

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in accordance with  
Article 45<sup>1</sup> of Regulation (EC) No1901/2006, as  
amended**

**Human Normal Immunoglobulin**

**DE/W/0014/pdWS/001**

**Marketing Authorisation Holder(s)**

Baxter S.A, Biotest, C.A.F.-D.C.F., CSL Behring,  
DEMO S.A., Grifols, Kedrion, Octapharma

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<sup>1</sup> The Art 45 Assessment Report includes also the assessment of one Art. 46 study for Vivaglobulin

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Human Normal Immunoglobulin
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	J06BA01/02
Pharmaceutical form(s) and strength(s):	See section VII

## **I. EXECUTIVE SUMMARY**

In 1952 Bruton identified the first case of X-linked agammaglobulinemia in an 8-year old boy and subsequently IgG was introduced as replacement therapy for primary immunodeficiencies (PID). The trials that followed were uncontrolled but so convincing as to render placebo-controlled trials unethical. Initially IgG therapy was given as subcutaneous injections (SCIG), which were later replaced by intramuscular injections (IMIG). In the 1970's IMIGs were modified to be rendered virtually free aggregates; other changes were made leading to the production of intravenous immunoglobulins (IVIG). In recent years the use of SCIG has become more widespread for home treatment of PID patients due to the greater convenience this route offers. The Immune Deficiency Foundation in the USA indicates that approximately 40% of PID subjects are less than or equal to 17 years of age.

In 1981 Imbach treated 13 children with acute and chronic ITP and achieved a significant raise in platelet count in 12/13; since then IVIG has become standard treatment in this setting. In the mid 1980's Kawasaki performed trials in children suffering from a multisystem vasculitis administering acetylsalicylic acid vs. acetylsalicylic acid + IVIG, the latter showing significantly better results. This result has been replicated in numerous trials. In the late 1980's studies an NIH study in 372 children with congenital AIDS and hypogamma-globulinemia proved efficacy for this indication.

Thus, for the past 60 years IVIG, SCIG, and IMIG have been routinely given to children for a wide variety of disorders with good efficacy and safety results.

IVIGs, SCIGs and IMIGs are plasma-derived products that have been and still are under rigid standards of donor testing, the Eur. Pharmacopoeia and regulatory review. The dosing is by body weight and often tailored according to individual needs; PK studies have not revealed major differences between adults and children suffering from the same disorder. Side-effects are well known and detailed in the CHMP core SPC. Individual products may differ in their IgA content, pH, stabilizers and although these could theoretically give rise to a different efficacy/safety profile, no main differences have been seen between the adult and pediatric population. Obvious PK differences between IVIG and SCIG products are also the same in the adult and pediatric population and have been documented over the past 30-40 years. However, older studies may be of limited quality when viewed by current standards, mainly due to deficiencies such as lack of in-process controls?, on-site audits or irregular monitoring.

## **II. RECOMMENDATION**

The submitted documentation/publications are sufficient to conclude that no changes are necessary to the respective SmPCs/PILs.

## **III. INTRODUCTION**

For IVIGs, SCIGs or IMIGs 8 MAHs submitted 41 studies which included paediatric patients. This is in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The MAHs state that the submitted paediatric studies do not influence the benefit risk for their respective products (see section IV.3.1.) and that there is no need for a consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the clinical studies**

Immunoglobulins are plasma derived products that are administered either intravenously, subcutaneously or occasionally intramuscularly depending on the formulation. They contain pooled IgG from the plasma of over one thousand donors. Since the early 1980s, highly purified preparations of IgG for intravenous administration (IVIG) were developed by a number of manufacturers. In all non-modified products IgG functionality is retained (Fc function and Fab mediated activity) and the IgG subclass distribution is similar to that found in normal human plasma. More than 90% of the IgG consists of monomers and dimers. Due to differences in formulation between products (excipient, pH, IgA content) the side effect profile can differ. There is no paediatric formulation. The products are dosed by body weight. Immunoglobulins are used as a substitution therapy in primary immunodeficiencies (PID) and secondary immunodeficiencies in CLL and multiple myeloma, after bone marrow transplant and in children with congenital AIDS. They are further used for immunomodulatory purposes in Guillain-Barre Syndrome (GBS) and Kawasaki's disease. The indications, dosing, adverse events and warning statements are outlined in the core SPC and apply to all products, unless product specific parentheses are applied.

**Note:**

This report will not cover specific immunoglobulins or IgM products; nor will case reports or studies with less than ~15 total subjects be evaluated; although the latter have been reviewed by the assessor, they are not deemed to carry sufficient statistical weight to warrant any possible changes in the SPC or PIL.

Those products for which all completed studies had previously been submitted to the agencies will not be listed here. However, for some products submitted data have previously been evaluated in MR procedures; in these cases only brief summaries will be provided.

### **IV.2 < Non-clinical aspects >**

**N.a.**

### **IV.3 < Clinical aspects >**

#### **1. Introduction**

Immunoglobulins (IVIG, SCIG) are plasma-derived products that have been used in children for a variety of well-established indications over the past 60 years. Dosing is by body weight. All new products coming to the market or products with major changes in the manufacturing procedure have to perform studies in PID which regularly include children. PK parameters that are assessed in each PID study have, over the decades, shown no significant differences between the adult and pediatric population, nor have there been specific safety signals pertaining to children.

## The MAHs submitted reports for the following products:

1. Baxter
  - a. Gammagard /SD (19)
  - b. Subcuvia (2)
2. Biotest
  - a. Intratect (2 – already assessed)
3. C.A.F. – D.C:F.
  - a. Multigam (1 – not company –sponsored)
4. CSL Behring
  - a. Sandoglobin /Sandoglobulin Liquid (3 reviewed in MR procedure))
  - b. Vivaglobin /Beriglobin (2 reviewed in MR procedure + 1 Art. 46 )
5. Grifols
  - a. Flebogamma / Alphaglobin (5 + post-marketing reports)
6. Kedrion
  - a. Igvena (2 reviewed in MR procedure + post marketing reports - included as data were provided)
7. Octapharma
  - a. Octagam (3, 2 previously reviewed, 1 ongoing + post marketing reports)

### Not included

8. Sanquin
  - a) Nanogam (1 – ongoing)
9. Talecris
  - a) Gamunex (no unsubmitted studies)

## 2. Clinical studies

### 1. Baxter

Two products of the company were assessed:

- Gammagard /SD (intravenous) 19 studies (13 studies were reviewed by the assessor, the other reports were case reports or small studies (n<15))
- Subcuvia (subcutaneous) 2 studies

#### a) Gammagard

Of note are the 4 following publications reporting on GAMMAGARD administration in (premature) **neonates** with infections (Abzug et al., 1995, Baker et al 1992, Homan et al., 1990, Noya et al., 1988). These will be commented on in more detail. They are followed by 9 other reports covering a wide range of indications e.g. CMV infection post-transplantation, ITP, PID, post-streptococcal obsessive disorder, recurrent respiratory tract infections, autism, Kawasaki's disease. Only a brief statement will be made on these 9 trials.

**Abzug et al., 1995,  
Neonatal Enterovirus Infection: Virology, Serology and Effects of Intravenous Immune Globulin**

**Objective(s)**

Assessment of the effect of IVIg on symptomatic enterovirus infections in neonates

**Study design**

Prospective, randomized, controlled study on the virology and serological responses to symptomatic enterovirus infection in neonates and their mothers

**Study population /Sample size**

16 Neonates  $\leq$ 14 days of age and presumed enterovirus infection

**Treatments**

2 treatment groups: 0.75 g/kg BW (IVIg neutralizing titre  $\geq$  or  $<$  1:800 relative to viral isolate sample) Control group did not receive IVIG

**Baseline data**

11 neonates did not have detectable serum neutralizing antibody to their own viral isolates, despite the presence of neutralizing antibody in 9 of 11 mothers of these infants. Viremia and viruria were demonstrated in 8 and 7 neonates. Viremia was associated with onset of illness in the first 5 days of life, low initial serum neutralization titer

**Efficacy results**

Randomized administration of intravenous immune globulin (IVIg; 750 mg/kg) to nine neonates overall modestly increased serum neutralization titers but did not reduce the daily incidence of viremia and viruria compared with that of controls. However, receipt of IVIG containing a neutralization titer of  $\geq$ 1:800 to the patients' own viral isolates was associated with significantly higher serum neutralization titers and more rapid cessation of viremia and viruria.

**Safety results**

IVIg infusions were generally well tolerated. Possibly IVIG treatment related adverse events were observed in 3 patients (fever, tachycardia, tachypnea and fever).

**Rapporteur's comment**

This study, in 16 neonates with symptomatic enterovirus infections, shows that IVIG containing a neutralization titre of  $\geq$ 1:800 to the patients' own viral isolates was associated with significantly higher serum neutralization titres and more rapid cessation of viremia than in the non-treated control group. The AEs were in keeping with those seen in IVIG in general.

**Homan et al., 1990**

**Safety of intravenous immunoglobulin infusion in neonates at risk for sepsis.**

**Objective(s)**

Pilot study on the safety of IVIg, Gammagard, in 2 groups of very low birth weight ( $<$  1750g) neonates to treat and prevent infections

**Study design**

Safety study of IVIg in 2 groups: a) for the treatment of proven or suspected sepsis (treatment group) or b) for the prevention of prevention of sepsis (prevention group)

**Study population /Sample size**

20 premature neonates

**Treatments**

Single infusion of 0.5 g/kg BW over 3 hours in each group (n=10)

**Efficacy results**

Not applicable

**Safety results**

The infusion of 500 mg/kg BW IVIg was found to be safe in both groups of neonates. No instances of hypersensitivity, inflammatory or toxic reactions were detected. No differences were found in heart rate, respiratory rate, mean arterial blood pressure, or urine output in either group during or following the infusion compared with preinfusion values, except for a small but significant decrease in heart rate postinfusion in the prevention group. Likewise, serum glucose, sodium, serum glutamic oxaloacetic transaminase, and osmolality were unchanged 15 minutes and 6 hours following infusion. Urea nitrogen rose a small but significant amount in both groups. Hemoglobin concentration declined a small but significant amount 15 minutes post-infusion in the prevention group, but returned to baseline by 6 hours post-infusion. There were no changes in white blood cell count or platelet counts in either group.

