HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 October 2009

SUBCUVIA 160 g/l solution for injection
1 5 ml glass vial (CIP: 566 107-7)

SUBCUVIA 160 g/l solution for injection
20 5 ml glass vials (CIP: 566 108-3)

SUBCUVIA 160 g/l solution for injection
1 10 ml glass vial (CIP: 566 110-8)

SUBCUVIA 160 g/l solution for injection
20 10 ml glass vials (CIP: 566 111-4)

Applicant: BAXTER SAS

human normal immunoglobulin (plasma-derived)

ATC Code: J06BA01

List I

Medicine for hospital prescription only. Prescription by a physician practising in a blood transfusion facility permitted to deliver medicinal products to its patients is also authorised.

Date of initial MA (mutual recognition procedure): February 8, 2005
Date of indication extension (mutual recognition procedure): May 25, 2009

Reason for request: inclusion on the list of medicines approved for use by hospitals in the indication extension: “Replacement therapy for primary immunodeficiencies in **children**.”

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

human normal immunoglobulin (plasma-derived)

1.2. Indication

"Replacement therapy for adults and **children** in primary immunodeficiencies such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia,
- common variable immunodeficiency,
- severe combined immunodeficiency,
- IgG subclass deficiencies associated with recurrent infections.

Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections."

1.3. Dosage

"Replacement Therapy:
Treatment must be initiated and monitored under the responsibility of a physician experienced in the management of immunodeficiencies.
It may be necessary to adjust the individual patient's dosage to pharmacokinetic and clinical response. The following dosage regimens are given asa guideline.
The treatment must be adjusted to maintain an approximative level of 4 to 6 g/l of circulating IgG. .
Subcutaneous treatment must enable a constant residual IgG level (measured before the next injection). A loading dose of at least 0.2 to 0.5 g/kg per week (fractioned into several daily doses of 0.1 to 0.15 g/kg body weight and taken over several days of the week) is recommended. After the IgG steady state levels obtained, maintenance doses are administered at regular intervals to reach a cumulative monthly dose around 0.4 to 0.8 g/kg.
Residual levels must be measured in order to adjust the dose and administration intervals.
SUBCUVIA should preferably be administered by subcutaneous route.
SUBCUVIA may also be administered by intramuscular route. In this case, the cumulate monthly dose must be divided up into weekly or twice-weekly injections, in order to inject a small volume of solution each time. To reduce discomfort, the injections can be given in different parts of the body.

Method of administration
Human normal immunoglobulins may be administered by subcutaneous or intramuscular route.
SUBCUVIA must be administered subcutaneously. In exceptional cases, when subcutaneous administration is impossible, SUBCUVIA may be injected by intramuscular route.
Subcutaneous administration for home treatment should be introduced by a physician experienced in the management of immunodeficiencies for the patient's training. . The patient must be taught how to use a syringe driver, about injection techniques, how to keep a treatment diary and what to do in case of a severe adverse effect.
It is recommanded to use an initial speed of 10 ml/h/pump.
The initial injection speed can be increased by 1 ml/h/pump at each administration. The maximum recommended speed is 20 ml/h/pump. More than one pump may be used simultaneously.
A different injection site must be used every 5 to 15 ml.
Intramuscular injections must be carried out by a nurse or doctor."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

J Antiinfectives for systemic use
J06 Immune sera and immunoglobulins
J06B Immunoglobulins
J06BA Immunoglobulins, normal human
J06BA01 Immunoglobulins, normal human, for extravascular administration.

2.2. Medicines in the same therapeutic category

Comparator medicines: immunoglobulins administered by subcutaneous (SC) or intramuscular (IM) route with the same indications as SUBCUVIA:

- GAMMANORM 165 mg/ml solution for injection (plasma-derived human normal immunoglobulin)

In its opinion for inclusion on the list of medicines approved for use by hospitals of July 6, 2005, the Committee concluded: substantial AB, IAB III in terms of safety compared to intravenous immunoglobulins and in the management of primary and secondary immunodeficiencies, particularly in patients without a venous access line.

- VIVAGLOBIN 160 mg/ml solution for injection (plasma-derived human normal immunoglobulin)

In its opinion for inclusion on the list of medicines approved for use by hospitals of October 5, 2005, the Committee concluded: substantial ACB, IAB III for subcutaneous immunoglobulins shared with intravenous immunoglobulins.

