HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

The legally binding text is the original French version

OPINION

12 April 2006

Nanogam 50 mg/mL, solution for infusion
Glass vial 20 mL (CIP: 566 119-5)
Glass vial 50 mL (CIP: 566 120-3)
Glass vial 100 mL (CIP: 566 122-6)
Glass vial 200 mL (CIP: 566 123-2)
Glass vial 400 mL (CIP: 566 124-9)

Applicant: Laboratoire Français du Fractionnement et des Biotechnologies (LFB)

human normal immunoglobulin (plasma-derived)

List I.

Medicine for hospital prescription only

Date of Marketing Authorisation (MA) : 31/08/2005

Reason for request: inclusion on the list of drugs approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

human normal immunoglobulin (plasma-derived)

1.2. Indications

Replacement therapy

- Primary immunodeficiency syndromes such as:
  - congenital agammaglobulinaemia and hypogammaglobulinaemia,
  - common variable immunodeficiency,
  - severe combined immunodeficiency,
  - Wiskott-Aldrich syndrome.
- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.
- Children with congenital AIDS and recurrent infections.

Immunomodulation

- Idiopathic thrombocytopenic purpura (ITP), in children and adults at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain-Barré syndrome.
- Kawasaki disease.

Allogeneic bone marrow transplantation

1.3. Dosage

The dose and dosage regimen depend on the indication.

In replacement therapy, it may be necessary to adjust the dosage for each patient according to the clinical and pharmacokinetic response. The following dosage regimens are given for guidance.

- Replacement therapy in primary immunodeficiency syndromes

The aim of treatment is to ensure an immunoglobulin trough level (i.e. before the next infusion) of at least 4–6 g/L. It takes 3 to 6 months from the start of treatment to reach equilibrium. The recommended loading dose is 0.4–0.8 g/kg, followed by at least 0.2 g/kg every 3 weeks.

The dose needed to achieve a trough level of 6 g/L is approximately 0.2–0.8 g/kg/month. Once equilibrium is reached, the interval between doses varies from 2 to 4 weeks.

Trough levels should be measured in order to adjust the dose and the dosage interval.

- Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; replacement therapy in children with AIDS and recurrent infections

The recommended dose is 0.2–0.4 g/kg every 3 to 4 weeks.

- Idiopathic thrombocytopenic purpura

For the treatment of an acute episode, 0.8–1 g/kg/day on day 1, repeated on day 3 if necessary, or 0.4 g/kg/day for 2 to 5 days. The treatment can be repeated if relapse occurs.

Guillain-Barré syndrome

0.4 g/kg/day for 5–7 days.
Experience in children is limited.

- Kawasaki disease

A single dose of 2.0 g/kg. Patients should receive concomitant treatment with acetylsalicylic acid.

- Allogeneic bone marrow transplantation

Human normal immunoglobulin can be used as therapy before and after transplantation.

To treat infections and prevent graft-versus-host disease, the dose is individually tailored. Loading dose is usually 0.5 g/kg/week, starting 7 days before transplantation and continuing for up to 3 months after transplantation.

In case of persistent lack of antibody production, a dosage of 0.5 g/kg/month is recommended until the antibody level returns to normal.

Mode and route of administration

Human normal immunoglobulin should be administered intravenously, starting at a rate of 0.5 mL/kg/hour for 20 minutes. If well tolerated, the rate may be gradually increased to 1.0 mL/kg/hour and, once 20 mL has been administered without problems, up to a maximum of 3.0 mL/kg/hour at the end of infusion. In adults taking Nanogam regularly and who tolerate it well the rate can be increased to a maximum of 7.0 mL/kg/hour.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

J : ANTIINFECTIVES FOR SYSTEMIC USE
J06 : IMMUNE SERA AND IMMUNOGLOBULINS
J06B : IMMUNOGLOBULINS
J06BA : HUMAN NORMAL IMMUNOGLOBULINS
J06BA02 :Human normal immunoglobulins, for intravascular administration