**Rapporteur's comment**

These data from 20 neonates indicate that IVIG given at a single dose of 0.5 g/kg was not associated with any unlisted adverse effects

**Noya F, Rench MA, Garcia-Prats JA, et al. Disposition of an immunoglobulin in very low birth weight neonates. J Ped, 1988; 112: 278-283**

**Objective(s)**

Establishment of (PK) data on potential efficacy of IVIg in the prevention of late onset infection in very low birth weight neonates

**Study design**

Study on efficacy, tolerability, disposition and pharmacokinetics of IVIg Very low birth weight neonates (750 – 1500g);

**Study population /Sample size**

20 very low birth weight neonates

**Treatments**

Single doses, 2 dosage groups: 500 mg/kg BW or 750 mg/kg BW during the first 5 days of life

## PK results

Mean peak IgG concentrations were 1564 and 1316 mg/dL for the high-dose and low-dose groups, respectively. Mean IgG concentrations were very similar for both groups on post-infusion days 1, 4, 7, 14, 21, and 28. IgG concentrations remained above 300 mg/dL in seven of 10 infants in each group by day 21, and in six of the high-dose group and seven of the low-dose group by day 28. Mean elimination half-lives were 22.6 and 22.8 days in the high-dose and low-dose groups, respectively.

## Safety results

The infusions were well tolerated. Changes in haemoglobin, hematocrit and total hemolytic complement occurred as expected. No hepatotoxic effects were observed

### Rapporteur's comment

These data from 20 very low birth weight neonates show that IVIG given at single doses of 500 mg/kg or 750 mg/kg led to IgG concentrations remained above 300 mg/dl and t1/2 of ~22 days. The half-life data correspond to that seen in healthy adults.

**Baker CJ, Melish NM, Hall RT, et al. and the multicenter group for the study of immune globulin in neonates. Intravenous immune globulin for the prevention of nosocomial infection in low-birth-weight neonates. N Engl J Med 1992; 327 (4): 213-219**

## Objective(s)

Prevention of nosocomial infection in premature infants with very low birth weight

## Study design

Multi-center, placebo-controlled, double-blind study

## Study population /Sample size

588 premature, very low birth weight neonates (500 – 1500g)

## Treatments

5 IVIG/placebo infusions administered over 10 weeks. IVIG dose was 0,5 g/kg at each occasion or placebo (5% albumin, 0,9 NaCl) The 1st between day 3-7, the following 1 week later and then every 2 weeks until 5 infusions had been given or discharge

## Efficacy results

There was a significant reduction in the risk of a first nosocomial infection in the recipients of immune globulin as compared with the placebo recipients (relative risk, 0.7; 95% CI: 0.5 to 0.9). About 85% of the nosocomial infections were bacterial; the majority of these were caused by coagulase-negative staphylococci or *Staphylococcus aureus*. The neonates who received immune globulin had fewer mean days of hospitalization than the controls (62 vs. 68, P = 0.15); among the infants with infections, the difference in the mean length of the hospital stay was even greater (80 days vs. 101 days, P = 0.02).

## Safety results

The infusions were well tolerated, mild reversible adverse reactions occurred in 5 infants in each group (<1%, mild increases or decreases in blood pressure, heart rate or temperature).

**Rapporteur's comment**

This large placebo-controlled study in 588 very low birth weight neonates indicates that repeated IVIG infusions of 500 mg/kg each led to a reduction in the risk of a first nosocomial bacterial infection.

Three Cochrane systematic reviews of randomised controlled trials in nearly 6,000 patients suggest that IVIG is safe and reduces sepsis by about 15% when used as prophylaxis but does not reduce mortality in this situation.

When IVIG is used in the acute treatment of neonatal sepsis, however, there is a suggestion that it may reduce mortality by 45%. However, the existing trials of treatment were small and lacked long-term follow-up data.

**Barron KS et al**

**Treatment of Kawasaki syndrome: a comparison of two dosage regimens of intravenously administered immune globulin. J Pediatr. 1990 Oct;117(4):638-44.**

**Objective(s)**

The objective was to evaluate safety and efficacy of 2 IVIG dose regimens for reducing the incidence of coronary artery aneurysms in Kawasaki syndrome in

**Study design**

Multicenter, randomised, prospective clinical trial comparing two dosage regimens of IVIG.

**Study population /Sample size**

44 children with Kawasaki's disease.

**Treatments**

400 mg/kg daily for 4 days (22 patients) or 1 gm/kg as a single dose (22 patients). All patients received aspirin therapy, and all were enrolled within 7 days of onset of fever.

**Efficacy results**

The presence of coronary artery aneurysms was evaluated by means of two-dimensional echocardiography before infusion; at days 4 to 6, 14 to 21, and 42 to 49 after infusion; and at 1 year. Coronary artery aneurysms were detected in 3 of the 44 patients, including one patient receiving 400 mg/kg and two patients receiving 1 gm/kg (p value not significant). Patients receiving the 1 gm/kg dose had a faster resolution of fever and were discharged from the hospital approximately 1 day sooner than the 400 mg/kg group (p = 0.01). Although the relatively small sample size in this trial does not allow for a more definitive statement regarding the occurrence of coronary artery aneurysms, it appears that the 1 gm/kg dose is associated with a more rapid clinical improvement and a shorter hospital stay

**Safety results**

There were no serious adverse events to IVIG. Mild adverse reactions occurred in 4 children; 1 receiving 1 g/kg and 3 receiving 0.4 g/kg

**Boris M et al, Improvement in children with autism treated with intravenous gamma globulin Journal of Nutritional & Environmental Medicine, Volume 15, Issue 4 December 2005 , pages 169 - 176**

**Objective(s)**

Immune dysfunction has been associated with children with autism. One study found a beneficial response of intravenous gamma globulin (IVIG) therapy in autistic children. The present study further evaluated the administration of IVIG to these children.

**Study design**

Multicenter, randomised, prospective clinical trial in documented autistic children. Baseline and monthly Aberrant Behavior Checklists were completed on each child in order to measure the child's response to IVIG.

**Study population /Sample size**

26 autistic children.

**Treatments**

400 mg kg<sup>-1</sup> IVIG was administered each month for 6 months

**Efficacy results**

The participants' overall aberrant behaviors decreased substantially soon after receiving their first dose of IVIG. Further analysis of the total scores revealed decreases in hyperactivity, inappropriate speech, irritability, lethargy and stereotypy. However, 22 of the 26 children regressed to their pre-IVIG status within 2-4 months of discontinuing the IVIG.

Significant improvement occurred in autistic children receiving monthly IVIG. There is a reasonable rationale considering the risk/reward ratio to utilize IVIG therapy in children with autism. A well-controlled placebo double-blind study would be important to further clarify the use of IVIG in autism and its duration of benefits.

**Safety results**

No adverse events were observed.

**Flynn JT et al, Intravenous Immunoglobulin Prophylaxis of Cytomegalovirus Infection in Pediatric Renal Transplant Recipients, Am J Nephrol 1997; 17:146-152 (DOI: 10.1159/000169089)**

**Objective(s)**

The objective was to evaluate Gammagard® as a prophylaxis to CMV-negative children who received CMV-positive allografts and to compare the results with similar high-risk recipients transplanted prior to the use of IVIG.

**Study design**

Open-label study with IVIG as CMV prophylaxis and retrospective comparison to similar high-risk recipients transplanted prior to the use of IVIG.

**Study population /Sample size**

138 CMV negative children transplanted with CMV positive allografts.

**Treatments**

Gammagard 1 g/kg once weekly for 4 weeks after transplantation. The first dose was given within 72 hours of transplantation. Immunosuppressive therapy entailed prednisolone, azathioprine and ciclosporin A.

**Efficacy results**

Symptomatic CMV disease developed in 17% of the IvIgG recipients as compared with 71% of the untreated patients ( $p = 0.01$ ). The CMV infections that did occur in IvIgG recipients developed significantly later than in untreated children (median time of onset after transplantation 2.60 vs. 1.35 months;  $p < 0.05$ ) and generally were less severe, although 1 IvIgG recipient died despite prophylaxis. IvIgG administration did not affect the frequency of rejection or graft or patient survival. The authors concluded that IvIgG administration to high-risk pediatric renal transplant recipients may protect against post-transplantation CMV disease and may lessen the severity of infections that do develop in patients who receive it.

**Safety results**

There were no significant adverse reactions to IVIG.

**King SM et al, Randomized Comparison of Ganciclovir Plus Intravenous Immune Globulin (IVIG) with IVIG Alone for Prevention of Primary Cytomegalovirus Disease in Children Receiving Liver Transplants, by © 1997 The University of Chicago Press.**

**Objective(s)**

Primary objective was to determine the benefit of ganciclovir (5 mg/[kg · d]) for 30 days in addition to intravenous immune globulin (IVIG) for 16 weeks for prevention of primary cytomegalovirus (CMV) disease in children receiving liver transplants.

**Study design**

Randomized placebo-controlled trial

**Study population /Sample size**

56 children after liver transplantation. Two groups of patients (recipients of 29 ganciclovir plus IVIG and 27 recipients of IVIG alone)

**Treatments**

1 g/kg IVIG within 72 hours of liver transplantation, then 0.5 g/kg weekly for weeks 1-8 and biweekly for weeks 10-18.

**Efficacy results**

The incidence of CMV disease among the ganciclovir plus IVIG recipients and the IVIG alone recipients was 17% and 26%, respectively, and the time to disease in these recipients was 46 days and 32 days, respectively. There was no difference between groups in terms of survival; episodes of rejection, bacteremia, or fungemia; use of immunosuppressive agents; and incidence of leukopenia or thrombocytopenia. These results suggest that a 4-week course of ganciclovir with IVIG is not more effective than IVIG alone for prevention of primary CMV disease. Since short-term prophylaxis with ganciclovir may delay the onset of CMV disease, further studies with a longer course of ganciclovir prophylaxis are warranted.

**Safety results**

There were no significant adverse reactions to IVIG.

**Nydahl-Perrson K et al, Acta Paediatr. 1995 Sep;84(9):1007-9. A prospective, double-blind, placebo-controlled trial of i.v. immunoglobulin and trimethoprim-sulfamethoxazole in children with recurrent respiratory tract infections.**

**Objective(s)**

The objective was to compare (IVIG) and trimethoprim-sulfamethoxazole (TMS) treatment in children with recurrent bacterial respiratory tract infections

**Study design**

Prospective, double-blind, placebo-controlled study of iv immunoglobulin (IVIG) and trimethoprim-sulfamethoxazole (TMS) in children with recurrent respiratory tract infections

**Study population /Sample size**

23/24 children less than 12 years of age with recurrent bacterial respiratory tract infections.

**Treatments**

For 4 months: 0.4 g/kg every 4 weeks + placebo (n=8), trimethoprim-sulfamethoxazole (TMS) + placebo (n=8), Placebo + placebo (n=7)

**Efficacy results**

The 7 children given placebo for both IVG and TMS continued to have bacterial respiratory infections, while 14 of 16 children given active therapy with either IVIG or TMS became infection-free (p=0.002). No relation to IgG subclass level or between the two modalities of treatment was found. The authors concluded that most infection-prone children suffer from viral infections and are given antibiotics unnecessarily. Of the small group of children that have documented, repeated bacterial infections, prophylactic therapy with either IVIG or TMS can substantially diminish the number of infections.

