SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

IMMUNORHO 200 micrograms (1000 IU) Powder and solvent for solution for injection for intramuscular use
IMMUNORHO 300 micrograms (1500 IU) Powder and solvent for solution for injection for intramuscular use
IMMUNORHO 300 micrograms (1500 IU) Solution for injection for intramuscular use

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human anti-D immunoglobulin

Each 2 ml vial contains respectively 1000* IU or 1500* IU human anti-D immunoglobulin according to the pack size.
Each 2 ml pre-filled syringe contains 1500* IU human anti-D immunoglobulin.

*100 micrograms of human anti-D immunoglobulin correspond to 500 International Units (IU).

1 ml of solution for injection after reconstitution of the freeze-dried product with the solvent ampoule and 1 ml of solution for injection in pre-filled syringe contain:

	IMMUNORHO 300 micrograms (1500 IU) Vial	**IMMUNORHO 200 micrograms (1000 IU)** Vial	**IMMUNORHO 300 micrograms (1500 IU)** Pre-filled syringe
Human protein	25 - 180 g/l	25 - 180 g/l	25 - 180 g/l
of which IgG at least	90%	90%	90%
antibodies against the D antigen not less than	750 IU	500 IU	750 IU

The potency is determined using the European Pharmacopoeia assay. The equivalence in International Units of the International Reference Preparation is stated by the World Health Organization

Distribution of IgG subclasses (approximate values) :
IgG_1 66.0%
IgG_2 30.0%
IgG_3 2.5%
IgG_4 1.5%

The maximum content of IgA is 300 micrograms/ml
Produced from the plasma of human donors.

Excipient with known effect:
This product contains up to a maximum of 7.8 mg sodium per vial or 2 ml pre-filled syringe.

This is a translation of the Italian Summary of Product Characteristics (SPC).
As not all the information given applies to your country, please refer to your local SPC.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection
The freeze-dried preparation is a hygroscopic, white or slightly yellow powder or a solid, friable mass.

Solution for injection
The liquid preparation is clear and colourless or pale-yellow or light brown. During storage it may show formation of slight turbidity or a small amount of suspended particulate matter

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Rh(D) immunisation in Rh(D) negative childbearing age women

- Antenatal prophylaxis
  - Planned antenatal prophylaxis
  - Antenatal prophylaxis following complications of pregnancy including:

    Abortion/threatened abortion, ectopic pregnancy or hydatidiform mole, intrauterine fetal death (IUFD), transplacental haemorrhage (TPH) resulting from ante-partum haemorrhage (APH) , amniocentesis, chorionic biopsy, obstetric manipulative procedures e.g. external version, invasive interventions, cordocentesis, blunt abdominal trauma or fetal therapeutic intervention.

- Postnatal prophylaxis
  - Delivery of a Rh(D) positive (D, D^{weak}, $D^{partial}$) baby

Treatment of Rh(D) negative childbearing age women after incompatible transfusions of Rh(D) positive blood or other products containing red blood cells e.g. platelet concentrate.

4.2 Posology and method of administration

Posology

The dose of anti-D immunoglobulin should be determined according to the level of exposure to Rh(D) positive red blood cells and considering that 0.5 ml of packed Rh(D) positive red blood cells or 1 ml of Rh(D) positive blood is neutralised by approximately 10 micrograms (50 IU) of anti-D immunoglobulin.
Consideration should also be given to dose and dose schedule for human anti-D immunoglobulin for intramuscular use recommended in other official or Member States guidance
Prevention of Rh(D) immunisation in Rh(D) negative women:

- Antenatal prophylaxis. According to general recommendations, currently administered doses range from 50 – 330 micrograms or 250 - 1650 IU.
  - Planned antenatal prophylaxis:

A single dose at 28 - 30 weeks of gestation or two doses at 28 and 34 weeks.

- Antenatal prophylaxis following complications of pregnancy:
  A single dose should be administered as soon as possible and within 72 hours and if necessary repeated at 6 – 12 week intervals throughout the pregnancy.

