune RE Equine Plasma is a frozen plasma for intravenous administration (after thawing) to foals with either failure of passive transfer of immunity, or in foals with normal passive immunity to *Rhodococcus equi*. In foals where there is a failure of transfer of immunity from the mother the raised level of immunoglobulin has been demonstrated approximately 24 hours after administration but the duration of the effect is not known. In foals with normal transfer of immunity from the mother the raised level of immunoglobulin has been demonstrated approximately 24 hours after administration of Hypermune RE and raised levels though declining generally last for up to 21 days. It is used to support the foal's immature immune system and helps to prevent septic disease. The dose rate is 1 litre per 50 kg foal, aged between 24 hours and 6 days, to be administered only through a filtered, blood product infusion set. .

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC. The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The active substances are as follows:
Frozen Equine Plasma
Equine IgG ≥ 24 g/l
Equine Total Protein ≥ 50 g/l
Antibodies to *Rhodococcus equi* ≥ 40% (in house standard)

The product contains the excipient acid citrate dextrose-A to ensure citrate (ACD-A).

The container is a PVC with DEHP one-litre human plasma sterile transfer bag with two protective sterile ports. The whole bag is over wrapped with protective bubble wrap for storage and transport.

The choice of the adjuvant, vaccine strain and inactivating agent are justified. The inactivation process and the detection limit of the control of inactivation are correctly validated.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances comprise frozen equine plasma, equine IgG ≥ 24 g/l, equine total protein ≥ 50 g/l and antibodies to *Rhodococcus equi* ≥ 40% and are novel active substances. The active substance is manufactured in accordance with the principles of good manufacturing practice.
Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines.
The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

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

Scientific data and certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control tests during production

The tests performed during production include purity, inactivation and bacterial count. These are satisfactory.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include appearance/identification, sterility, total IgG, plasma protein level tests, *R.equi* antibodies, pH and freedom from extraneous agents. The final product control tests are all the same as Hypermune with the exception of the test for *R.equi* antibody levels. The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

The stability of the IgG and total protein components of Hypermune were established as 2 years. It has been established that the specific antibodies to *R.equi* are mainly IgG and may have similar qualities of stability when stored under the same conditions.

Stability data on the finished product has been provided in accordance with applicable guidelines, indicating the stability of the product throughout its shelf life when stored under the approved conditions

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf Life:
Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life once thawed: 24 hours

Special precautions for storage:
Store in a freezer (-30°C to -20°C)
Hypermune RE should be handled carefully when being unpacked and stored in the freezer. The bubble-wrap should not be removed as it protects the brittle frozen plastic which is susceptible to damage from careless handling such as being dropped or knocked in the freezer. Once thawed it should be stored in a refrigerator.

III. SAFETY ASSESSMENT

Laboratory trials

The company presented the results of a study conducted in compliance with EU requirements on an EU approved GLP site designed to investigate the safety for foals of the administration of one dose, and the repeated administration of one dose in the target animal of Hypermune RE.

Groups of foals were treated with Hypermune RE with the recommended dose (20 ml/kg equivalent to 1 litre per 50 kg) on two occasions 21 days apart. Another group of foals were treated with saline and so acted as controls. The foals had normal passive transfer, were between 37 and 53 hrs old and 29-36 kg in weight. Local anaesthetic was given prior to administration of Hypermune RE. Plasma packs were weighed before and after the contents were administered to determine volume administered.

Clinical observations (appetite, demeanour, local injection site and respiration and heart rate) and general health observations were undertaken. The general checks were conducted twice daily and clinical observations were made before treatment, after 4 hrs then daily for 14 days after each administration. Rectal temperatures, respiration rate and heart rate were recorded at the same time each day until day 4 after each administration. Body weight was assessed on the day of and prior to treatment and at the end of the monitoring period. Blood samples were taken and analysed for total protein, equine IgG and *R.equi* antibodies. These were taken on the day of and prior to each treatment, then on days 1 and 14.

