SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TEGELINE 50 mg/ml, powder and solvent for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin* ..... 50 mg
per 1 ml of reconstituted solution

After reconstitution:
- 10 ml vial contains 0.5 g of human normal immunoglobulin,
- 50 ml vial contains 2.5 g of human normal immunoglobulin,
- 100 ml vial contains 5 g of human normal immunoglobulin,
- 200 ml vial contains 10 g of human normal immunoglobulin.

* The powder contains a maximum IgA content of 17 mg/g of protein and contains traces of pepsin of animal origin.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- ***Replacement therapy in:***
  - primary immunodeficiency with hypogammaglobulinaemia or functional humoral immunodeficiency,
  - children with congenital AIDS and recurrent infections,
  - secondary immunodeficiency of humoral immunity, in particular:
    - chronic lymphatic leukaemia or myeloma with hypogammaglobulinaemia associated with recurrent infections,
    - allogeneic bone marrow transplantation with hypogammaglobulinaemia associated with an infection.

- ***Immunomodulation:***
  - idiopathic thrombocytopenic purpura (ITP) in adults or children at high risk of bleeding or prior to undergoing a medical or surgical procedure, in order to correct the platelet count,
  - Birdshot retinochoroidopathy,
  - Guillain Barré syndrome in adults,
  - Multifocal motor neuropathy (MMN)

- ***Kawasaki disease***

4.2. Posology and method of administration

Posology

The dose and dosage regimen is dependant on the indication (replacement therapy or immunomodulation) and the half-life of the intravenous normal human immunoglobulin (IVIg) *in vivo* in immunodeficient patients.

The following dosage regimens are given as a guideline:

- **Replacement therapy in primary immunodeficiency syndromes:**

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/l. In the presence of persistent infections, trough IgG levels could be brought to 8 or 10 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4-0.8 g/kg depending on the circumstances (infection), followed by at least 0.2 g/kg every 3 weeks. The dose required to obtain trough levels of 6 g/l is approximately 0.3 g/kg/month with a range of 0.2-0.8 g/kg/month. The dosage interval when steady state has been reached varies from 2-4 weeks. More frequent infusions can be required if the patient develops infections.
In replacement treatment of primary immunodeficiency, serum IgG concentrations must be measured prior to each infusion in order to monitor the activity of treatment and, where applicable, to adjust the dose or administration interval.

- **Replacement therapy in secondary immunodeficiency:**

The recommended dose is 0.2-0.4 g/kg every three to four weeks in order to maintain trough IgG levels (measured before the next IVIg infusion) of at least 4 to 6 g/l.

Replacement therapy for primary and secondary immunodeficiencies can be administered at home in patients previously treated with TEGELINE in the hospital for at least 6 months without adverse events. The administration must be initiated and monitored by a nurse or an individual having received specific training from the hospital team responsible for the patient.

- **Idiopathic Thrombocytopenic Purpura (ITP):**

For the treatment of an acute episode, 0.8-1 g/kg/day on day one, which may be repeated once within 3 days, or 0.4 g/kg daily for 2 to 5 days. The treatment can be repeated if severe relapse occurs.

- **Treatment of Birdshot retinochoroidopathy:**

The initial dose is 1.6 g/kg over 2 to 4 days, every 4 weeks for 6 months. Maintenance doses are 1.2 g/kg over 2 to 4 days every 4 to 10 weeks.

- **Guillain-Barré syndrome in adults:**

0.4 g/kg/day for 5 days.

- **Multifocal Motor Neuropathy (MMN)**

The posology for the initial treatment is 2 g/kg administered over 2 to 5 days and repeated every 4 weeks for 6 months.
The posology for maintenance treatment is 2 g/kg administered over 2 to 5 days. The interval between TEGELINE administrations and the duration of maintenance treatment should be adapted to the time until reappearance of symptoms in each individual patient.
In the absence of therapeutic effects, treatment with TEGELINE could be interrupted after a minimum of 3 months and a maximum of 6 months of treatment.