- Postnatal prophylaxis. According to general recommendations, currently administered doses range from 100 to 300 micrograms or 500 to 1500 IU. If the lower dose (100 micrograms or 500 IU) is administered, a test should be performed to determine the extent of foetal-maternal haemorrhage.

  For postnatal use, the product should be administered to the mother as soon as possible within 72 hours of delivery of an Rh positive (D, D^{weak},$D^{partial}$) infant. If more than 72 hours have elapsed, the product should not be withheld but administered as soon as possible.

  The postnatal dose must still be given even when antenatal prophylaxis has been administered and even if residual activity from antenatal prophylaxis can be demonstrated in maternal serum.

If a large foeto-maternal haemorrhage [> 4 ml (0.7%-0. 8% of women)] is suspected, e.g. in the event of foetal/neonatal anaemia or intrauterine foetal death, its extent should be determined by a suitable method e.g. Kleihauer-Betke acid elution test to detect foetal HbF (foetal hemoglobin) or flow cytometry which specifically identifies Rh(D) positive cells. Additional doses of anti-D immunoglobulin should be administered accordingly (10 micrograms or 50 IU per 0.5 ml foetal red blood cells).

Incompatible transfusions of red blood cells.

The recommended dose is 20 micrograms (100 IU) of anti-D immunoglobulin per 2 ml of transfused Rh(D) positive blood or per 1 ml of RBC concentrate.
It is recommended the consultation with a specialist in transfusion medicine in order to evaluate the feasibility of a red cell exchange procedure to reduce the load of D positive red cells in circulation and to define dose of anti-D immunoglobulin required to suppress immunization. Follow-up tests for D-positive red cells should be performed every 48 hours and additional anti-D should be administered until there are no detectable D-positive red cells in circulation. In any case, due to possible risk of haemolysis it is suggested to not exceed a maximum dose of 3000 micrograms (15000 IU).
The use of an alternative intravenous product is recommended as it allows to achieve adequate plasma levels immediately. If no intravenous product is available, a very high dose should be administered intramuscularly for a period of several days (see section 4.4).

Paediatric population
The safety and efficacy of IMMUNORHO in children have not been established. The appropriate dosage should be calculated with the advice of a specialist in transfusion medicine.

Method of administration

Intramuscular use
If a large volume (> 2 ml for children or > 5 ml for adults) is required, it is recommended to administer the medicine in divided doses at different sites.

If intramuscular administration is contraindicated (bleeding disorders), an alternative intravenous product should be used.

Overweight patients

In case of overweight/obese patients the use of an intravenous anti-D product must be considered (see section 4.4).

For instruction on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

4.4 Special warnings and precautions for use

Ensure that IMMUNORHO is not administered into a blood vessel, because of the risk of shock.
In case of postnatal use, the product is intended for maternal administration. It should not be given to the new-born infant.

Hypersensitivity

True hypersensitivity reactions are rare, but allergic type responses to anti-D immunoglobulin may occur.
IMMUNORHO contains a small quantity of IgA. Although anti-D immunoglobulin has been used successfully in selected IgA deficient individuals, individuals who are deficient in IgA have the potential for developing anti-IgA antibodies and may have anaphylactic reactions after administration of plasma derived medicinal products containing IgA. The physician must therefore weigh the benefit of treatment with IMMUNORHO against the potential risks of hypersensitivity reactions.
Rarely, human anti-D immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who have tolerated previous treatment with human immunoglobulin.
Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

Haemolytic reactions

Patients receiving very high doses of anti-D immunoglobulin due to incompatible transfusion, should be monitored clinically and by biological parameters because of the risk of haemolytic reaction.

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Although thromboembolic events have not been observed in patients receiving IMMUNORHO, those patients should be sufficiently hydrated before use of immunoglobulins.
Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity), especially when high doses of IMMUNORHO are prescribed.
Patients should be informed about first symptoms of thromboembolic events including dyspnea, pain and swelling of a limb, focal neurological deficits and chest pain, and should be advised to contact their physician immediately upon onset of symptoms.