2.3. Medicines with a similar therapeutic aim

Immunoglobulins administered by intravenous (IV) route:

- ENDOBULIN 50 mg/ml powder and solvent for solution for injection
- OCTAGAM 50 mg/ml solution for infusion
- SANDOGLOBULIN 120 mg/ml solution for infusion (IV)
- TEGELINE 50 mg/ml powder and solvent for solution for infusion
- KIOVIG 100 mg/ml solution for infusion
- PRIVIGEN 100 mg/ml solution for infusion
- GAMMAGARD 50 mg/ml powder and solvent for solution for infusion *(population restricted to patients suffering from IgA deficiency and especially those having developed anti-IgA antibodies)*.

3. ANALYSIS OF AVAILABLE DATA

In support of its application, the firm submitted:

- bibliographical data, particularly data enabling the efficacy and safety of SUBCUVIA to be evaluated in the extension of its indications for children,
- intermediate results of a post-MA observational study, the PASS (Post Authorization Safety Surveillance) study. As only the poster presentation of the study is available, its results are presented for information purposes only.

3.1. Analysis of bibliographical data

Of all the bibliographical data submitted by the company, three were retained.

- One case-control study[1] to produce a retrospective evaluation of GAMMABULIN (predecessor of SUBCUVIA[2]) in 26 children aged 1.5 months to 15 years, suffering from primary immunodeficiencies and treated for a median duration of 2 years (6 months to 3.5 years). Fifteen children were pretreated with immunoglobulins (Ig) administered by intravenous (IV) method. Two groups were therefore created, those previously untreated (group A, n=11) and those pretreated (group B, n=15).
After 6 months' treatment, in group A, normal IgG concentrations were reached by all patients. In group B, the IgG level was maintained after SC administration of Ig.
The SC route was preferred to the IV route. According to parents, SC administration improves quality of life even though there are more injections than with the IV route. This was a subjective evaluation in the form of 2 concise questionnaires[3] rather than validated scales.
All patients felt pain in the injection area. No severe infections occurred.

- One observational study[4,5], the objective of which was to determine, after 6 months' treatment, the impact of switching from IV to SC in terms of safety and quality of life for children suffering from primary immunodeficiencies pretreated with IV immunoglobulins (Ig) with steady levels of IgG >5 g/l.
The primary endpoint was safety (following parameters evaluated: blood pressure, heart rate, body weight and temperature, blood and biochemical findings).
The secondary endpoints were: quality of life[6], the use of healthcare resources[7,] documented bacterial infections[8], IgG levels, and patients' preference for IV or SC treatment.

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1 Gaspar J et al. Immunoglobulin replacement treatment by rapid subcutaneous infusion. Arch Dis Child. 1998; 79: 48-51

2 SUBCUVIA is the same product as GAMMABULIN with an additional viral inactivation stage.

3 One evaluating SC injections, the other comparing the two administration methods after at least 6 months' treatment

4 Fasth A. et al. Quality of life and health care resource utilization among children with primary immunodeficiency receiving home treatment with subcutaneous human immunoglobulin. J Clin Immunol. 2008; 28 (4): 370-78.

5 Fasth A. et al. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. Acta Pædiatrica. 2007;96: 1474–147.

6 The quality of life was assessed upon inclusion, at 3 and 6 months, using the validated CHQ questionnaire (Child Health Questionnaire) comprising 9 evaluation areas: overall health, physical function, behaviour, social limitations, pain, self-esteem, mental health, child's health, emotional effect). The questionnaire for children includes 80 items and the one for parents includes 54. The overall score ranges from 0 to 100, with a high score corresponding to a better quality of life.

7 The use of healthcare resources was determined, upon inclusion and then after 3 and 6 months, using an 11-item questionnaire evaluating the level of school absenteeism or absences from other activities, the duration of antibiotic treatment, the number or duration of hospital stays, the number of consultations due to infection, etc.

8 An infection was identified as severe when antibiotics were required, serious if hospital admission was necessary.

Twelve children aged 1.7 to 17.1 were included (median age: 10.9), with a median IgG level of 12.1 g/l (7.0 to 20.6 g/l). The median IV Ig pretreatment duration was 2.9 years (0.2 – 8.3 years). The median dose of SUBCUVIA was 109 mg/kg/week (56 to 159 mg/kg/week), from twice weekly to once every two weeks.

No difference was observed in terms of safety. All patients had at least one adverse effect, the one most often observed being a reaction in the injection area[9].
Compared to baseline, after 6 months' treatment, an improvement in quality of life was observed for the following items:

- mental health, change in condition of health and family activities according to the parents' evaluation,
- emotional and social aspects and overall health, depending on the child.

After 6 months, there was a decrease in school absenteeism.
The rate of infection during the study (2 per month) was similar to the one observed during IV pretreatment (2.4 per month).
The Ig levels were steady compared to baseline (median level 11.5 to 13.2 g/l).
A preference for SC treatment was reported.
It is not known whether the improvement in quality of life is due to switching from IV to SC method, or switching from hospital to home treatment or both.
The study authors feel that prospective studies are needed to confirm these results.