**Safety results**

There were no significant adverse reactions to IVIG.

**Ochs H et al, Efficacy of a New Intravenous Immunoglobulin Preparation in Primary Immunodeficient Patients; Clinical Therapeutics 9: 512 – 522; 1987**

**Objective(s)**

The objective was to evaluate efficacy and safety of Gammagard in PID patients

**Study design**

Prospective, open-label study

**Study population /Sample size**

17 PID children.

**Treatments**

400 mg/kg at 4 weekly intervals for 1 year.

**Efficacy results**

Efficacy was determined by the number of acute and new chronic infections as well as by the number of prescriptions filled for antibiotics. These results were compared with those reported for similar preparations. The incidences of infection and antibiotic usage were as

low as or lower than those reported with other preparations. Thus we conclude that this new intravenous immunoglobulin product is a safe, effective prophylactic treatment for patients who have primary immunodeficiency.

### **Safety results**

In assessing safety, the incidence of adverse reactions during the first 48 hours after each infusion and long-term changes in laboratory values were considered. Results showed a low (4.4%) incidence of acute adverse reactions, and no serious reactions or significant changes were noted in any of the laboratory test results.

**Perlmutter SJ et al; Lancet. 1999 Oct 2; 354(9185):1153-8. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood.**

### **Objective(s)**

The objective was to evaluate whether plasma exchange or IVIG would be better than placebo (sham IVIG) in reducing severity of neuropsychiatric symptoms in children with severe, infection-triggered exacerbations of obsessive-compulsive disorder (OCD) or tic disorders, including Tourette syndrome

### **Study design**

Randomised, placebo-controlled trial of IVIG vs. plasma-exchange

### **Study population /Sample size**

29 children (5-14) with severe, infection-triggered exacerbations of obsessive-compulsive disorder (OCD) or tic disorders,

### **Treatments**

1 g/kg daily for 2 days (n= 9), PE 5 cycles of 2 weeks (n=10), placebo (n= 10)

### **Efficacy results**

At 1 month, the IVIG and plasma exchange groups showed striking improvements in obsessive-compulsive symptoms (mean improvement on children's Yale-Brown obsessive compulsive scale score of 12 [45%] and 13 [58%], respectively), anxiety (2.1 [31%] and 3.0 [47%] improvement on National Institute of Mental Health anxiety scale), and overall functioning (2.9 [33%] and 2.8 [35%] improvement on National Institute of Mental Health global scale). Tic symptoms were also significantly improved by plasma exchange (mean change on Tourette syndrome unified rating scale of 49%). Treatment gains were maintained at 1 year, with 14 (82%) of 17 children "much" or "very much" improved over baseline (seven of eight for plasma exchange, seven of nine for IVIG). The authors interpret these results as follows: Plasma exchange and IVIG were both effective in lessening of symptom severity for children with infection-triggered OCD and tic disorders. Further studies are needed to determine the active mechanism of these interventions, and to determine which children with OCD and tic disorders will benefit from immunomodulatory therapies

### **Safety results**

Children tolerated PE well; IVIG related AEs were nausea, vomiting and headache.

**Stratta RJ et al, Transplantation. 1991 Jan;51(1):90-7. Successful prophylaxis of cytomegalovirus disease after primary CMV exposure in liver transplant recipients.**

**Objective(s)**

The objective was to compare IVIG + acyclovir to prevent CMV in liver transplanted patients to data of untreated historical controls

**Study design**

Non-randomised, open-label study comparing IVIG + acyclovir to prevent CMV to data of 21 historical controls (non-treated). During a 38-month period, the authors studied 320 liver transplants in 283 recipients (202 adults, 81 children). CMV disease was documented in 85 patients (30.0%) The major risk factor for CMV disease was primary CMV exposure (transplanting a seropositive allograft into a seronegative recipient).

**Study population /Sample size**

24 children/42 patients with primary CMV exposure .

**Treatments**

IVIG; 0.5 g/kg at weekly intervals for 6 week , acyclovir i.v .8 h after transplantation and oral thereafter for 3 months

**Efficacy results**

CMV prophylaxis resulted in a dramatic reduction in the incidence of CMV disease (71.4% vs. 23.8%, (P less than 0.01). All cases of CMV were treated with intravenous ganciclovir (5 mg/kg b.i.d. for 14 days), with 5 patients in the control group developing recurrent CMV disease (33.3% relapse). In the 16 patients receiving prophylaxis who did not develop CMV disease, all developed positive CMV-IgG titers with the passive administration of IgG. However, none developed any evidence of CMV infection or viral shedding as assessed by IgM titers and surveillance viral cultures. Four deaths occurred (all control patients), but none were related to CMV disease. Overall patient and graft survivals after primary CMV exposure were 90.5% and 82.2%, respectively, after a mean follow-up of 14 months. The authors concluded that primary CMV exposure is a major risk factor for CMV disease in liver transplant recipients. Intravenous IgG plus acyclovir is safe and effective in preventing CMV infection and disease in this setting. Because of the scarcity of donor organs, we do not advocate protective matching to avoid primary CMV exposure but rather recommend prophylaxis to prevent CMV disease in this high-risk group.

**Safety results**

There were no significant adverse reactions to IVIG.

**Taratino MD et al, J Pediatr. 1999 Jan;134(1):21-6. Treatment of childhood acute immune thrombocytopenic purpura with anti-D immune globulin or pooled immune globulin.**

**Objective(s)**

Primary objective was to evaluate the effectiveness of initial treatment of children with acute immune thrombocytopenic purpura (ITP) with anti-D immune globulin (anti-D) or pooled IgG immune globulin (IVIg).

**Study design**

Retrospective chart review on the efficacy of IVIG or anti-D in children with acute ITP

**Study population /Sample size**

27 acute ITP children.

**Treatments**

Anti-D at 45 to 50 microg/kg (WinRho SD, NABI) or IVIg at 0.8 to 1 g/kg (Gammagard SD).

**Efficacy results**

Time to achieve a platelet count  $\geq 20 \times 10^9 /L$  ( $20,000/mm^3$ ) was  $1.54 \pm 0.51$  days in the IVIg group ( $n = 13$ ) and  $1.26 \pm 0.82$  days in the anti-D group ( $n = 14$ ) ( $P = .34$ ). Time to achieve a platelet count  $\geq 40 \times 10^9 /L$  ( $40,000/mm^3$ ) was  $1.77 \pm 0.74$  and  $1.49 \pm 1.01$  days for the IVIg and anti-D groups, respectively ( $P = .32$ ). Children given IVIg were hospitalized for  $2.1 \pm 0.87$  days, whereas those given anti-D were hospitalized for  $1.94 \pm 1.08$  days. A net decrease in hemoglobin concentration was observed after receipt of IVIg ( $9.1 \pm 7.3$  g/L [ $0.91 \pm 0.73$  g/dL]) and after anti-D therapy ( $4.5 \pm 10.3$  g/L [ $0.45 \pm 1.03$  g/dL],  $P = .23$ ). The authors concluded that in this retrospective analysis anti-D was as effective as IVIg for the treatment of acute ITP in children. However, randomized, controlled trials are needed to establish the role of anti-D in the treatment of acute ITP in children.

**Safety results**

No patient required intervention for hemolysis. No symptoms related to anemia were reported.

**b) Subcuvia**

Ugazio AG, Duse M, Plebani A, Notarangelo LD, Burgio GR: "Subcutaneous infusion of gamma globulins in the management of agammaglobulinemic patients" - Birth Defects 19: 213-5, 1983

**Objective(s)**

Safety and efficacy of SCIG in PID patients in home setting

**Study design**

Prospective, open trial for 3-9 months (compared to former i.m. injections)

**Study population /Sample size**

14 PID children (4-15 years)

**Treatments**

SCIG (Immuno, Wien) loading dose 100mg/kg daily for 5-10 days, then 50 -100 mg/kg once /week, 5-10 infusions in hospital, after that home treatment

**Efficacy results**

IgG serum levels were higher under SCIG treatment (80%-170% of normal age range) compared to i.m. (155\_60% of normal age range). Additionally SCIG was preferred by all children over 6 compared to the former i.m. injections.

**Safety results**

No major side-effects were recorded, some rare painful injection site reactions occurred.

## **Fasth A, Nyström J, 2007; Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency**

### **Objective(s)**

Primary objective was to evaluate safety and tolerability of home treatment with a 16% ready-to-use human normal immunoglobulin solution for subcutaneous administration in PID children previously receiving intravenous immunoglobulin (IVIg) treatment. Secondary objectives were to evaluate the efficacy of SCIg 16% through documented bacterial infections, IgG trough levels, quality of life (Child Health Questionnaire (CHQ)), healthcare resource utilisation and patient preference.

### **Study design**

Prospective, open-label study

### **Study population /Sample size**

12 PID children.

### **Treatments**

Subcuvia 16%

### **Efficacy results**

SCIg 16% consistently maintained high IgG trough levels, and the rate of bacterial infections was not different from that seen with previous IVIg treatments. The rate of infections observed in the study (2 per month) was comparable with the data reported by Chapel (2000).

### **Safety results**

There were no significant changes from baseline in vital signs or laboratory parameters. Most adverse events (311 of 328) were mild injection site reactions that, in most cases, resolved after 1-2 months. Home-based SCIg treatment was well tolerated.

### **Rapporteur's comment on studies for Gammagard /SD and Subcuvia**

Altogether, 19 publications were identified reporting paediatric use of GAMMAGARD/ GAMMAGARD S/D and 2 for Subcuvia.. 15 of these were reviewed in this assessment (case reports, studies < 15 patients were not assessed) Data is heterogeneous, with a number of publications relating to experimental or last-resort therapies.

Given the heterogeneity of the indications no clear recommendations can be given to any changes in the SmPC/PIL. The largest study by Baker et al did not convincingly show a benefit for the prevention of nosocomial infections in premature infants with very low birth weight. As a large international placebo-controlled study with various IVIG products (INIS) is currently being completed to resolve the question of whether IVIG can prevent or reduce the risk of sepsis in premature neonates, these data should be awaited prior to any alterations in SmPCs or the core SmPC/PIL.

Not all studies provided detailed safety related data, thereby limiting any precise conclusions. The adverse events corresponded to those listed in the coreSmPC. The results reflect the overall good tolerability of this class of products spanning all pediatric age groups including premature infants and thus do not warrant a different wording in the SmPC than hitherto.