All foals remained in good health throughout the duration of the study. Rectal temperatures remained in the normal range and there was no clinical difference between the control and Hypermune RE group. Respiration rates remained around the normal range for foals throughout the study, again with no difference between the groups. The same was observed with heart rate. The data shows that Hypermune RE administered to foals as per the manufacturer's instructions is safe for use.

No studies were carried out on the safety of one administration of an overdose. This is because the administration of a two-fold overdose of Hypermune RE would present an unacceptable risk of circulatory volume overload. The administration of a second dose within 24 hours is contraindicated on the SPC for Hypermune RE.

No investigation of effect on reproductive performance was conducted because the product is intended for administration to foals during the first few weeks of life and would not be given to brood or pregnant mares. The use of Hypermune RE in pregnant or lactating mares is contraindicated on the SPC.

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

Residues

As for the parent product, Hypermune, the dose in the foal is distributed from and not accumulated at the injection site and a withdrawal period of zero days is therefore acceptable for Hypermune RE.

Interactions

Evidence from the field suggests tetanus antitoxin can safely be used with Hypermune RE

The SPC states:

Safety and efficacy data are available which demonstrate that Hypermune-RE can be administered on the same day but not mixed with tetanus antitoxin. No information is available on the safety and efficacy of Hypermune-RE when used with any other veterinary medicinal product except the product mentioned above. A decision to use this product before or after any other veterinary medicinal product therefore needs to be made on a case by case basis. As with colostrum derived passive immunity, the passive immunity transferred by Hypermune-RE may interfere with response to vaccine. It is recommended that this is considered when starting a vaccine programme with due adherence to the vaccine manufacturer's instructions.

User Safety

Satisfactory information on user safety is provided in the form of a user risk assessment. Suitable warnings are included in the SPC:

Administer only using a blood giving set to minimise risk of self-injection. In case of accidental contact with skin, wash affected areas thoroughly with warm soapy water.

Field studies

The company also presented the results of a study designed to evaluate field safety and efficacy of equine plasma containing specific antibodies to *R.equi*. (Hypermune RE) following intravenous administration to 2 day old foals with normal and low levels of serum IgG, and following a second transfusion at 29 days of age.

A group of thoroughbred foals were treated twice with 1 litre Hypermune RE 28 days apart. Most of the foals in the group had normal passive transfer (NPT) and a smaller number of foals had failure of passive transfer (FTP). Clinical observations were carried out immediately prior to treatment, after 4 hrs then daily for 14 days. Rectal temperature, heart rate and respiration rate were recorded at the same time but only up to day 4. Body weight was assessed prior to and on the day of treatment and at the end of the study. Blood samples were collected prior to each treatment, then on days 1 and 14 and assayed for total serum protein, total serum IgG and *R.equi* specific antibodies.

All but one of the foals showed no adverse reaction to the plasma transfusion. The one foal that showed a mild transient reaction after the second transfusion showed signs of increased heart and respiration rate, mild distress and pruritis for 4hrs. The plasma administered to this foal was from a 10 litre harvest the rest of which was used to transfuse subsequent foals which showed no reactions. This foal received plasma from a different donor on the previous occasion and showed no reaction. This suggested that this was an iodosyncratic reaction specific to this foal. The applicant refered to literature which showed that 33% of foals receiving 950 mls of commercial plasma experienced minor reactions. It was therefore considered that reactions are rare and present a low risk providing foals are closely monitored during transfusion.

No overall effects on clinical parameters were observed after either transfusion with no statistically significant difference in pre and post transfusion heart rate or respiration. There was a significant decrease in temperature from pre-transfusion values. Apart from the one foal already mentioned no adverse reactions were observed.