- According to the authors of a recent literature review[10] (based on international studies), SC administration of Ig to adults and children is well tolerated, could be used for patients who have suffered from adverse effects with IV administration, would enable normalised or elevated IgG levels to be maintained and protect against infections, would enable outpatient treatment as there is no need for venous access, would not require pretreatment with corticosteroids or antihistamines and would improve patient quality of life. The same conclusions are found in another study[11].

3.2. Results of PASS study[12]

This is an observational study, whose primary objective was to document the safety of SUBCUVIA.
The secondary objectives were to analyse clinically documented bacterial infections and changes in IgG levels.
The inclusion criteria were as follows: primary or secondary immunodeficiencies with recurrent infections, patients requiring Ig replacement therapy, pretreated with IV or SC Ig other than SUBCUVIA with steady IgG levels ≥ 5 g/l, or patients previously untreated with Ig.

The results of an intermediate analysis (not foreseen in the protocol) relating to data on the evaluation of 14 children aged 0.6 to 12.7 (median age: 4.5 years) are available. Ten of these patients were previously treated and 4 previously untreated with immunoglobulin replacement therapy[13].
The patient follow-up duration was 6 months.

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9 With redness, swelling and localised heat. These reactions, which disappeared on their own within 2 hours, became less frequent after 1 to 2 months' treatment.
10 Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. Biodrugs 2007; 21: 105-116.
11 Gardulf A. et al. Replacement Therapy and self-therapy at home improve the health-related quality of life in patients with primary antibody deficiencies. J Allergy Clin Immunol. 2006; 6: 434-442
12 Post-Authorisation Safety Surveillance of SUBCUVIA in immunodeficiency. Study results are still being analysed, as it commenced in March 2006 and enrolment was completed in December 2007 (79 patients included in all). For the 14 children included in the intermediate analysis, the last visit was scheduled before the end of October 2007.
13 Of these, two patients did not have the inclusion criteria required; they were only included in the safety analysis.

Results:
Treatment-related adverse effects (local reactions in the injection area) were reported in 3/14 patients.

The analysis of bacterial infections compared the data over the 12 months prior to the first administration of SUBCUVIA and concerned the 12 children able to be evaluated (8 patients pretreated with IgG and 4 previously untreated with any Ig replacement therapy).
The median number of monthly bacterial infections (documented or otherwise) was 0.33 (0.00 – 0.83) in previously untreated patients and 0.08 (0.00 – 0.50) in pretreated patients.
Compared to baseline, median IgG levels increased in all patients (from 7.6 to 9.6 g/l). In previously untreated patients, this median level increased from 5.6 (1.5 – 13.9) to 8.7 g/l (7.8 – 13.4), and in pretreated patients from 7.9 (6.0 – 10.6) to 10.0 g/l (7.8 – 11.0).

3.3. Conclusion

The bibliographical data submitted by the company and the post-MA PASS study do not enable any formal conclusions to be drawn as to the efficacy and safety of SUBCUVIA in subcutaneous (SC) administration in the treatment of primary immunodeficiencies in children.
Indeed, the methods of these studies, all exploratory, limit the validity of their results (case-control study with memorisation biases, insufficient consideration for confusion biases, non-comparative observational study, small number of patients monitored, etc.).
According to their authors, these studies suggest a good level of safety and efficacy for SC SUBCUVIA but in the absence of comparative studies on children and more rigorous methods, no conclusions can be drawn.
A study comparing with IV administration of immunoglobulins would have enabled the benefits of SC administration to be assessed.
There are no studies comparing immunoglobulins administered by SC route.

The analysis of the data from the last international PSUR (January 2003 – December 2007) for SUBCUVIA is in line with the information on risks in the current MA (SPC amended January 14, 2009).

The most frequent adverse effects reported were general disorders (chills, malaise), administration site anomalies (swelling, local pain), skin and subcutaneous tissue conditions (urticaria, pruritis), gastrointestinal disorders (nausea), and nervous system problems (headaches).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Primary immunodeficiencies lead to an increase in the frequency and severity of infections, particularly bacterial infections, affecting essentially the lungs and ENT.
Immunoglobulins are the treatment of choice for these primary immunodeficiencies concomitant to anti-infectious, curative and preventive treatments.
SUBCUVIA is used in the context of preventive treatment.
The efficacy/adverse effects ratio of SUBCUVIA is high.
Alternative medicinal products exist.

Public health benefit:
Despite their severity, the burden of primary immunodeficiencies is small as they are rare conditions.
The public health need is covered by SC or IV immunoglobulins currently available.
SUBCUVIA is an additional alternative treatment.