## 2. Biotest

### a) Intratect

- **Study 941**

A phase III study was performed to demonstrate efficacy, safety and pharmacokinetic properties of Intratect in patients with primary immunodeficiency syndromes (PID) with hypo- or agammaglobulinemia. The age of the patients ranged from 6 - 43 years

- **Study 957**

A phase III/IV study, which was to extend the database of Intratect use in the PID setting and to demonstrate efficacy, safety and pharmacokinetic properties. Mean age was  $18.1 \pm 10.8$  years and ranged between 6 and 48 years. 19 patients were between 6 and 12 years old, 17 were 13 -20, 8 were 21-30, 2 were 31 - 40 and 5 patients were 40-48 years old.

#### **Rapporteur's comment on studies for Intratect**

These studies included children between 6 and 18 years of age. The data were not specifically evaluated according to age group. The IgG concentrations were within the normal ranges for the age groups. Normal IgG ranges (in g/L) are between 6.00-13.00 for 6-9 year-olds, 7.00-14.00 for 10-13 year-olds and 7.00-16.00 for adults, demonstrating a large overlap in normal values for adults and children.

These data have previously been evaluated in MR procedures and will therefore not be assessed again here.

## 3. C.A.F. – D.C.F

### **a) Multigam**

(Manufacturer: Biotest Pharma GmbH (Germany) corresponding product of Biotest Pharma GmbH: Intratect)

**Pilot study (B03920072075) on the effect of intravenous immunoglobulin (IVIG) infusion on total and serotype-specific anti-pneumococcal antibodies in paediatric patients with primary immunodeficiency (PID) and after bone marrow transplantation (Poster 2010). Not a company-sponsored study**

#### **Objective(s)**

To determine the trough and peak levels of plasma Pneumococcal polysaccharide antibody (PnAbs) in plasma from regularly IVIG-treated PID and BMT patients.

#### **Study design**

A non-interventional prospective multicentre study of PID and BMT paediatric patients. 16 individual ELISAs (serotypes: 1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 12F, 14, 18C, 19A, 19F, and 23F) according to WHO guidelines.

- Total protective serotype-specific PnAbs: Pre-incubation with C-PS
- Serotype specific PnAbs: pre-incubation with C-PS & serotype 22F

#### **Study population /Sample size**

A total of 22 PID patients and 18 BMT patients have been enrolled in 7 clinical centres. All patients are < 18 years old. Only 2 patients have been evaluated until now. The elaboration of all raw data not yet been finalised.

## Treatments

Multigam 400 mg/kg, 6 infusions

## Results

In 2 patients abundant functional PnAbs against 16 serotypes in patient plasma. The trough and peak PnAb levels comply with WHO13 specifications established for Pn vaccines to ensure protection against invasive pneumococcal infection.

### Rapporteur's comment on studies for Multigam

No conclusions can be drawn at present, as there is currently only data on 2 patients available (from the material (poster) that was submitted).

## 4. CSL Behring

### a) Sandoglobulin / Sandoglobulin Liquid

Three studies were presented by the company for Sandoglobulin / Sandoglobulin Liquid.

- **SAGL 351**  
A randomized, double-blind, controlled study on the safety, efficacy, pharmacokinetics and viral safety Sandoglobulin liquid (IGIV F10) in comparison with Sandoglobulin (SAGL) in 34 patients with PID. Ages ranged from 12 -59.
- **ZLB 97\_030**  
An open-label study on efficacy, tolerability and safety of Sandoglobulin Liquid in comparison to Sandoglobulin in adult patients with chronic ITP
- **SAGL 352**  
An open-label study in 6 paediatric patients with acute ITP, single daily infusions of 0.4 g IgG/kg Sandoglobulin or Sandoglobulin Liquid for (or for up to) 5 days

### Rapporteur's comment on studies for Sandoglobulin / Sandoglobulin Liquid

These 3 studies have already been assessed within a MR-procedure by the RMS UK and therefore will not be reviewed at length in this assessment.

In the PID study **351** no differences were seen in trough IgG levels, Cmax levels or safety parameters between the age groups.

Furthermore, no major difference was seen in responder rate and time to response in the adult and paediatric ITP population. However, as the numbers in the children's study were small (n=6) and the population was suffering from acute ITP (which is known to respond better to IVIG) no clear conclusions can be drawn.

### b) Vivaglobin

**Study CE 1200 – 3001 and CE 1200-3002, Vivaglobin in patients with PID (in USA + Canada and in Europe respectively).**

**Rapporteur's comment on studies for Vivaglobin CE 1200 – 3001 and CE 1200-3002**

The 2 prospective, uncontrolled studies were performed in PID patients with Vivaglobin. Twenty-two children were included, 14 in the European study. These trials have been reviewed in an MR-procedure and will not be detailed here.

In Study CE 1200-3002 a separate sub-study PK analysis was performed for the following age groups: 6 - <12 years (n=12)  $\geq 12 - \leq 16$  (n= 2), >16 - < 65 (n= 24), and  $\geq 65$  (n= 3). Although in some groups the numbers are too small to draw any firm conclusions, the overall pattern was that the median IgG levels, C<sub>max</sub>, t<sub>max</sub> did not differ substantially between the different age groups. In the efficacy part of the study the children achieved similar levels to the adults and juveniles (8.5 vs. 8.6 -9.0 g/L). Furthermore older patients (> 65 years) did not differ from other adults in their IgG levels.

For both studies none of the children experienced a serious bacterial infection (efficacy parameter) and the safety profile was similar to adults.

**Study ZLB 06\_005 CR Vivaglobin in previously untreated patients with PID – Art. 46 Paediatric study****Objective(s)**

Efficacy and safety study of Vivaglobin in previously untreated patients (PUPs) with PID

**Study design**

Prospective, open-label study

**Study population /Sample size**

8 PID children of a total of 18 patients

**Treatments**

Loading dose of 100 mg/kg for 5 consecutive days

**Efficacy results**

17/18 patients had IgG increases to > 5 g/L by day 12 and all patients reached this level by Day 19 SCIg 16% consistently maintained high IgG trough levels and the rate of bacterial infections was not different from that seen with previous IVIg treatments. The rate of infections observed in the study (2 per month) was comparable with the data reported by Chapel (2000),

**Safety results**

None of the 7 SAEs were deemed related to the product. 6 patients initially had 42 injection site reactions, but local reactions apparently declined over time

**Rapporteur's comment on study Study ZLB 06\_005 CR with Vivaglobin**

The study indicates that subcutaneous treatment in previously untreated patients (PUPs) with PID may be possible without an intravenous loading dose. However the small sample size (n=8) of the study does yet not warrant a change in the SmPC/PIL.

## 5. Grifols

### Flebogamma 5% + Alphaglobin

The company submitted 5 reports on trials and post marketing observation studies:

- 1- Clinical study to evaluate the safety, efficacy, and pharmacokinetics of Flebogamma® [Immune globulin Intravenous (human)] for replacement therapy in primary immunodeficiency diseases (PID) - Grifols 04-01.
- 2- A Single-Centre, Non-Blinded, Randomised, Parallel Comparison of the Efficacy and Safety of Intravenous Versus Rapid Subcutaneous Infusion of Immunoglobulin in Paediatric Patients with Primary Immunodeficiency Disease - IG704.
- 3- Multicentric postmarketing observation study Alphaglobin® 9301 - AGL9301
- 4- Multicentre Post Marketing Observation Study - AWB9401,
- 5- Monocenter Post Marketing Observation Study, Alphaglobin® ATG 9304 (former name: 9302) - ATG9304.
- 6- Monocenter Post Marketing Observation Study Alphaglobin® ATG 9410 - ATG9410

**TABLE 9. Summary of Flebogamma Pediatric Information from Clinical Studies**

Study Identifier	Proposed Dose (mg/kg)	Diagnosis <sup>a</sup>	Pediatric Subjects	Number of infusions	Subjects with Adverse Events	Infusions with Adverse Events
GRIFOLS 04-I	300-600 every 3 or 4 weeks	PID	5	73	5	18 <sup>b</sup>
IG704	200-400 every 3 weeks	PID	8	72	8	20 <sup>b</sup>
AGL9301	370 (mean dose) <sup>c</sup>	PID, ITP, malignancy, SID, abortion	24	24-144 <sup>d</sup>	5	9
AWB9401	269 (mean dose) <sup>c</sup>	PID, ITP, malignancy, SID	13	36	0	0
ATG9304	321 (mean dose) <sup>c</sup>	Cancer, fever, infections	30	68	1	1
ATG9410	240 x 6	Hutchinson-Guilford	1	6	0	0

<sup>a</sup>PID = Primary immune deficiency; SID = Secondary immune deficiency; ITP = Idiopathic thrombocytopenic purpura.

<sup>b</sup>Defined as infusions with any adverse event(s), regardless of relationship, that occurred during an infusion or within 72 hours after the end of the infusion.

<sup>c</sup>Actual dose administered.

<sup>d</sup>Cannot determine subset attributable to pediatric subjects.

## **Study 04 -01 Safety, efficacy, and pharmacokinetics of Flebogamma for replacement therapy in PID**

### **Objective(s)**

Safety, efficacy, and pharmacokinetics of Flebogamma for replacement therapy in primary immunodeficiency diseases (PID) and whether it exhibits the therapeutic efficacy as determined by the U.S. FDA criterion of  $\leq 1$  serious infection/subject/year.

### **Study design**

Prospective, open-label, multi-center clinical trial

### **Study population /Sample size**

5 PID children of a total of 51 patients

### **Treatments**

300-600 mg/kg every 3 or 4 weeks for 12 months

### **Efficacy results**

Subjects who received Flebogamma infusions of 300-600 mg/kg had a serious bacterial infection rate of 0.061 infections/subject/year (3 infections over a total of 49.14 subject years; 98% CI = 0.011- 0.183), which satisfies the FDA efficacy criterion of  $\leq 1$  serious bacterial infection/subject/year.

- The mean rates of subjects missing work/school, being hospitalized, or visiting a physician/ER, were low in subjects treated with Flebogamma; for each parameter, the mean rate was less than 10 days or visits/subject year. There were no other infections documented by positive radiograph or fever.
- The pharmacokinetic behavior of the Total IgG levels, IgG subclass levels, and the IgG antibody levels to specified antigens followed similar patterns in subjects with PIDs.

### **Safety results**

Most subjects (96%) experienced at least 1 AE during the study. The most common AEs were headache, sinusitis, pyrexia, upper respiratory tract infection, nasal congestion, sore throat, cough, diarrhea, rhinorrhea, pain, back pain, fatigue, arthralgia, asthma aggravated, bronchitis, conjunctivitis, injection site reaction, and productive cough. Most AEs were mild or moderate in intensity. The AEs most commonly considered to be related to study drug were pyrexia, headache, rigors, and injection site reaction.

