(English translation of official Dutch version)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VariQuin 200 IU solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human varicella immunoglobulin prepared from plasma of human donors.

The product contains 100 - 180 grams of protein per litre. The protein fraction consists of at least 90 % immunoglobulin G (IgG). The varicella antibody concentration is at least 100 IU/ml. The maximum IgA concentration is 6 g/l.

VariQuin is dispensed in a filling size of 200 IU.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection for intramuscular administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis against varicella zoster virus (VZV) infection in at risk patients exposed to varicella (chickenpox) or herpes zoster:

- pregnant women with negative VZV immune status especially up to early in the third trimester
- neonates whose mothers develops varicella infection within 7 days before and 7 days after delivery
- neonates whose mothers have no history of varicella and/or a negative immune status
- premature infants <28 weeks of gestation or new-borns with low birth weight
- adults and children with no history of varicella and/or a negative immune status, receiving immunosuppressive therapy including steroids, cytostatic agents, radiotherapy, recent stem cell transplantation, or who have congenital or acquired immunodeficiency disorders and are not receiving replacement therapy with immunoglobulin.

4.2 Posology and method of administration

Posology:
Newborns with body weight up to 2 kg: 1 ml
Persons with body weight of 2-10 kg: 1 vial of 2 ml
Persons with body weight of 10-30 kg: 2 vials of 2 ml
Persons with body weight of more than 30 kg: 3 vials of 2 ml

Administration to neonates where the mother has experienced varicella in the period from 7 days before to 7 days after delivery should be carried out as soon as possible.
In other cases administration should be carried out as soon as possible, preferably within 3 days, but

at the latest within 10 days after the contact with a varicella patient.

It is recommended that the administration be repeated if re-exposure takes place more than three weeks after the first administration.

Method of administration:
Human varicella immunoglobulin should be administered slowly and deep via the intramuscular route. It is recommended that the product is brought to body temperature before administration.

If a large volume (>2 ml for children or >5 ml for adults) is required, it is recommended to administer this in divided doses at two sites.

If intramuscular administration is contraindicated (haemorrhagic diathesis) the injection can be administered subcutaneously. However, it should be noted that there are no clinical efficacy data to support administration by the subcutaneous route.

4.3 Contra-indications

Hypersensitivity to any of the components.

Hypersensitivity to human immunoglobulins.

4.4 Special warnings and special precautions for use

Ensure that VariQuin is not administered into a blood vessel, because of the risk of shock.

True hypersensitivity reactions are rare.

It is not worthwhile to administer VariQuin in cases where varicella is clinically manifest.

VariQuin does not prevent herpes zoster in persons who have had varicella, or who exhibit antibodies against varicella zoster virus. Nor is the course of herpes zoster affected by the product.

VariQuin contains a small quantity of IgA. Individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA. The physician must therefore weigh the benefit of treatment with VariQuin against the potential risks of hypersensitivity reactions.

Rarely, human varicella 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.

<u>Thromboembolism</u>
Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as advanced age, 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). Patients should be informed about first symptoms of thromboembolic events including shortness of breath, 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.

Patients should be observed at least 20 minutes after administration.

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 virus hepatitis A virus. 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. It is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that VariQuin 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.

4.5 Interactions with other medicinal products and other forms of interaction

Live attenuated virus vaccines
Immunoglobulin administration may interfere with the development of an immune response to live attenuated virus vaccines such as rubella, mumps and varicella for a period of up to 3 months. After administration of this product, an interval of at least 3 months should elapse before vaccination with live attenuated virus vaccines.

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 tests.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B and D, may interfere with some serological tests for red cell allo-antibodies, for example the antiglobulin test (Coombs’ test).

4.6 Pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

4.7 Effects on ability to drive and use machines

There are no indications that immunoglobulins may impair the ability to drive or use machines.

4.8 Undesirable effects

There are no robust data on the frequency of undesirable effects from clinical trials. The following

undesirable effects have been reported:

MedDRA Standard System Organ Class	Undesirable effect	Frequency
Immune system disorders	Hypersensitivity, anaphylactic shock*	Rare
Nervous system disorders	Headache	Rare
Cardiac disorders	Tachycardia	Rare
Vascular disorders	Hypotension	Rare
Gastrointestinal disorders	Nausea, vomiting	Rare
Skin and subcutaneous tissue disorders	Skin reaction, erythema, pruritis	Rare
Musculoskeletal and connective tissue disorders	Arthralgia	Rare
General disorders and administration site conditions	Fever, malaise, chills At the injection site: pain and sensitivity**, swelling, erythema, induration, warmth, pruritis, rash	Rare Not known***

* Please refer to section 4.4 “Special warnings and precautions for use” for an explanation.
** This can be reduced by dividing larger doses over several injection sites.
*** Not known: cannot be estimated from the available data.
See section 4.4 for safety with regards to transmissible agents.

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 Netherlands Pharmacovigilance Centre Lareb, website: www.lareb.nl.

4.9 Overdose

Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins

– Human varicella immunoglobulin ATC code: J06BB03

Human varicella immunoglobulin contains mainly immunoglobulin G (IgG) with a specifically high content of antibodies against varicella zoster virus.

5.2 Pharmacokinetic properties

Following intramuscular administration, the immunoglobulin administered to the patient is gradually released into the circulation from the intramuscular depot. The maximum concentration is achieved after two to three days.

Human varicella 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.

5.3 Preclinical safety data

Immunoglobulins are normal components of the human body. Animal studies of the toxicity following a single administration are not relevant, as higher doses will result in an overdose. Research into the toxicity of repeated administration and the toxicity for the embryo/foetus cannot be performed due to the induction of and the disruption by antibodies. No research has been performed into the effects of the product on the immune system of neonates.
As clinical research has not revealed any indications for oncogenic or mutagenic effects of immunoglobulins, experimental studies – particularly in heterologous species – is not deemed necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, 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.
The product should be used immediately after piercing the vial.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

VariQuin is supplied in a colourless glass vial (of glass type I) fitted with a bromobutyl rubber stopper and sealed with an aluminium cap. The filling size is 2 ml.

6.6 Special precautions for disposal and other handling

The product should preferably be brought to body temperature before use.

The colour can vary from colourless to pale-yellow up to light brown. During the storage period, a slight cloudiness or formation of a small amount of precipitation might occur. This is no impediment to clinical use.

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

7. MARKETING AUTORISATION HOLDER

Sanquin Plasma Products B.V.

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1066 CX Amsterdam
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8. MARKETING AUTORISATION NUMBER(S)

RVG 16948.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 February 1997

10. DATE OF REVISION OF THE TEXT

Latest partial revision concerns section 4.4: 14 September 2016