- **Kawasaki disease:**

1.6 to 2.0 g/kg should be administered in divided doses over 2 to 5 days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Posology and method of administration

Indication	Dose	Frequency of injections	Associated treatment
Replacement therapy:			
Primary immunodeficiency	- Starting dose: 0.4-0.8 g/kg - Maintenance dose: 0.2-0.8 g/kg	every 2-4 weeks to obtain trough IgG level of at least 6 g/l. In the presence of persistent infections, trough IgG levels could be brought to 8 or 10 g/l.	
Secondary immunodeficiency	0.2-0.4 g/kg	every 3-4 weeks to obtain trough IgG level of at least 4-6 g/l	
Immunomodulation:			
Idiopathic thrombocytopenic purpura	0.8-1 g/kg or 0.4 g/kg/day	on day 1, possibly repeated once within 3 days for 2-5 days	
Birdshot retinochoroiditis	- Starting dose: 1.6 g/kg over 2-4 days - Maintenance dose: 1.2 g/kg over 2-4 days	every 4 weeks for 6 months every 4-10 weeks	
Guillain-Barré syndrome in adults	0.4 g/kg/day	for 5 days	
Multifocal Motor Neuropathy (MMN)	- Starting dose : 2 g/kg over 2-5 days -Maintenance dose : 2 g/kg over 2-5 days	every 4 weeks for 6 months The interval between TEGELINE administrations and the duration of maintenance treatment should be adapted to the time until reappearance of symptoms in each individual patient.	
Kawasaki disease	1.6-2.0 g/kg or 2 g/kg	in several doses for 2-5 days in one dose	acetylsalicylic acid

Method of administration

TEGELINE is presented in the form of a powder to be reconstituted at the time of use with water for injections as described in the instructions shown in the section entitled "Instructions for use, handling and disposal".

IVIg must only be infused intravenously as a single dose immediately after reconstitution.

Flow rates should be adjusted to take account of clinical tolerability and should not exceed 1 ml/kg/h during the first half hour. They may then be increased gradually to a maximum of 4 ml/kg/h.

Do not use solution which is cloudy or has deposits.

4.3. Contraindications

This medicinal product is contraindicated in the following situations:

- Hypersensitivity to homologous immunoglobulins, especially in cases of IgA deficiency when the patient has antibodies against IgA.
- Hypersensitivity to any of the components in the preparation.

4.4. Special warnings and special precautions for use

Diagnosis of Multifocal Motor Neuropathy (MMN) requires clinical examination in a certified reference centre for peripheral neuropathies or neuromuscular diseases.

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under section entitled "Posology and method of administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently:
- in case of high rate of infusion (see section "Method of administration"),
- in patients with hypo- or agammaglobulinemia, with or without IgA deficiency, especially during the first IVIg infusion or if the previous IVIg treatment was more than 8 weeks prior.

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies.

Rarely, IVIg can induce a sudden fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Potential complications can often be avoided by ensuring:
- that infusion rates are carefully monitored;
- the tolerability of the IVIg dose by administering a slow initial infusion (1 ml/kg/h);
- that the glucose content (2g/g of IgG) is taken into account in case of latent diabetes, where transient glycosuria could appear, diabetes or low sugar diet;
- that patients are carefully monitored throughout the infusion period in order to detect potential signs of intolerance.

There is a greater risk of arterial and venous thrombosis in association with rapid intravenous infusions (see section 4.2. "Method of administration"), especially in patients at risk for vascular complications.

Cases of acute renal failure have been reported in patients receiving IgIV therapy. In most cases, risk factors have been identified, such as a pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, the concomitant use of nephrotoxic drugs or age over 65.

In these patients, IVIg administration requires:
- adequate hydration prior to the initiation of the IVIg infusion,
- monitoring of urine output,
- measuring serum creatinine levels,
- avoidance of concomitant use of loop diuretics.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number.
In patients at risk, the use of IVIg products that do not contain sucrose may be considered.

The infusion should be stopped immediately if any allergic or anaphylactic reactions occur. In case of shock, the standard medical treatment for shock should be implemented.