The applicant concluded from this particular study that the administration of 1 litre of Hypermune RE to 2 day old foals with a repeat dose given to the foals 27 days later is well tolerated. A mild transfusion reaction was observed in one animal but this was considered not related to the product as such, but was a reaction specific to transfusion in that foal and the foal was not permanently adversely affected.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

A study was carried out to evaluate the safety and efficacy of Hypermune RE plasma when used according to the manufacturer's instructions in two day old foals with a repeat dose administered 21 days later. The method is described in section III (Safety Aspects) of this discussion.

Total protein, IgG and *R.equi* antibodies
IgG, Total protein (TP) and R equi antibody levels were measured in each foal after transfusion. The study showed that total protein, IgG and *R.equi* specific antibodies increased after each transfusion to these foals which had had Normal Passive Transfer. For such foals the study supported the claim that the product raises levels of circulating *R.equi* specific antibodies.

Field Trials

The company presented the results of a study designed to evaluate field safety and efficacy of equine plasma containing specific antibodies to *R.equi*. (Hypermune RE) following Intravenous administration to 2 day old foals with normal and low levels of serum IgG, and following a second transfusion at 29 days of age.

Results of this study supported the laboratory study in that there was an increase in equine IgG and *R.equi* specific antibodies after each transfusion as claimed on the SPC.

A further study was conducted to gather data to support the prophylactic[1] efficacy of passively derived *R.equi* specific antibodies in reducing the incidence and severity of disease associated with *R.equi* infection.

[1] prophylaxis means to prevent the development of a disease

A group of 2 day old foals from two different foaling seasons (2002 and 2003) were used. Foals were assigned a case number and their date of birth and history recorded. All 2003 foals were treated with 1 litre of Hypermune RE on two occasions 28 days apart. Blood samples were collected at 12-36 hrs of age and analysed for IgG and *R.equi* antibodies. The age of onset of disease, severity and duration of treatment were also recorded.

There was a decrease of 20% in the incidence of *R.equi* infections in the foals treated with Hypermune RE in 2003 compared to the incidence in untreated foals in 2002. Those that did develop the disease in 2003 were classified as non-severe cases. Weather records showed that spring 2003 had less rainfall and more sunshine. These conditions favour *R.equi* proliferation and increased levels of dust in paddocks which is also a factor predisposing to disease. Although the numbers were small, the incidence of *R.equi* disease in 2003 was considerably reduced compared to 2002 therefore it appears the use of Hypermune RE may have reduced the incidence of *R.equi* on this farm.

In 2006 a field study was conducted on a large stud farm with a severe Rhodococcus problem. In the study a group of foals received Hypermune RE at approximately 1 day old and a second dose was administered approximately 28 days later; a second group of foals received ordinary plasma, at the same ages and another group of foals received no plasma. Samples were collected for analysis and clinical observations made and recorded in compliance with the study protocol.

The final report demonstrates that following the first transfusion at day 1, there was a significant rise in anti-*R.equi* antibodies in the group that had received Hypermume RE. In contrast, there was no significant rise in anti-*R.equi* antibodies in the group receiving normal plasma. Following the second transfusion at day 30, similar observations were made in the two groups.

The clinical data indicated that of the foals which received Hypermune RE two thirds required no treatment and demonstrated fewer lung abscesses than the foals in each of the other groups. In contrast, out of the group which received alternative plasma half did require treatment; and of those which received no plasma, just over two thirds required treatment. It was also noted that in the group that received no plasma the majority of affected foals were seroconverting, but in spite of developing high levels of antibody significant disease and significant pathology became evident. This was not the case with the foals receiving Hypermune RE although the levels of *R.equi* antibody were lower during the week prior to the second transfusion.

This study supports the claim that Hypermune RE augments the foal's immune system with specific anti-*R.equi* antibody to pathogenic strains.

Hypermune RE can contribute to a significant reduction in the amount and severity of disease caused by *Rhodococcus equi* in foals
It was noted in the study report that the foals receiving Hypermune RE co existed with foals which did not. Therefore, it is reasonable to assume that the exposure to infection was greater than if the whole population had received Hypermune RE

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)