- The proportion of infusions for which an AE suspected to be related to study drug was reported either during the infusion or within 72 hours after infusion completion was small (approximately 8%). The frequency of related AEs appeared to be higher for subjects on the 21-day infusion schedule than that for subjects on the 28-day infusion schedule, although the clinical significance of this result is unclear.
- No subjects died, no subjects withdrew from the study because of AEs, and 8 subjects experienced 10 SAEs, of which 2 were considered related to study drug: pain and chest pressure sensation. Both events occurred in the same subject, and although the subject has a documented history of cardiovascular abnormalities, the Investigator could not completely rule out a relationship with the study drug.

### **Rapporteur's comment on Study 04-01 with Flebogamma**

Only 5 pediatric patients were included, thus no clear conclusions can be drawn; the efficacy and safety results for pediatric subjects (those  $\leq 16$  years old) appeared to be generally similar to those for the overall subject population.

**IG704****A Single-Centre, Non-Blinded, Randomised, Parallel Comparison of the Efficacy and Safety of Intravenous Versus Rapid Subcutaneous Infusion of Immunoglobulin in Paediatric Patients with Primary Immunodeficiency Disease****Objective(s)**

Efficacy and safety study, comparing intravenous Flebogamma 5% (control group) with rapid subcutaneous infusion of an intramuscular immunoglobulin (active group) in pediatric PID

**Study design**

This was a single-centre, non-blinded, randomized, parallel, phase III efficacy and safety study, comparing intravenous Flebogamma 5% (control group) with rapid subcutaneous infusion of an intramuscular immunoglobulin (active group) in the treatment of pediatric patients with primary immunodeficiency diseases. The study was done in one centre in the UK. The study ran from December 1999 – August 2001 (it was cancelled due to a poor recruitment rate: 17 (15 treated) – 60 intended, 6 months of treatment (28 weeks)

**Study population /Sample size**

8 PID children (with Flebogamma) of a total of 15 patients

**Treatments**

Of the 15 subjects treated, 8 of them received 9 infusions of Flebogamma 5%, so the total number of infusions was 72. The mean total dose was 141 g. Patients in the SC arm received usually 65-135 mg/kg per week.

**Efficacy results**

Trough IgG levels expressed as a percentage of the geometric mean titre of healthy age-matched controls were not statistically different between products (64% for the Flebogamma arm and 86% for the subcutaneous arm). Although trough levels tend to be higher by the subcutaneous route, for both routes they are well above the lower limit of their age and weight-related normal range and above the minimum considered to be effective in these patients (4-6 g/l). The mean percentage of the geometric mean titre of normal age-matched controls at 6 months was 82.4 % (subcutaneous arm) and 69.2 % (IVIG arm) without significant differences. Normalised levels by dose administered at 6 months were slightly higher for the subcutaneous arm (8.66 g/l) than for the IVIG arm (6.82) with a p value of 0.044. The clinical efficacy for both products was confirmed with the absence of differences in the mean number of days with infections (5 and 7).

**Safety results**

All of 105 adverse events recorded were considered by the investigator as not serious adverse events. Forty adverse events (38.09%) were unexpected adverse events and 65 (61.90%) were expected adverse events. In the subcutaneous group, 34 (12%) infusions were associated with adverse events suspected to be related to HLP-SCIG. In the control group the rate was 17% (12/72). There were no significant differences between groups by means of the Chi-square test. The main related AE was headache.

**Rapporteur's comment on Study IG 704 with Flebogamma**

This study was cancelled due to a low recruitment rate and only 15 subjects received treatment while the original plan was to include 60 patients, therefore no definitive conclusions can be drawn. For the 8 Flebogamma treated patients IgG trough levels were above 4-6 g/l.

Although the AE rate was higher in the IVIG group compared to the SCIG group this did not reach statistical significance.

## Study 9301 post-marketing observation with Alphaglobin

### Objective(s)

Multicentre post marketing observation study Alphaglobin to evaluate drug under routine conditions for tolerability

### Study design

6 month post marketing observation

### Study population /Sample size

89 patients in 20 hospitals + 5 practices of established doctors: **24** patients (12 m, 12 f) were  $\leq 18$  years (mean age: 7.5 + / - 4.6 years), 61 patients  $\geq 18$  years (mean age: 53.1 + / - 17.9 years) and 4 patients data about age are lacking. Range: 0.2 - 82 years. The main indications were ITP, secondary Immunodeficiency syndrome (65 patients), malignomas (35 patients), infections (21 patients), and habitual abortion (12 patients)

### Treatments

Depending on the indication each patient received 1-6 infusions

	All Patients (Valid Observations)	Patients Younger/Equal 18 Years (Valid Observations)	Patients Older 18 Years (Valid Observations)	Patients without Statement in the Age Question (Valid Observations)
Dose [mg/kg weight]	286.00 (191)	369.99 (78)	236.62 (106)	98.86 (7)
Total Amount of Infusion [g]	14.02 (297)	12.73 (78)	14.12 (204)	19.60 (15)
Length of Infusion [h]	2.27 (289)	3.20 (72)	1.94 (202)	2.39 (15)
Flow Rate at the Beginning of the Infusion [drops/min.]	25.15 (185)	12.64 (42)	27.30 (129)	42.86 (14)
[ml/h]	52.60 (47)	61.45 (29)	38.82 (17)	30.00 (1)
Flow Rate for the Rest of the Infusion [drops/min.]	50.33 (177)	38.53 (34)	51.53 (129)	66.86 (13)
[ml/h]	78.29 (49)	57.94 (31)	116.47 (17)	60.00 (1)

### Efficacy results

N.a. (tolerability study)

## Safety results

No major changes were seen before and after administration of Alpaglobin for erythrocytes, haemoglobin, lymphocytes, temperature, heart rate, blood pressure in both the younger and older population. Leukocytes were lower in children, but still within the norm ranges. Thrombocytes were higher in the paediatric population but also within the norm ranges. For thrombocytes in the ITP sub-population see tables below. There were 9 AEs (mainly headaches) in 5 children and 6 in 5 adults.

### ITP sub-population

- All Patients (N = 89) -

Thrombocytes (/mm <sup>3</sup> )	Mean Difference (before/ after)	Std. Dev.	Minimal Difference (before/ after)	Maximal Difference (before/ after)	Mean Absolute Value before	Mean Absolute Value after	Valid Cases for Difference Calculation
ITP	-123,435	97,745	-7,000	-326,000	(N=22) 23,650	(N=20) 148,300	20
Remaining Indications	2,809	90,001	1,000	-363,560	(N=63) 200,928	(N=51) 215,484	51

- Patients younger/ equal 18 years (N = 24) -

Thrombocytes (/mm <sup>3</sup> )	Mean Difference (before/ after)	Std. Dev.	Minimal Difference (before/ after)	Maximal Difference (before/ after)	Mean Absolute Value before	Mean Absolute Value after	Valid Cases for Difference Calculation
ITP	-120,744	95,375	-13,000	-326,000	(N=13) 12,638	(N=11) 126,727	11
Remaining Indications	-13,900	119,186	9,000	265,000	(N=11) 280,364	(N=10) 254,700	10

- Patients older 18 years (N = 61) -

Thrombocytes (/mm <sup>3</sup> )	Mean Difference (before/ after)	Std. Dev.	Minimal Difference (before/ after)	Maximal Difference (before/ after)	Mean Absolute Value before	Mean Absolute Value after	Valid Cases for Difference Calculation
ITP	-135,400	33,024	-7,000,000	-311,000	(N=10) 37,900	(N=10) 173,300	10
Remaining Indications	-6,717	13,904	1,000	-363,560	(N=51) 180,846	(N=38) 202,703	38

### Rapporteur's comment on Study 9301 with Alpaglobin

The post-marketing observational study covers a wide range of indications (also off-label). In the ITP sub-study both the younger (n=24) and older patients (n=61) achieved norm values for their platelet counts, whereby the children had slightly lower mean counts but also had had lower initial mean values.

No significant differences were seen in both the younger and adult population with regard to tolerability of Alpaglobin in the post marketing setting.

## Study 9304 post-marketing observation with Alphaglobin in paediatric oncology

### Objective(s)

Monocenter post marketing observational study to evaluate Alphaglobin for tolerability (and therapeutic properties) in pediatric oncology patients

### Study design

Monocenter post marketing observational study from November 1993 and June 1995.

### Study population /Sample size

30 juvenile patients (21 male, 18 female, 1 missing value) from 3 to 17 years (mean 10 years) Most children had a carcinoma or a tumour (e.g. acute lymphocytic leucemia) and an affection of the bone marrow (condition after chemotherapy, thrombocytopenia).

### Treatments

68 infusions of Alphaglobin (about 2 infusions and 1 lot per patient) were administered in 3.42 hours, the length of the whole treatment was on the average 10 days. In total 850 g IgG were infused. The mean dose was 13 g per infusion (170 mg/kgBW) and 28 g per patient and the mean speed of the infusion was 57 mg/min or 190 mg/kgBW/min. All patients received antibiotics and a further 50 different products were administered.

### Efficacy results

In 59% of all administrations the status was assessed as "better", in 7% as "worse" and in 24% as "unchanged" after each infusion. At the end of the study the status was rated as "better" in 90%, "unchanged" in 3%, "worse" in no case, and in 7% no judgement was given.

### Safety results

The vital signs recorded before each infusion and directly after each infusion remained stable. An increase of leukocytes (plus 6.06 gpt/l) and of thrombocytes (plus 23.26 gpt/l) was observed, each compared to the initial value. The rest of the blood count remained stable. Blood cultures and viral titers gave no reference upon infections during treatment. C-reactive protein decreased in 18 of 22 patients (decrease minus 7.65 mg/l). For 44% of the patients the tolerability of therapy was evaluated finally as "very good", for 53% as "good" and for one patient (3%) as "bad". This patient had the only reported adverse event ("fever" and "shivering" after infusion). The relation to the infusion was evaluated as "likely". The adverse event rates were 1.47 % (1 of 68 infusions) and 3.33 % (1 of 30 patients).

### Rapporteur's comment on Study 9304 with Alphaglobin

No clear conclusions can be drawn from the data of the heterogenous pediatric oncological population in this post-marketing observational study. No distinct safety signals were detected.

### ATG 9410 (only one patient is 11 years old- thus not reviewed in this report)

## **AGL 9401 Multicentre Post Marketing Observation Study with Alphaglobin**

### **Objective(s)**

Multi-center (21 hospitals, 2 practices) post marketing observational study to evaluate Alphaglobin for safety

### **Study design**

This study was a post-marketing observation study in 23 sites in Germany, conducted to obtain information on safety of Alphaglobin under routine conditions.

### **Study population /Sample size**

13/ 92 subjects were less than 18 years of age; this pediatric group consisted of 5 females and 8 males suffering from PID, secondary immunodeficiencies and ITP.