Patients should be kept under observation for at least 20 minutes after the end of the infusion. In the case of a first IVIg infusion, patients should be kept under observation for at least 1 hour after the end of the infusion.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to the transmission of infective agents cannot be totally excluded. This also applies to pathogens of hitherto unknown nature. The risk of transmission of infective agents is however reduced by:
- selection of donors by a medical interview and screening of each donation for the three major pathogenic viruses HIV, HBV, HCV;
- testing of plasma pools for hepatitis C virus genomic material;
- removal/inactivation procedures included in the production process that have been validated using model viruses and are considered effective for HIV, HBV and HCV.

The viral removal/inactivation procedures may be of limited value against certain particularly resistant viruses.

This medicinal product contains 8 mg of sodium per 10 ml, which is to be taken into account in patients following a strict low salt diet.

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

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months, the efficacy of vaccines containing live attenuated viruses such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines.

A repeat test for post-vaccination protective antibodies may be required in patients who have received vaccines containing live attenuated viruses (measles, rubella, mumps, varicella) during the 2 weeks before infusion of this product, with a view to recalling the patient for a booster if necessary.

Interference with serological testing

After injection of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patients blood may result in misleading positive results in serological testing.

This medicinal product contains anti-erythrocyte antibodies; administration may therefore be followed by a transient positive Coombs test.

4.6. Pregnancy and lactation

Pregnancy

No reproduction studies have been performed with TEGELINE in animals and there is limited experience in the study of pregnant women. Although no undesirable reactions have been reported on the fœtus, IVIg should not be administered to pregnant women unless the need for treatment has been clearly established.

Lactation

The proteins contained in IVIg are normal constituents of human plasma. Their secretion in breast milk should not cause adverse effects in neonates.

4.7. Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8. Undesirable effects

- Side effects due to administration of IVIg occur more frequently in patients suffering from primary immunodeficiencies.

- As for other IVIg products, reactions such as chills/hyperthermia occasionally accompanied by headache, nausea, vomiting, allergic reactions, high or low blood pressure, and moderate arthralgia or back pain may occur.

- The risks of anaphylactic reactions are higher during rapid intravenous infusions (see section entitled "Method of administration") and in agammaglobulinaemic patients with IgA deficiency and in hypogammaglobulinaemic patients who have never received immunoglobulins or whose last IVIg treatment was given more than 8 weeks prior. Rapid infusion rate could even cause arterial and venous thromboses, particularly in patients at risk for vascular complications.

- Occasional cases of hypotension and anaphylactic shock have been reported even in patients who have not suffered hypersensitivity reactions during previous injections.

- Rare cases of isolated high blood pressure have been reported in patients receiving IVIg.

- As with other IVIg preparations, rare regressive cutaneous reactions, often eczematiform, rare cases of reversible haemolytic anaemia/haemolysis, cases of increased serum creatinine level and(or) acute renal failure and very rare cases of transient increases in transaminases have been reported.

- Cases of reversible aseptic meningitis have been reported with IVIg especially in patients with idiopathic thrombocytopenic purpura. This meningitis is reversible and disappears within a few days following termination of the treatment.

- Rare cases of thrombosis have been reported in association with IVIg, mainly in elderly patients and in patients who are at risk for cerebral or cardiac ischemia, overweight or suffering from severe hypovolemia.

- Early onset of rapidly reversible asymptomatic leuconeutropenia may be observed, particularly in patients treated with high doses.

4.9. Overdose

Although no cases of TEGELINE overdose have been reported, overdose could predispose the patient to certain dose-dependent side effects (see section entitled "Undesirable effects") such as aseptic meningitis, renal insufficiency, blood hyperviscosity.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins,
human normal immunoglobulin, ATC code: J06BA02.