2.2. Medicinal products in the same therapeutic category

Intravenous administration
- Endobulin 50 mg/mL, powder and solvent for solution for injection
- Gammagard* 50 mg/mL, powder and solvent for solution for infusion
- Octagam 50 mg/mL, solution for infusion
- Sandoglobulin 1 g, powder for solution for infusion
- Sandoglobulin 12 g, powder and solvent for solution for infusion
- Sandoglobulin 3 g, powder and solvent for solution for infusion
- Sandoglobulin 6 g, powder and solvent for solution for infusion
- Tegeline 50 mg/mL, powder and solvent for solution for infusion

**restricted population comprising patients with IgA deficiency, particularly those who have developed anti-IgA antibodies.*

Subcutaneous or intramuscular administration
- Gammanorm, 165 mg/mL, solution for injection

- Subcuvia 160 mg/mL, solution for injection
- Vivaglobin 160 mg/mL, solution for injection (subcutaneous route)

2.3. Medicinal products with a similar therapeutic aim

All medicinal products with the same indications as Nanogam.

3 ANALYSIS OF AVAILABLE DATA

Two trials were submitted in the dossier, one (KB97003A) in 18 patients with hypogammaglobulinaemia, the other (KB98001-IVIG-L) in 24 patients with idiopathic thrombocytopenic purpura.

Trial KB97003A

A 6-month open-label multicentre trial in 18 patients with primary agammaglobulinaemia or hypogammaglobulinaemia, aged 18 and over, who had received a total of 158 infusions.

Nanogam infusions were given every 2, 3 or 4 weeks, at doses of 150, 225 or 300 mg/kg respectively.

Infusion rate varied according to tolerability.

All patients had previously been given immunoglobulin infusions.

Asessment criteria

- Efficacy
  - Minimal IgG concentration : concentration measured prior to each immunoglobulin injection for 6 months.
  - IgG half-life.
  - Number of days off school/ work.
  - Number of days admitted to hospital.
  - Number of episodes of infection.
  - Number of episodes of fever.
  - Use of antibiotics.
- Safety
  - Vital signs.
  - Undesirable effects.
  - Laboratory test parameters.

Efficacy results

- Minimal IgG concentration :
  - before Nanogam: 6.7± 1.2 g/L
  - after Nanogam: 6.8 ± 1.2 g/L.
- IgG half-life: 30.9 ± 11.3 days (95% CI: 25.3 – 36.6).
- 6 patients had to miss school or work because of infections.
- Mean number of days absence: 5 ± 2.6 days.
- 2 patients were admitted to hospital: 1 for a severe respiratory infection and 1 for a subclavian vein thrombosis at the site of a Port-a-Cath implanted 6 weeks previously.
- 25 infections occurred in 12 patients.

- Mean number of infections per period per patient: 1.3 ± 1.5, equivalent to 2.6 episodes of infection per year.
- 27.8% of patients had an episode of fever.
- Mean duration of fever: 6.1 days.
- Antibiotics were prescribed 37 times, in 15 patients.

Safety results

Overall, 55.5% of patients had one or more undesirable events potentially connected to the drug, occurring at least once during the trial period.

Undesirable events reported were those commonly occurring with immunoglobulin infusion (skin rashes, fever, shivering, sweating, dyspnoea, general malaise, diarrhoea, tachycardia, hypotension, headache and lower back pain).

Two serious undesirable events were recorded (one severe respiratory infection and one subclavian vein thrombosis at the site of a Port-a-Cath implanted 6 weeks previously), neither of which could be imputed to the use of Nanogam.

Infusion rate variation trials showed that a rate of 8 mL/min could be achieved in 10 patients. In the others, a lower rate was adopted, either because the patient refused an increased rate, or because a lower rate was better tolerated.

Trial KB98001

An open-label multicentre trial in 24 patients over 18 years old with chronic idiopathic thrombocytopenic purpura.