Interference with serological testing
After injection of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies (e.g. Coombs' test) particularly in Rh(D) positive neonates whose mothers have received antenatal prophylaxis.

Overweight/obese patients
In overweight/obese patients, due to the possible lack of efficacy in case of intramuscular administration, an intravenous anti-D product is recommended.

Information on safety with respect to transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses.
Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV).
The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.
There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that IMMUNORHO is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Warnings on excipients
This medicinal product contains up to 7.8 mg sodium per vial or prefilled syringe of 2 ml, equivalent to 0.38 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population
No specific measures or monitoring are required for the paediatric population.

4.5 Interactions with other medicinal products and other forms of interactions

Live attenuated virus vaccines
Active immunisation with live virus vaccines (e.g. measles, mumps or rubella) should be postponed for 3 months after the last administration of anti-D immunoglobulin, as the efficacy of the live virus vaccine may be impaired.
If anti-D immunoglobulin needs to be administered within 2-4 weeks of a live virus vaccination, the efficacy of such a vaccination may be impaired.

Paediatric population.
Although specific interaction studies have not been performed in the paediatric population, no difference between adults and children is to be expected.

4.6 Fertility, pregnancy and lactation

Pregnancy
This medicinal product is intended for use in pregnancy.

Breast-feeding
This medicinal product can be used during breast-feeding. Immunoglobulins are excreted in human milk.

Fertility
No studies have been conducted on fertility with IMMUNORHO. Clinical experience with human anti-D immunoglobulin suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

IMMUNORHO has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.
Rarely human immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administrations.
Local reactions at infusion site: swelling, soreness, redness, induration, local heat, itching, bruising and rash.

Tabulated list of adverse reactions
The table below has been drawn up according to the MedDRA system organ classification (SOC and Preferred Term Level) . The table reports undesirable effects associated with the use of human anti-D immunoglobulin for intramuscular use.

There are no robust data on the frequency of adverse reactions derived from clinical trials.

Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity, anaphylactic shock	not known
Nervous system disorders	Headache	not known
Cardiac disorders	Tachycardia	not known

MedDRA System Organ Class	Adverse reaction	Frequency
Vascular disorders	Hypotension	not known
Gastrointestinal disorders	Nausea, vomiting	not known
Skin and subcutaneous tissue disorders	Skin reaction, erythema, itching pruritus	not known
Musculoskeletal and connective tissue disorders	Arthralgia	not known
General disorders and administration site conditions	Fever, malaise, chill At the injection site: swelling, pain, erythema, induration, warmth, pruritus, rash, itching.	not known

Paediatric population
No specific data are available on paediatric population.

For safety with respect to transmissible agents, see section 4.4.

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.

4.9 Overdose

Consequences of an overdose are not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins, immunoglobulins, specific immunoglobulins: anti-D (Rh) immunoglobulin; ATC code: J06BB01.
Anti-D immunoglobulin contains specific antibodies (IgG) against the D (Rh) antigen of human erythrocytes.

During pregnancy, and especially at the time of childbirth, fetal red blood cells may enter the maternal circulation. When the woman is Rh(D)-negative and the fetus Rh(D)-positive, the woman may become immunised to the Rh(D) antigen and produce anti-Rh(D) antibodies which cross the placenta and may cause haemolytic disease of the newborn. Passive immunisation with anti-D immunoglobulin prevents Rh(D) immunisation in more than 99% of cases provided that a sufficient dose of anti-D immunoglobulin is administered soon enough after exposure to Rh(D)-positive fetal red blood cells.
The mechanism by which anti-D immunoglobulin suppresses immunisation to Rh(D)-positive red cell is not known. Suppression may be related to the clearance of the red cells from the circulation before they reach immunocompetent sites or, it may be due to more complex mechanisms involving recognition of foreign antigen and antigen presentation by the appropriate cells at the appropriate sites in the presence or absence of antibody.

Paediatric population

No specific studies of efficacy and safety are available on paediatric population.