TEGELINE contains mainly immunoglobulin G (IgG). This product has been prepared from pooled plasma from a maximum of 20,000 donations. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

This preparation contains a broad spectrum of antibodies with opsonising and neutralising activity against infectious agents and toxins:

- IgG content is not less than 97% and the mean content is 97.6%.
- The immunoglobulin G subclass distribution is as follows:
  IgG_1 = 58.8%; IgG_2 = 34.1%; IgG_3 = 5.4% ; IgG_4 = 1.7%.
- Antibody titres:

– antibacterial:	antistreptolysin O	≥	6000 IU/g of total protein,
– antiviral:	anti-CMV	≥	210 IU/g of total protein,
	anti-HBs	≥	69 IU/g of total protein,
	anti-hepatitis A	≥	1100 IU/g of total protein,
	anti-measles	≥	620 IU/g of total protein,
	anti-shingles-varicella	≥	90 IU/g of total protein.

- Preservation of the biological functions of the immunoglobulins has been confirmed by an Fc function test.

The mechanism of action of immunomodulation using IVIg is multifactorial and involves both humoral and cellular immunity.

5.2. Pharmacokinetic properties

IVIg are immediately and completely bioavailable after intravenous administration. It is distributed relatively rapidly between the plasma and the extravascular fluid, after approximately 3-5 days, equilibrium is reached between the intra- and extravascular compartments.

The half-life of TEGELINE measured in patients with primary immunodeficiency is 36.4 ± 16.5 days. The half-life of IVIg may vary depending on the immune status of the patient.
IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

5.3. Preclinical safety data

The preclinical safety data do not suggest that TEGELINE has any mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder: sucrose and sodium chloride.
Solvent: water for injections.

6.2. Incompatibilities

Human normal immunoglobulin must not be mixed with any other product and(or) medicinal product.

6.3. Shelf life

3 years
It is recommended that the product be administered immediately after reconstitution. The solution has, however, been shown to be stable within a period of 24 hours after reconstitution.

6.4. Special precautions for storage

Do not store above 25°C. Protect from light. Do not freeze.

6.5. Nature and contents of container

Powder in a vial (glass) + 10 ml, 50 ml, 100 ml or 200 ml of solvent in a vial (glass) with halobutyl stoppers and a transfer system containing an outlet with a sterilising filter and a filter needle (10 ml presentation) or an infusion kit with a filter (50 ml, 100 ml and 200 ml presentations) - box of 1.

6.6. Instructions for use, handling and disposal

Use current guidelines for aseptic procedure.

Reconstitution:

- If necessary, bring the two vials (powder and solvent) to ambient temperature.
- Remove the protective cap from the solvent vial (water for injections) and from the powder vial
- Disinfect the surface of each stopper.
- Remove the translucent protective sheath from the transfer set and completely insert the exposed needle into the centre of the stopper of the solvent vial while simultaneously twisting the needle.
- Remove the second protective cover sheath from the other end of the transfer set.
- Keeping both vials horizontal (vented spike pointing upwards), quickly push the free end of the needle into the centre of the stopper of the powder vial. Ensure that the needle always remains immersed in the solvent to avoid releasing the vacuum prematurely.
- Immediately place the system upright in the vertical position, keeping the solvent vial directly above the powder vial, to allow the solvent to transfer into the powder.
- During the transfer, direct the jet of solvent over the whole surface of the powder. Ensure that all of the solvent is transferred.
- The vacuum is automatically released at the end of the transfer procedure (sterile air).
- Remove the empty vial (solvent) with the transfer system.
- Gently swirl for a few minutes with a rotating movement to avoid the formation of foam until the powder has completely dissolved.
- The powder should be completed dissolved in less than 30 minutes.

The reconstituted product should be examined visually to ensure that it does not contain particulate matter. The reconstituted solution should be clear or slightly opalescent.

Do not use solution which is cloudy or has deposits.

Administration:

- 10 ml presentation: connect the filter needle to a syringe and draw up the reconstituted solution.
- 50 ml, 100 ml and 200 ml presentations: connect the vial containing the reconstituted solution to the administration kit provided with a non sterilising 15 µm filter.
- Flow rates should be adjusted based on clinical tolerance and should not exceed 1 ml/kg/h during the first half-hour. They may then be increased gradually to a maximum of 4 ml/kg/h.
- The solution should be injected intravenously as a single dose immediately after reconstitution.

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