### **Treatments**

Mean dose per infusion was 269 mg/kg for all subjects. For subjects with idiopathic thrombocytopenic purpura it was 776 mg/kg. For those less than 18 years of age, the dose was 351 mg/kg. The pediatric group received from 1 to 6 infusions, for a total of 36 infusions

### **Efficacy results**

The 2 pediatric patients with ITP received 400 mg/kg in 3 and 5 consecutive days and their platelet count increased from 8,000 to 285,000 and 361,000 platelets/mm<sup>3</sup> respectively

### **Safety results**

There were no adverse events reported in 36 infusions in these 13 subjects.

### **Rapporteur's comment on Study 9401 with Alphaglobin**

No changes in the SmPC/PIL are warranted from this PMOS in this heterogeneous group of 13 pediatric patients.

### **Rapporteur's general comment on studies with Alphaglobin and Flebogamma**

No changes in the SmPC/PIL are warranted from the studies submitted for pediatric patients. The patient population covered mainly PID, secondary immunodeficiencies and ITP, but also some off-label uses. For the established indications the expected efficacy and safety outcomes were seen.

The warning on the excipient sorbitol should be maintained due to the rarity of fructose intolerance and due to its possible fatal outcome in non-diagnosed patients.

## 6. Kedrion

### Note of the company

To date, Kedrion S.p.A. is the Marketing Authorisation Holder of the following IVIg products, authorised in Italy with the following commercial names:

**IG VENA** (KeYven and Venital – identical national authorised products in IT)

IG VENA was first authorised in Italy through a National Procedure in April 1984.

In year 2006 the product was approved following a Mutual Recognition Procedure (end of procedure October 26th) in the following Member States: Italy (RMS) Austria, Germany, Greece, Poland and Portugal (CMSs). KeYven and Venital

The starting date of the PSUR (Jan 2002) is associated with the institution in Italy of a national Pharmacovigilance net aimed to collect cases of ADRs occurring in the Italian territory. This national Pharmacovigilance net, called NSIS (“Nuovo Sistema Informativo Sanitario”), is active since November 2001; previously collected data is not considered reliable.

### **Rapporteur’s comment on data with IgVena Studies**

The 2 studies that have been conducted with Ig VENA, one in primary immunodeficiency syndromes.(PID) (**KB028**) and one in ITP in adults were already assessed by the RMS IT within a MRP (**IT/H/0130/001/MR**) and will not be reviewed again here; suffice is to say that the studies both complied with the relevant CHMP Guidelines for IVIGs. The dosage and dosage regimens used corresponded to the recommendations of the core SmPC **KB028** was a prospective open label trial, primarily aimed at assessing the PK profile of Ig VENA in 16 patients, 9 women and 7 men of age ranging from 14 to 60 years, with PID.

No adverse event was reported in the PID or ITP trials. This is a somewhat meagre outcome as AEs would be expected with IVIG therapy.

### **PSUR**

From January 1st 2002 to December 17th, 2009, 46 Individual Case Safety Reports (80 ADRs) have been received by the Marketing Authorisation Holder, concerning the product, of which 10 (15 ADRs) experienced by children (bronchospasm, hypertonia, erythema/rash 3x, petit mal epilepsy, cough, enterocolitis, vomiting 3x, headache 2x, meningitis, whereby the latter 3 AEs are expected) Rash and changes in blood pressure have been seen with IVIG administration in general. There is no patient data on the petit mal epilepsy case, however, a relationship to the product is unlikely as this has not been described for IVIGs. Case reports in the literature even describe favourable outcomes for some forms of epilepsy treated with IVIG. Infectious enterocolitis is seen in patients with PID, therefore this is not seen as a side effect of IVIG..

The reported AEs do not give rise to new safety signals or differing safety signals in children.

# Octapharma

## Octagam 5%

In total, 14 clinical studies with Octagam 5% have been conducted by Octapharma, and more than 400 patients (of any age) have been enrolled in these trials. With the exception of Study GAM-NL-002, all other studies have already been submitted to several health authorities.

*Table 1 Overview on Study Details*

Study ID Phase Country [Reference]	Design	Period	No. of Patients 1) Total 2) ≤ 16 yrs of age	Indications/ Observation Period	Criteria Studied	Submission Status
GAM-04 Phase III Poland [1]	open prospective interventional	03.1997 to 12.1997	1) n=16 2) n=15	PID / 6 months	efficacy IgG levels safety	EU, US, CAN, AUS, et al
OCTA-06 Phase III US [2]	open prospective interventional	05.2000 to 12.2001	1) n=46 2) n=11	PID / 12 months	efficacy IgG levels PK safety	US, CAN, AUS, et al
GAM-NL-002 Phase IV Netherlands	open prospective interventional	11.2000 to 01.2002	1) n=11 2) n=11	PID, HIV / 4 weeks	IgG levels PK safety	Not submitted

US United States; EU European Union; CAN Canada; AUS Australia

The following table provides an overview on the suitability of data with respect to the paediatric population.

*Table 2 Suitability of Study Data for Assessment of Paediatric Data*

Study ID	Pharmacokinetics	Efficacy	Safety
GAM-04	✓	✓	✓
OCTA-06	only done in adults	✓	✓
GAM-NL-002	✓	not done at all	✓

### **GAM 04 Clinical study to demonstrate the efficacy of Octagam for replacement therapy in primary immunodeficiency syndromes (PID)**

#### Note of the company.

This study was performed in order to fulfil the European regulatory requirements in force at time of conductance. The study may be regarded as the pivotal trial for registration of *octagam 5%* in Europe. The study report has already been submitted to the PEI in May 1999.

#### **Objective(s)**

To document the pharmacokinetic (PK) characteristics, efficacy and (viral) safety of octagam 5% in patients suffering from primary immunodeficiency (PID) disorders

#### **Study design**

Open, prospective study in PID patients.

**Study population /Sample size**

17 patients (15 male, 2 female), patients' age ranged from 10.5 to 16.8 (median 14.0),

**Treatments**

0.2 to 0.4 g/kg every 3 weeks in order to obtain trough levels above 4 g/L, for a period of 6 months. All patients were previously treated with IVIG preparations.

**Efficacy results**

The clinical efficacy was assessed as very good, as the number of days with infections or fever, and the number of days out of school were remarkably low, and the type and severity of infections was comparable to those observed in the normal population. No severe infections leading to hospitalisation were observed. It is also noteworthy that the number of infectious episodes was lower, when IgG plasma levels were maintained around 6 g/L than when the IgG plasma levels were around 4 g/L.

**Safety results**

In total, 26 adverse events (AEs) were reported in 12 patients, thereof, only 2 events (in 1 paediatric patient) were probably related to treatment (mild fever). No infusion had to be stopped due to safety problems, and none had to be given at a reduced speed. Complete recovery was observed for all events. Furthermore, no passive transmission of anti-A/anti-B isoagglutinins was demonstrated. In terms of viral safety, no HIV, HCV or HBV infections were observed during the study period. As all patients were previously treated, they were all anti-HBs positive at baseline. No HAV or parvovirus B19 infection was observed, moreover, passive transmission of anti-HAV and anti-parvovirus B19 specific antibodies could be clearly demonstrated.

<b>OCTA -06 Clinical study to evaluate the safety, efficacy and pharmacokinetics of Octagam for replacement therapy in primary immunodeficiency diseases (PID)</b>
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Note of the company.

This study was performed in order to fulfil the FDA regulatory requirements with the objective to obtain a marketing authorisation for the *octagam 5%* in the US. The study may be regarded as the pivotal trial for registration of *octagam 5%* in the US, Canada, Australia, and various other countries in the rest of the world.

**Objective(s)**

To document the pharmacokinetic (PK) characteristics, efficacy and (viral) safety of octagam 5% in patients suffering from primary immunodeficiency (PID) disorders

**Study design**

Multi-center multiple-dose, open-label study in patients with PID conducted in the US

**Study population /Sample size**

46 patients, Age ranged from 6 to 74 years with a mean of 31.5 years, 11 patients were 16 years or younger.

**Treatments**

IVIG 300 to 450 mg/kg every 21 days or 400 to 600 mg/kg every 28 days for 12 months.

## Efficacy results

A subset of 14 patients aged between 10 and 70 years underwent PK assessments, however, only 2 of the 14 were below 16 years old, therefore no specific PK analysis was made. Three patients (6.5%) experienced a total of 5 serious infection episodes, all of these 3 patients older than 16 years. Based on the total enrolment of 46 patients for a total of 43.54 patient-years, the estimated rate was 0.115 serious infections per patient per year, with a 98% confidence interval of 0.033 to 0.279.

Table 6 Secondary Efficacy Endpoints OCTA-06

Endpoint	Total Population (n=46)	Adult Population (n=35)	Paediatric Population (n=11)
Number (%) of patients who missed at least 1 day of work/school	30 (65%)	21 (60%)	9 (82%)
Number (%) of patients who were hospitalised at least once	4 (9%)	2 (6%)	2 (18%)
Number (%) of patients who visited a physician/emergency unit at least once	27 (59%)	23 (66%)	4 (36%)

## Safety results

In the paediatric population, 5 subjects experienced 22 ADRs. The most common treatment-related ADR was headache (7 patients, 15%; 18 events; thereof 3 children with 10 events). All of the paediatric patients had at least 1 AE. A number of isolated, diverse AEs were reported, and the Investigators did not suspect a relationship to study medication in most cases. The AEs that occurred in at least 5 patients included sinusitis (7 patients, 64%), upper abdominal pain and vomiting (each 6 patients, 55%), nasal congestion and headache (each 5 patients, 45%).

Ten paediatric patients experienced 47 AEs that occurred during or within 30 minutes after an octagam 5% infusion. Three patients experienced 10 headaches associated with octagam 5% infusions. Other peri-infusion AEs that Investigators suspected might be related to octagam 5% included cough, ecchymosis, back and chest pain, vomiting, tremor, acne, changes in ASAT, and tympanic membrane disorder. Two paediatric patients experienced serious AEs. One had cellulitis and the second had gastroenteritis, ketonuria, abdominal pain, and pseudomembranous colitis. Investigators did not suspect that any of these serious AEs were related to study medication. None of the paediatric patients discontinued the study because of AEs and none died.

Three adult patients had 3 incidences of ASAT > 2.5 x upper normal limit. Four patients (thereof, 2 children) had 25 incidences of serum creatinine above the upper normal limit. All 4 patients had relatively stable creatinine levels throughout the study. Thus, the clinically significant creatinine values do not appear to be indicative of acute renal dysfunction. No patients experienced clinically significant abnormalities of ALAT, LDH, or bilirubin. There were no important vital sign or laboratory abnormalities among the paediatric population.