The inclusion criterion was a platelet count of around $20x10^9$/L with a high risk of bleeding or requiring surgery.

Intravenous infusions of Nanogam were given according to 3 schedules: 1 g/kg for 1 day, 1 g/kg for 2 consecutive days or 400 mg/kg for 5 consecutive days.

The trial lasted 14 days.

Assessment criteria

- Efficacy
  - Increase in platelet count: platelets were counted once daily for 7 days after the start of treatment, then on day 10 and day 14.
  - Platelet response was assessed according to the following parameters:
    - period during which platelet count was above baseline,
    - number of responders (platelet count $\geq 50 \times 10^9$/L)
    - period during which platelet count was $\geq 50 \times 10^9$/L,
    - time taken to reach maximal platelet count,
    - time taken to reach platelet count $\geq 50 \times 10^9$/L,
  - In cases of bleeding: resolution of bleeding, number, duration and type.
  - In cases of surgery: tendency to bleed during and just after surgery.
  - Number of platelet and/or red blood cell transfusions.
- Safety
  - Vital signs.
  - Undesirable effects.
  - Laboratory test parameters.

Efficacy results

- All patients (n=24) had an increased platelet count after each injection.
- 17 patients had a platelet count above the baseline until day 14.
- 20 patients were defined as responders (platelet count ≥50 x 10^9/L).
- Three patients were given corticosteroids in addition to Nanogam and could not be defined as responders.
- At day 14, 12 patients had a platelet count ≥50 x 10^9/L.
- Maximal platelet count was between 15x10^9/L and 569 x10^9/L (mean = 149.4 x 10^9/L).
- In 7 patients this maximal platelet count was recorded on day 7.
- 13 patients achieved a platelet count ≥50 x 10^9/L at day 2 and day 3.
- Two patients each had 2 nosebleeds.
- No other bleeding event was recorded.
- No bleeding problems occurred in 2 patients undergoing surgery or 1 patient who had a dental extraction.
- No patients required any other transfusions.

Safety results

Undesirable events were recorded for 10 of the 61 infusions administered.

Thirty-one undesirable events were reported, in 12 patients.

Most were mild events such as headache and shivering.

Around half the undesirable events were regarded as potentially connected with Nanogam.

Conclusion

The two trials demonstrated that:

- the efficacy of Nanogam in treating hypogammaglobulinaemia and correcting thrombopenia occurring in idiopathic thrombocytopenic purpura, is similar to that of other intravenous immunoglobulin (IVIg) products;
- safety is similar to that of other IVIg products and to published results.

NB: No clinical trial was submitted for the indication "Allogeneic bone marrow transplantation".

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In replacement therapy

- Primary immunodeficiency syndromes such as:
  - congenital agammaglobulinaemia and hypogammaglobulinaemia,
  - common variable immunodeficiency,
  - severe combined immunodeficiency,
  - Wiskott-Aldrich syndrome.
- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.
- Children with congenital AIDS and recurrent infections.

Immunodeficiencies requiring replacement therapy with Immunoglobulins are rare, serious, life-threatening conditions.

This drug is for use as part of preventive therapy.
The efficacy/safety ratio is substantial.
There are alternative therapies (other IVIg products).

Public health benefit

- Despite their seriousness, primary and secondary immunodeficiencies are not a heavy burden on public health because they are rare conditions.
- The public health need is covered by currently available immunoglobulins. Having an additional immunoglobulin available is nevertheless useful since shortages (e.g. supply problems) may occur.
- The contribution of Nanogam in terms of morbidity and mortality or quality of life cannot be quantified on the basis of the data available.
- Nanogam is not expected to have an additional impact on morbidity and mortality compared to other IVIg products.
- In the current state of knowledge and given the other therapies available, it is not therefore expected that Nanogam will benefit public health.

The actual benefit of this medicinal product is substantial.