Given the data available (particularly the absence of comparative studies and rigorous methods), it is impossible to quantify any impact on morbidity, mortality and quality of life.
Given its administration method, this immunoglobulin is likely to have an impact on the healthcare system, like the others, as it can be taken at home and not solely in a hospital environment. However, this impact is not currently documented.
Consequently, this product is not expected to benefit public health in its indication extension.

The actual benefit of SUBCUVIA is substantial.

4.2. Improvement in actual benefit

In light of the data available, the Transparency Committee feels that SUBCUVIA does not provide any improvement in actual benefit (IAB V) compared to the other immunoglobulins administered by subcutaneous route for replacement therapy in children suffering from primary immunodeficiencies.

4.3. Therapeutic use [14,15]

Treatment with IVIg concerns patients with primary immunodeficiencies with antibody production deficiencies. The benefit of this humoral immunodeficiency replacement therapy has been established.
In adults, this is most often a common variable immunodeficiency, the severity of which can vary from one patient to another.
In children this treatment concerns all genetic immunodeficiency varieties responsible for an IgG deficiency and/or an antibody production deficiency: agammaglobulinaemia; IgG and IgA deficiency with hyper-IgM; hypogammaglobulinaemia and/or isolated antibody production deficiency or occurring during primary T-lymphocyte immunodeficiencies. IVIg treatment can also be recommended in primary immunodeficiencies in one or more IgG subclasses associated or not with an IgA deficiency in the event of recurrent infections. An isolated IgA deficiency is not an indication for IVIg treatment.
IVIg treatment reduces the frequency of infections, the use of antibiotics, and absenteeism from school and work. IVIg prevent chronic sinus and bronchial infections.
The treatment must ensure a residual IgG level (i.e. before the next IVIg injection) of no doubt at least 5 g/l and close to 8 g/l. After the start of IVIg treatment, the steady state is reached in 3 to 6 months.
Subcutaneous administration can be substituted for the IV method.

SUBCUVIA is indicated in replacement therapy for secondary immunodeficiencies, with antibody production deficiency, in myeloma or chronic lymphocytic leukaemia associated with recurrent infections. In this indication, there is no clinical data supporting the efficacy and safety of immunoglobulins administered by subcutaneous route.

Therapeutic use of SUBCUVIA
In these conditions, the therapeutic use of SUBCUVIA (subcutaneous or intramuscular immunoglobulin) is the same as for other human normal immunoglobulin-based products with the same indications that are used intravenously.
The Ig doses used for SUBCUVIA are identical to those of IVIg.
SUBCUVIA is an additional means of treatment.

[14] CEDIT. Committee for the assessment and distribution of technological innovations. Primary immunodeficiencies with antibody production deficiency, including bone marrow allograft in patients with primary immunodeficiency. Recommendations for good use of polyvalent IVIg. AP–HP IVIg expert committee. 1/11/2006, available at http://cedit.aphp.fr/index_pub.html
[15] CEDIT. Secondary immunodeficiencies with antibody production deficiency, particularly chronic lymphocytic leukaemia and myeloma associated with repeat infections. Recommendations for good use of polyvalent IVIg. AP-HP IVIg expert committee. 1/11/2006, available at http://cedit.aphp.fr/index_pub.html

SUBCUVIA can be used by patients for which the intravenous route is impossible or very difficult (patients who can no longer find a peripheral vein, children) or for whom an IV injection of immunoglobulins is poorly tolerated, or autoimmune patients, who can benefit from therapeutic education and who have friends or family present and available for home treatment.
SC administration also facilitates outpatient treatment.
The IgA content (4.8 mg/ml) enables closely monitored administration to patients with an IgA deficiency.

4.4. Target population

The target population of SUBCUVIA in the indication extension comprises children under the age of 12 with primary immunodeficiencies.
According to CEREDIH[16] data, the prevalence of patients with hereditary immunodeficiencies was estimated on August 10, 2009 as 4.1 patients for every 100,000 inhabitants.
The population aged 0 to 12 is around 10,400,000 (INSEE data on January 1, 2009).
The target population is therefore thought to be around 450 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication extension and at the dosage stated in the marketing authorisation.

The Committee calls the DGS, DSS and CEPS' attention to the fact that in September 2005 a post-listing study was requested to compare, under real conditions, the prevention of infections and the safety of subcutaneous immunoglobulins with that of intravenous immunoglobulins. The Committee feels that it is regrettable that to date the study has still not been set up and would like the study requested in 2005 to be extended to children under the age of 12.

16 Hereditary Immunodeficiency Reference Centre https://www.ceredih.fr/index.php?page=connexion