## **GAM-NL-002 Study to investigate the PK characteristics of octagam 5% in young (< 10 years) children with primary or secondary immunodeficiencies (due to HIVinfection)**

### Note of the company:

The full study report has not been submitted to the PEI so far, but results were briefly presented in one of the submitted PSURs (i.e. Edition 13, dated 30-Oct-2006, submitted to PEI in 2008).

### **Objective(s)**

To investigate the PK characteristics of Octagam 5% in young (< 10 years) children with primary or secondary immunodeficiencies (due to HIV infection)

### **Study design**

Prospective, non-randomised, non-controlled, open labelled single centre, phase IV study conducted in the Netherlands.

### **Study population /Sample size**

11 paediatric patients were enrolled, 6 were suffering from PID and 5 from HIV infection (1-10 years of age)

### **Treatments**

All patients received a single administration of octagam 5% at the dose they usually received as regular substitutive treatment. All patients had to be on Octagam 5% for at least 6 months prior to study entry.

### **PK results**

The decreases in levels of total IgG, plasma IgG and IgG subclasses followed a mono-exponential decay. The Tmax values were observed at around 3 hours except for IgG3 and IgG4 which were delayed up to 11 and 26.6 hours, respectively. The reason for this delay in the time to reach Cmax for IgG3 and IgG4 may be an artefact arising from the very low plasma levels involved. The mean estimated terminal half-lives for total IgG, IgG1, IgG2 and IgG3 were similar ( $37.8 \pm 18.2$ ,  $37.9 \pm 29.2$ ,  $36.3 \pm 22.6$ ,  $31 \pm 25.7$  days, respectively) and longer for IgG4 ( $64.4 \pm 21.8$  days). The mean MRT values were also similarly ranked for total IgG, IgG1, IgG2, IgG3 (from 46.5 to 56.6 days) but longer for IgG4 (91.6 days). Total body clearance varied from  $40 \pm 19$  mL/day (total IgG) to  $61 \pm 44$  mL/day (IgG3) and volume of distribution was ranged between  $1782 \pm 346$  and  $1890 \pm 1075$  mL for the total IgG and all subclasses except IgG4 ( $4191 \pm 2683$  mL).

### **Safety results**

In this study, only 1 mild AE (paronychium) was reported which was assessed as unrelated to octagam 5%. No routine clinical laboratory tests were performed in the study

## **Octagam POST-MARKETING DATA**

### Note of the company

*octagam 5%* is registered in about 67 countries. Post-marketing data for *octagam 5 %* are available from a large pharmacovigilance study and from spontaneous reporting, summarised in PSURs at regular intervals.

In total, 15 PSUR covering the period from February 1995 to September 2008 have been compiled to date. Editions 1 to 14 have been submitted to the PEI so far. The pharmacovigilance study (GAM-1-02-D) is ongoing and was initiated when *octagam 5%* was approved in Germany in February 1995. The survey involves physicians at both hospitals and local practices documenting infusion episodes

under normal treatment conditions; informed consent is not required. Data collected within a period of 10 years were published in 2007.

3,653 infusions in 395 children (below 16 years of age) were documented so far.

*Table 8 Paediatric Patients in German Pharmacovigilance Study (GAM-1-02-D)*

	No. of Patients	No. of ADRs*	Patients with ADRs	No. of Infusions	No. of ADRs*	Infusions with ADRs
Total	9,671	363	4%	146,927	454	0,3%
< 16 years	395	31	8%	3,653	51	1,4%
11-15 years	102	12	12%	1,472	19	1,3%
6-10 years	95	10	11%	1,085	21	1,9%
0-5 years	198	9	6%	1,096	11	1,0%

\* Numbers are different because patients may have experienced more than just 1 ADRs.

The company has also analysed safety data available at the Central Drug Safety Unit of Octapharma. In total, 14% of the cases that were reported for the product occurred in the paediatric population (below 18 years of age). This corresponds to the age structure of the total population, where adolescents represent about 16% (source: Statistisches Bundesamt, <http://www.destatis.de/bevoelkerungspyramide>).

**Rapporteur's comment on data with Octagam 5% Studies**

The studies in PID patients both in the US and in the EU showed the expected characteristics for PK, efficacy and safety in the pediatric population and do not call for an alteration of the SmPC/PIL. The PK data from the study in patients with primary or secondary immunodeficiencies (due to HIVinfection) shows fairly wide ranges of half-lives esp. for the various IgG subclasses. It is a well described phenomena that half-lives of IVIGs vary in the PID population – this seems to be no different in the pediatric PID population.

**Post marketing data**

The pharmacovigilance study (GAM-1-02-D) is ongoing and final results are awaited.

**Recent reports (2010) of noticeably increased rates of thromboembolic events including ischemic stroke, myocardial infarction, pulmonary embolism, intracranial venous thrombosis, deep vein thrombosis led to the suspension of the marketing authorisation of Octagam in the EU. The exact cause of the problems could not be identified with certainty. The suspension will remain in place until the problem has been rectified.**

### 3. Discussion on clinical aspects

The 41 studies submitted by 8 MAHs using different IVIG/SCIG brands encompassed different qualities of studies from large placebo-controlled trials to smaller, open, non-controlled studies (very small studies and individual case reports were not assessed).

No head-to-head studies have been performed to address possible differences between various brands of IVIGs (e.g. IgA content, pH, stabilizers, sugars) which may give rise to a different safety profiles. However, even if this data were obtainable, it is not likely that this would manifest itself as a difference between the adult and pediatric population. In general side-effects of IVIGs and SCIGs are well known and detailed in the core SmPCs, the specific side effects of individual excipients are also addressed therein.

In the submitted studies the indications mainly covered the “established” indications of the core SmPCs (for IVIG and SCIG/IMIG), i.e. PID and ITP. These are the indications in which studies should be performed to obtain MA as required by the guidelines.

Primary immunodeficiencies (PID) are a group of inherited diseases that affect the development or activity of the immune system. Published literature does not report differences in etiopathogenesis, clinical manifestations and prognosis, genetic background between paediatric and adult population (whereby common variable immunodeficiency CVID often is not diagnosed until adolescence or adulthood due to lack of recognition/understanding of the underlying disorder). The PK half-life values seen in PID patients are extremely variable; this applies to all preparations of IgG. Thus, the IVIG administration, which in any case is given by body weight, can be further tailored to suit the individual patient’s needs. For PID patients possibly very rare aspects of IVIGs may come to light in the future through the information gathered in the European Society for Immunodeficiencies (ESID) registry, but this does not affect the current SmPCs.

In the paediatric population ITP might develop in an acute or a chronic form. While the acute manifestations are benign and often self limiting disorders presenting mild clinical symptoms which usually do not require treatment, the chronic form is identical to that observed in adults. Literature data show that the efficacy of IVIg treatment in the paediatric population as well as in adults and the posologies used for both populations are the same. As with PID the dosing is by body weight.

The submitted studies also covered a variety of off-label, experimental indications such as autism or post-streptococcal obsessive disorder. Here there is insufficient data to draw any conclusions. It may be worth following up on such off-label indications with further studies, if the MAHs so wish.

The age ranges spanned from the premature very low birth-weight neonates to adolescents, thus covering all the necessary age groups.

The studies were partly investigator driven, partly company initiated; some had been performed in the 1980s, some are still ongoing, such as a large pharmacovigilance trial covering 10 years by Octapharma.

**Thus, the data was fairly heterogeneous, and some of the older studies may be of limited quality from today's point of view. Nevertheless, no distinct differences could be discerned for PK, safety and efficacy aspects between adults and children.**

## V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

### ➤ Overall conclusion

IVIGs, SCIGs and IMIGs are plasma-derived products that are under rigid standards of donor testing, the Eur. Pharmacopoeia and regulatory review. The dosing is by body weight and often further tailored according to individual needs.

The 41 studies submitted by 8 MAHs in the “established” indications of the core SmPC and in other indications showed heterogeneity in design, quality, indication, age of pediatric population and in the time period they were performed. However, the PK, efficacy and safety studies have not revealed major differences between adults and children suffering from the same disorder and thus confirm the experience of the past 60 years with IVIG, SCIG, and IMIG which have been routinely given to children for the “established” indications. Regarding the off-label indications, data are not considered sufficient to draw any conclusions and it may be worthy to follow up on such off-label indications with further studies.

The safety profile is described in the core SmPC.

It is concluded that no changes to the product information i.e., SmPCs/PILs are considered necessary.

### ➤ Recommendation

**No further action required**

## VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

**Note: Only products** are included for which the MAHs have indicated in the line listings (January 2008) that paediatric studies were finalised before the Paediatric Regulation came into force in January 2007 but not yet (January 2008) submitted to the NCAs and the submitted data has been assessed in this worksharing procedure. **Not included** Nanogam (Sanquin) as the study has not yet finished. **Included** IG Vena (Kediron) as data were submitted following the request letter by the “Agency” (EMA). **Included** Vivaglobulin (CSL Behring) – Art. 46

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
Baxter AG, Vienna	DK	SUBCUVIA	160 mg/ml	Solution for Injection	Human Normal Immunoglobulin	14224
Baxter S.A., Belgium	EE	GAMMAGARD S/D	2500 mg/50 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	336601
Baxter S.A., Belgium	EE	GAMMAGARD S/D	5000 mg/96 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	336701
Baxter S.A., Belgium	EE	GAMMAGARD S/D	10,000 mg/192 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	336501
BAXTER (HELLAS) E.P.E.	EL	GAMMAGARD S/D	5000 mg/96 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	2873831-10-1996
N.V. Baxter S.A., Belgium	FI	GAMMAGARD S/D	500 mg/10mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	10547
N.V. Baxter S.A., Belgium	FI	GAMMAGARD S/D	2500 mg/50 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	10547
N.V. Baxter S.A., Belgium	FI	GAMMAGARD S/D	5000 mg/96 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	10547

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
N.V. Baxter S.A., Belgium	FI	GAMMAGARD S/D	10,000 mg/192 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	10547
BAXTER S.A.S. Maurepas	FR	GAMMAGARD S/D	500 mg/10mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	NL 19019
BAXTER S.A.S. Maurepas	FR	GAMMAGARD S/D	500 mg/10mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	NL 19019
BAXTER S.A.S. Maurepas	FR	GAMMAGARD S/D	500 mg/10mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	NL 19019
BAXTER AG	IE	Gammagard S/D.Human Normal Immunoglobulin for Intravenous Administration	500 mg/10mL 2500 mg/50 mL 5000 mg/96 mL 10,000 mg/192 ml	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	PA167/79/004
BAXTER SpA (Italia)	IT	GAMMAGARD	500 mg/10 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	033240019
BAXTER SpA (Italia)	IT	GAMMAGARD	2500 mg/50 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	033240021
BAXTER SpA (Italia)	IT	GAMMAGARD	5000 mg/96 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	033240033
BAXTER SpA (Italia)	IT	GAMMAGARD	10.000 mg/192 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	033240045