In immunomodulation

- Idiopathic thrombocytopenic purpura (ITP), in children and adults at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain-Barré syndrome.
- Kawasaki disease.

Diseases requiring immunomodulatory therapy are rare, serious, life-threatening conditions.

This drug is for use as part of curative therapy.
The efficacy/safety ratio is moderate.
There are alternative therapies (other IVIg products).

Public health benefit

- Despite their seriousness, these diseases are not a heavy burden on public health because they are rare.
- The public health need is covered by currently available immunoglobulins.
- Having an additional immunoglobulin available is nevertheless useful since shortages (e.g. supply problems) may occur.
- The contribution of Nanogam in terms of morbidity and mortality or quality of life cannot be quantified on the basis of the data available.
- Nanogam is not expected to have an additional impact on morbidity and mortality compared to other IVIg products.
- In the current state of knowledge and given the other therapies available, it is not therefore expected that Nanogam will benefit public health.

The actual benefit of this medicinal product is substantial.

In the allogeneic bone marrow transplantation

Human normal immunoglobulins can be used as therapy before and after transplantation.

This drug is for use as part of preventive treatment.
The efficacy/safety ratio is substantial.

Public health benefit

- Despite its seriousness, allogeneic bone marrow transplantation is not a heavy burden on public health because it is rare.
- The public health need is covered by currently available immunoglobulins. Having an additional immunoglobulin available is nevertheless useful since shortages (e.g. supply problems) may occur.
- The contribution of Nanogam in terms of morbidity and mortality or quality of life cannot be quantified on the basis of the data available.
- Nanogam is not expected to have an additional impact on morbidity and mortality compared to other IVIg products.
- In the current state of knowledge and given the other therapies available, it is not therefore expected that Nanogam will benefit public health.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

Nanogam does not offer any Improvement in Actual Benefit (IAB V) compared to other IVIg products.

4.3. Therapeutic use

According to CEDIT (Committee for Evaluation and Diffusion of Innovative Technologies) guidelines on normal immunoglobulins by the IV route.

❖ Primary and secondary immunodeficiency syndromes

Immunoglobulin therapy is used in patients with primary and secondary immune deficiencies (e.g. chronic lymphocytic leukaemia and myeloma) with impaired antibody formation.

In adults, this tends to be a common variable immunodeficiency, which varies in seriousness from one patient to another.

In children, this therapy is used for all types of genetic immune deficiencies that cause immunoglobulin deficiency and/or impaired antibody formation: agammaglobulinaemia, hypogammaglobulinaemia and/or impaired antibody formation, whether of single antibodies or as part of a primary T lymphocyte immune deficiency.

Immunoglobulin therapy may also be recommended for primary immune deficiencies of one or several immunoglobulin subgroups, with or without IgA deficiency, in patients with repeated infections. On the other hand, IgA deficiency alone is not an indication for immunoglobulin therapy.

High-dose immunoglobulin therapy is recommended for the enterovirus meningoencephalitis seen in some genetic immune deficiencies. Immunoglobulin therapy reduces frequency of

infective episodes, use of antibiotics, and absence from school or work. Immunoglobulins prevent chronic sinus and bronchial infections.

The treatment should ensure an immunoglobulin trough level (i.e. prior to the next immunoglobulin injection) of at least 5 g/L.

Equilibrium is achieved in 3-6 months after the start of immunoglobulin therapy.

Side effects of taking IVIg are common in patients with primary immune deficiencies. Most can be avoided by using a low, carefully monitored infusion rate. It is advisable to ensure that immunoglobulins are well tolerated by beginning with a test dose (5 mg/kg) administered slowly (2 mL/min). If undesirable effects occur, the infusion should be preceded by intravenous antihistamines or corticosteroids.

❖ Children with congenital AIDS and recurrent infections

Replacement immunoglobulin therapy is now indicated only in HIV-infected children with recurrent pulmonary or ENT infections of bacterial origin (mostly pneumococcal) that are resistant to the preventive treatment usually prescribed (sulfamethoxazole-trimethoprim).