5.2 Pharmacokinetic properties

Human anti-D immunoglobulins for intramuscular administration is slowly absorbed into the recipient's circulation and reaches a maximum after a delay of 2-3 days.
Human anti-D immunoglobulin has a half-life of about 3-4 weeks. This half-life may vary from patient to patient.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Paediatric population
No specific studies of efficacy and safety are available on paediatric population.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body.
In animals single dose toxicity testing is of no relevance since higher doses result in overloading. Repeated dose toxicity testing and embryo-foetal toxicity studies are not practicable due to the induction of and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied.
Since clinical experience provides no hint for carcinogenic and mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder and solvent for solution for injection

Powder ampoule:
Glycine
Sodium chloride
Solvent vial
Water for injections

Solution for injection in pre-filled syringe
Glycine
Sodium chloride
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

3 years.
Reconstituted product should be used immediately.

6.4 Special precautions for storage

Powder and solvent for solution for injection
Store below 25°C.
Do not freeze.
Keep in the original container and in the outer carton in order to protect from light.

Solution for injection
Store in a refrigerator . (2°C - 8°C)
Do not freeze.
Keep in the original container and in the outer carton in order to protect from light.

6.5 Nature and contents of container

IMMUNORHO 200 micrograms (1000 IU):
Type I glass vial containing 200 micrograms of powder; Type I glass ampoule containing 2 ml of solvent;

IMMUNORHO 300 micrograms (1500 IU):
Type I glass vial containing 300 micrograms of powder; Type I glass ampoule containing 2 ml of solvent;

2 ml of solution in pre-filled syringe (type I glass), with a plunger stopper made of rubber (halobutyl) and pre-sealed needle.

6.6 Special precautions for disposal and handling

Powder and solvent for solution for injection
IMMUNORHO should be brought to room or body temperature before use.

1. Remove the central protection from the rubber stopper containing the freeze-dried;
2. Draw the content of the solvent ampoule with an injection syringe;
3. Inject the liquid into the vial containing the freeze-dried. During this phase, make sure not to lacerate the rubber stopper of the vial in order to avoid contamination of the reconstituted solution;
4. Gently shake and draw the reconstituted solution with the syringe; change the needle and inject.

The imperfect solubilisation results in a loss of potency.
Total reconstitution should be obtained on overage within 5 minutes.
The product after reconstitution is a colourless to pale-yellow liquid. Reconstituted products should be inspected visually for the possible particulate matter or discoloration prior to administration.
Do not use solutions that are cloudy or have deposits.

The freeze-dried product should be used immediately after reconstitution with the solvent.

Solution for injection
The product should be brought to room or body temperature before use.
The liquid preparation is clear and colourless or pale-yellow or light brown. Do not use solutions that are cloudy or have deposits.
Screw in the plunger shaft of the pre-filled syringe and inject.

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

7 MARKETING AUTHORISATION HOLDER

Kedrion S.p.A. - Loc. Ai Conti, 55051 Castelvecchio Pascoli, Barga (Lucca), Italy.

8 MARKETING AUTHORISATION NUMBERS

In Italy

IMMUNORHO "200 mcg powder and solvent for solution for injection for intramuscular use" 1 powder vial 10 ml + 1 solvent ampoule 2 ml
n° 022547020
IMMUNORHO "300 mcg powder and solvent for solution for injection for intramuscular use" 1 powder vial 10 ml + 1 solvent ampoule 2 ml
n° 022547018
IMMUNORHO "300 mcg solution for injection for intramuscular use" Pre-filled syringe of 2 ml
n° 022547044

In Ethiopa

IMMUNORHO "300 mcg powder and solvent for solution for injection for intramuscular use" 1 powder vial 10 ml + 1 solvent ampoule 2 ml

First authorization n°: KED/ITA/001

Renewal authorization n°: 05660/07488/REN/2020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION IN ETHIOPIA

Date of first authorisation: 06 December 2016
Date of latest renewal: 12 February 2021

10 DATE OF REVISION OF THE TEXT IN ITALY

30 September 2018

This is a translation of the Italian Summary of Product Characteristics (SPC).
As not all the information given applies to your country, please refer to your local SPC.