Rhophylac®

(Anti RhD Immunoglobulin)

Public Summary of Risk Management Plan

(Extract from the EU Risk Management Plan Version 4.0; June 2015)

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Rh incompatibility is a condition that occurs during pregnancy if a woman has Rh-negative blood and her baby has Rh-positive blood. "Rh-negative" and "Rh-positive" refer to whether the patient´s blood has Rh factor. Rh factor is a protein on red blood cells. If a patient has Rh factor, the patient is Rh-positive. If the patient doesn't have it then the patient is Rh-negative. Rh factor is inherited (passed from parents to children through the genes). Most people are Rh-positive.

Whether the patient has Rh factor doesn't affect the patient´s general health. However, it can cause problems during pregnancy.

During pregnancy, red blood cells from the unborn baby can cross into the mother's bloodstream through the placenta. If the mother is Rh-negative, her immune system treats Rh-positive fetal cells as if they were a foreign substance and makes antibodies against the fetal blood cells. These anti-Rh antibodies may cross back through the placenta into the developing baby and destroy the baby's circulating red blood cells. Because it takes time for the mother to develop antibodies, firstborn infants are often not affected unless the mother had past miscarriages or abortions that sensitized her immune system. However, all children she has afterwards who are also Rh-positive may be affected.

In a large prospective series including over 300,000 consecutive patients, about 1% of pregnant women had alloantibodies (an antibody that occurs naturally against foreign tissues from a person of the same species) detected in the first trimester. Of these, about 60% were not associated with a risk of Rh incompatibility of the fetus and newborn; the remaining 40% consisted of anti-D antibodies (8% of the total) and non-anti-D antibodies associated with a risk of Rh incompatibility of the fetus and newborn (32% of the total).

Population data suggest that the incidence of RhD negativity is highest among Basques (36%). Seven percent of black people have this blood type. Less than 1% of the Native American and Asian populations have this phenotype. In the UK, about 16% of the white population is RhD negative.

In 2005, it was estimated that about 65,000 RhD-positive babies were born in the UK to women who were RhD negative (accounting for 10% of all births). In the US, the Centers for Disease Control and Prevention reported in 1991 the incidence of Rh haemolytic disease to be 1 in 1000 live births.

VI.2.2 Summary of treatment benefits

Injections of Rh immune globulin can keep the mother´s body from making Rh antibodies. This medicine helps prevent the problems of Rh incompatibility. If a mother is Rh-negative, she will need this medicine every time she has a baby with Rh-positive blood.

Other events also can expose a woman to Rh-positive blood, which could affect a pregnancy. Examples include a miscarriage, invasive prenatal tests during pregnancy, injury to the abdomen during pregnancy or blood transfusion. If the women are treated with Rh immune globulin right after these events, Rh incompatibility during the next pregnancy can be avoided.

The treatment benefit with RhD immunoglobulins is that Rh incompatibility is almost completely preventable.

If the father of the infant is Rh-positive or if his blood type cannot be confirmed, the mother is given an injection of Rh immunoglobulin during the second trimester. If the baby is Rh-positive, the mother will get a second injection within a few days after delivery.

Rhophylac has been shown to be effective in clinical trials with 592 Rh (D) negative women.

Unknowns relating to treatment benefits

To date no unknowns relating to treatment benefits have been identified.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe allergic reaction accompanied by fall in blood pressure (hypotension) or a shock-like state (Hypersensitivity/anaphylactic reactions)	Anaphylaxis was rare and affects 1 to 10 users in 10,000. If a woman has a known allergy to human immunoglobulins, human albumin or to any of the other ingredients of Rhophylac, the woman is at increased risk. No death cases were reported-even with severe reactions.	Do not use Rhophylac in patients who have an allergy to • human immunoglobulins, • human albumin or to any of the other ingredients of Rhophylac.

Risk	What is known	Preventability
The risk of lack of efficacy with IM administration in obese patients	Reports on lack of effect in obese women in connection with intramuscular administration of Rhophylac have been received. Intramuscular injection in obese individuals may not reach the intended site and is deposited into fatty tissue from which absorption is erratic and incomplete.	The administration of Rhophylac into a vein is recommended when Rhophylac is administered to obese women.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)	Preventability
Haemolysis in Off label use treatment of immune thrombocytopenic purpura (ITP) in Rh(D) positive individuals	Use of Rhophylac in ITP is not approved in the European Economic Area (EEA) but it is approved in countries outside the EEA and is also discussed in the scientific literature. There is a chance that some doctors in the EEA may want to use Rhophylac in ITP, thereby it becomes an “off label use". One complication which has been reported to be associated with the use in ITP is the occurrence of haemolysis, i.e. when red blood cells are destroyed by the anti-D antibodies that are contained in Rhophylac. Only very few cases have been reported for Rhophylac.	Rhophylac should only be used in patients who are Rh (D) negative, as described in the product information

Risk	What is known (Including reason why it is considered a potential risk)	Preventability
Transmission of infectious agents	Rhophylac is made from human blood plasma (this is the liquid part of the blood). When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include: ● Careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and ● The testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses and other types of infections. The measures taken for Rhophylac are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus and hepatitis C virus. The measures may	Doctors may recommend to consider a vaccination against hepatitis A and B if patients regularly/repeatedly received human plasma derived products. It is strongly recommended that every time that Rhophylac is given, the date of administration, the batch number and the injected volume should be recorded.

Risk	What is known (Including reason why it is considered a potential risk)	Preventability
	be of limited value against non-enveloped viruses such as hepatitis A virus and parvovirus B19. Immunoglobulins like Rhophylac have not been associated with hepatitis A or parvovirus B19 infections. This is possibly because antibodies against these infections are also present in immunoglobulins. These antibodies may help prevent hepatitis A or parvovirus B19 infections.	

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The Summary of Product Characteristics and the Package leaflet for Rhophylac can be found in the Rhophylac's EPAR page.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

No studies are planned or ongoing.

Studies which are a condition of the marketing authorisation

There are no studies that are a condition of marketing authorization.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	Rev:30-Nov-2010/ version 2.0	Updated according to Volume 9A of the Rules Governing Medicinal Products in the European Union and according to the EU RMP template (EMEA/192632/2006), respectively.	Formal update. No change to the Pharmacovigilance System