❖ Idiopathic thrombocytopenic purpura (ITP) in children and adults

1. ITP in children

ITP in children is usually an acute disease that resolves spontaneously. IVIg may be indicated from the outset if platelet count is below 20.10^9/L (20 000/mm^3) and if there is a marked haemorrhagic syndrome (e.g. extensive purpura, mucous bleeding, spontaneous nosebleed). IVIg is also indicated when a medical or surgical procedure carries a risk of bleeding or when corticosteroid therapy is ineffective.

Acute ITP: the efficacy of IVIg is often short-lived, at 15–21 days.

Persistent/chronic ITP**:** maintenance therapy with IVIg is therefore indicated only in rare serious and chronic forms that are resistant to other therapies, or if the other therapies are contraindicated.

2. ITP in adults

Treatment procedures are similar to those proposed for the paediatric forms but progression to the chronic form is much more common.

Acute ITP: IVIg may be indicated from the outset if platelet count is below 20.10^9/L (20 000/mm^3) and if there is a marked haemorrhagic syndrome (e.g. extensive purpura, mucous bleeding, spontaneous nosebleed).

Chronic ITP: since repeated IVIg injections rarely produce a prolonged response, their value in this indication is not proven.

❖ Guillain-Barré syndrome in adults

Guillain-Barré syndrome in adults can be treated either with plasma exchange or with IV immunoglobulin.

IVIg improves and hastens motor recovery in patients with Guillain-Barré syndrome, leading to earlier release from intensive care, easier return to walking and improved long-term functional prognosis.

Immunoglobulin is indicated in the following cases:

- inpatients in specialist intensive care for Guillain-Barré syndrome, who have walking difficulties, and/or require respiratory assistance, and/or are bedridden, should always be given IV therapy if there is no contraindication (e.g. renal failure or known allergy).
- Guillain-Barré syndrome patients with no motor deficiency, or whose motor or sensory symptoms are in spontaneous regression, require only close monitoring in hospital. In contrast, IVIg is indicated in patients with stable symptoms or especially with worsening motor or sensory deficiency.

❖ Kawasaki disease

Acetylsalicylic acid and immunoglobulins have been shown to be effective in preventing coronary aneurisms. Acetylsalicylic acid is administered as soon as the diagnosis is suspected, at the usual initial dose of 5–10 mg/kg/day, for at least three months. IVIg should also be given as soon as the diagnosis has been confirmed on the basis of the defined criteria.

The currently recommended dosage is 1 g/kg/day for 2 days.

One course of treatment is usually enough, but a second course is indicated if fever persists or recurs. There is no evidence to suggest that one immunoglobulin product is superior to another.

❖ Allogeneic bone marrow transplantation

Allogeneic bone marrow transplantation in patients with hereditary immunodeficiency

Administration of IVIg to prevent post-transplant infections in patients with confirmed hypogammaglobulinaemia is similar to that in nontransplanted patients (see primary immune deficiencies with impaired antibody formation).

Therapeutic use of Nanogam

In these diseases, the place of Nanogam is the same as that of other IV human normal immunoglobulin based products with the same indications.

Nanogam is not indicated in patients with immunoglobulin A deficiency who have anti-IgA antibodies.

4.4. Target population

There is no reliable epidemiological evidence on which to base an accurate assessment of the patient population suitable for immunoglobulin therapy in the various diseases for which Nanogam is indicated.

According to data from CEDIT covering 63% of human normal immunoglobulin used in the Paris regional university hospital group (AP-HP), 1138 patients have been treated with human normal immunoglobulin.

AP-HP represents 14.8% of human normal immunoglobulin use in France. Extrapolating these data to all hospitals suggests around 4000 patients are likely to be treated with human normal immunoglobulin.

4.5. Transparency Committee Recommendations

The Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services for the indications and at the doses given in the Marketing Authorisation.