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
Baxter S.A., Belgium	LV	GAMMAGARD S/D 10 g powder and solvent for solution for infusion	10,000 mg/192 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	02-0113
Baxter S.A., Belgium	LV	GAMMAGARD S/D 2,5 g powder and solvent for solution for infusion	2500 mg/50 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	96-0443
Baxter S.A., Belgium	LV	GAMMAGARD S/D 5 g powder and solvent for solution for infusion	5000 mg/96 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	02-0112
Baxter S.A., Belgium	PL	GAMMAGARD S/D	500 mg/10mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	7560
Baxter S.A., Belgium	PL	GAMMAGARD S/D	2500 mg/50 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	7561
Baxter S.A., Belgium	PL	GAMMAGARD S/D	5000 mg/96 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	7562
Baxter S.A., Belgium	PL	GAMMAGARD S/D	10,000 mg/192 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	7563
Baxter Médico-Farmacêutica, Lda.	PT	Gammagard S/D	45 mg/ml	Powder and solvent for solution for infusion	Human immunoglobulin g;	023/93
Baxter S.A., Belgium	SE	GAMMAGARD S/D	500 mg/10mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	11826
Baxter S.A., Belgium	SE	GAMMAGARD S/D	2500 mg/50 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	11826
Baxter S.A., Belgium	SE	GAMMAGARD S/D	5000 mg/96 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	11826
Baxter S.A., Belgium	SE	GAMMAGARD S/D	10,000 mg/192 mL	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	11826

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
Baxter Healthcare Ltd	UK	GAMMAGARD S/D	0.5g	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	PL/0116/0242
Baxter Healthcare Ltd	UK	GAMMAGARD S/D	10g	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	PL/0116/0245
Baxter Healthcare Ltd	UK	GAMMAGARD S/D	2.5g	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	PL/0116/0243
Baxter Healthcare Ltd	UK	GAMMAGARD S/D 5 g	5g	Powder and solvent for solution for infusion	Human Normal Immunoglobulin for Intravenous Administration	PL/0116/0244
Baxter Healthcare Ltd	UK	SUBCUVIA Human Normal Immunoglobulin	160 mg/ml	Solution for Injection	Human Normal Immunoglobulin	PL 0016/0385
Biotest Pharma GmbH,	CY	Intratect	50 g/l	Solution for infusion	Human normal immunoglobulin for intravenous use (IVIg)	S00367
C.A.F.-D.C.F. cvba-scr1	BE	Multigam	20 ml	Solution for infusion	Human normal immunoglobulin	11 IS 14 F 12
C.A.F.-D.C.F. cvba-scr1	BE	Multigam	50 ml	Solution for infusion	Human normal immunoglobulin	11 IS 15 F 12
C.A.F.-D.C.F. cvba-scr1	BE	Multigam	100 ml	Solution for infusion	Human normal immunoglobulin	11 IS 16 F 12
C.A.F.-D.C.F. cvba-scr1	BE	Multigam	200 ml	Solution for infusion	Human normal immunoglobulin	11 IS 17 F 12
CSL Behring NV	BE	Sandoglobuline	1 g 3 g 6 g 12 g	Powder for solution for infusion	Human normal immunoglobulin	1318 BR 1 F 12 1318 BR 2 F 12 1318 BR 3 F 12 1318 BR 4 F 12
CSL Behring GmbH	DE	Sandoglobulin	1 g 3 g 6 g 10 g	Powder for solution for infusion	Human normal immunoglobulin	124 a /84
CSL Behring GmbH	DK	Sandoglobulin	1 g 3 g 6 g	Powder for solution for infusion	Human normal immunoglobulin	217198

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
CSL Behring Ltd., UK	EL	Sandoglobulin	3 g 6 g 12 g	Powder for solution for infusion	Human normal immunoglobulin	12995/2-10-2007
CSL Denmark ApS	IS	Sandoglobulin	1 g 3 g 6 g 12 g	Powder for solution for infusion	Human normal immunoglobulin	822908 829001 829002 829003
CSL Behring GmbH	IT	Sandoglobulina	1 g 3 g 6 g 12 g	Powder for solution for infusion	Human normal immunoglobulin	025 199011 025 199023 025 199035 025 199047
CSL Behring GmbH	LU	Sandoglobulin	1 g 3 g 6 g 10 g	Powder for solution for infusion	Human normal immunoglobulin	1013/82120384 1013/82120385 1013/82120386 1013/89090758
CSL Behring GmbH	PL	Sandoglobulina	1 g 3 g 6 g 12 g	Powder for solution for infusion	Human normal immunoglobulin	860 9909860 9917860 9925354 9789
CSL Behring GmbH	UK	Sandoglobulin	1 g 3 g 6 g 12 g	Powder for solution for infusion	Human normal immunoglobulin	PL 15036/0020 PL 15036/0021 PL 15036/0022 PL 15036/0023
CSL Behring GmbH	DE	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	PEI.H.03095.01.1
CSL Behring GmbH	AT	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	2-00308
CSL Behring GmbH	BE	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	BE 271896 BE 317405 BE 317396 BE 271887
CSL Behring GmbH	CZ	Vivaglobin (Art. 46)	5 ml 10 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	59/207/04-C

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
CSL Behring GmbH	DK	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	36804
CSL Behring MEPE Greece	EL	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	53832/17-07-2009
CSL Behring GmbH	FI	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	19361
CSL Behring GmbH	FR	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	NL 30464
CSL Behring GmbH	GB	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	PL 15036/0016
CSL Behring GmbH	HU	Vivaglobin (Art. 46)	10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	OGY-T-9938/01 OGY-T-9937/01
CSL Behring GmbH	IR	Vivaglobin (Art. 46)	3 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	
CSL Behring GmbH	IT	Vivaglobin (Art. 46)	3 ml  5 ml  10 ml  20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	037882065/M (1x3) 037882077/M (10x3)  037882014/M (1x5) 037882026/M (10x5)  037882039/M, 037882091/M, 037882040/M, 037882053/M  037882089/M
CSL Behring GmbH	LX	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	1013/051000012

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
			20 ml			
CSL Behring GmbH	NL	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	RVG 31149
CSL Behring GmbH	NO	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	04-2768
CSL Behring GmbH	PL	Vivaglobin (Art. 46)	5 ml 10 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	12118
CSL Behring GmbH	PT	Vivaglobin (Art. 46)	3 ml  5 ml  10 ml  20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	5039532(1x3), 5039540 (10x3)  5270582 (1x10ml), 5270681 (10x10ml), 5270780 (20x10ml)  5039557 (1x20), 5039565 (10x20)
CSL Behring GmbH	SL	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	59/0260/04-S
CSL Behring GmbH	ES	Vivaglobin (Art. 46)		Solution for injection (subcutaneous use)	Human normal immunoglobulin	67247
CSL Behring GmbH	SE	Vivaglobin (Art. 46)	3 ml 5 ml 10 ml 20 ml	Solution for injection (subcutaneous use)	Human normal immunoglobulin	21203
DEMO S.A.	EL	FLEBOGAMMA	0,05	Solution for infusion	Human normal immunoglobulin (IVIg)	61410/04/11-2-2005
Grifols Deutschland GmbH	DE	FLEBOGAMMA 5%	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	526a/91
Instituto Grifols, S.A.	CZ	FLEBOGAMMA 5% (0.5 - 2.5 - 5 - 10 g)	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	59/153/95-C

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
Instituto Grifols, S.A.	CZ	PASTEURISED HUMAN IMMUNOGLOBULIN GRIFOLS 16% SOLUTION	160 mg/ml	Solution for injection	Human normal immunoglobulin	59/838/99-C
Instituto Grifols, S.A.	ES	FLEBOGAMMA I.V. 5%	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	60465
Instituto Grifols, S.A.	ES	GAMMAGLOBULINA HUMANA PASTEURIZADA GRIFOLS 160 mg/ml	160 mg/ml	Solution for injection	Human normal immunoglobulin	44859
Instituto Grifols, S.A.	HU	FLEBOGAMMA 5% 0,5 g oldatos infúzió	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	OGYI-T-10247/01
Instituto Grifols, S.A.	HU	FLEBOGAMMA 5% 10 g oldatos infúzió	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	OGYI-T-10250/01
Instituto Grifols, S.A.	HU	FLEBOGAMMA 5% 2,5 g oldatos infúzió	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	OGYI-T-10248/01
Instituto Grifols, S.A.	HU	FLEBOGAMMA 5% 5 g oldatos infúzió	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	OGYI-T-10249/01
Instituto Grifols, S.A.	IE	FLEBOGAMMA 5%	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	PA 849/4/1
Instituto Grifols, S.A.	IT	FLEBOGAMMA (100 ml)	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	A.I.C. 029249051
Instituto Grifols, S.A.	IT	FLEBOGAMMA (200 ml)	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	A.I.C. 029249063
Instituto Grifols, S.A.	IT	FLEBOGAMMA (50 ml)	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	A.I.C. 029249048
Instituto Grifols, S.A.	NL	FLEBOGAMMA	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	RVG 17435
Instituto Grifols, S.A.	PL	FLEBOGAMMA IV PASTERYZOWANY ROZTWÓR	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	7410

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
Instituto Grifols, S.A.	PL	FLEBOGAMMA IV PASTERYZOWANY ROZTWÓR	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	7411
Instituto Grifols, S.A.	PL	FLEBOGAMMA IV PASTERYZOWANY ROZTWÓR	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	7412
Instituto Grifols, S.A.	PL	FLEBOGAMMA IV PASTERYZOWANY ROZTWÓR	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	7413
Instituto Grifols, S.A.	PT	Flebogamma IV Líquida Pasteurizada	50 mg/ml	Solution for infusion	Immunglobulin;	202/94
Instituto Grifols, S.A.	RO	FLEBOGAMMA 5% (10 ml)	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	7019/2006/01
Instituto Grifols, S.A.	RO	FLEBOGAMMA 5% (100 ml)	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	7019/2006/03
Instituto Grifols, S.A.	RO	FLEBOGAMMA 5% (200 ml)	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	7019/2006/04
Instituto Grifols, S.A.	RO	FLEBOGAMMA 5% (50 ml)	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	7019/2006/02
Instituto Grifols, S.A.	SK	FLEBOGAMMA 5%	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	59/0426/97-S
Instituto Grifols, S.A.	SK	PASTEURISED HUMAN IMMUNOGLOBULIN GRIFOLS 16% SOLUTION SOL INJ 16%	160 mg/ml	Solution for injection	Human normal immunoglobulin	59/0188/02-S
Instituto Grifols, S.A.	UK	FLEBOGAMMA 5%	5%	Solution for infusion	Human normal immunoglobulin (IVIg)	PL 12930/0007
KEDRION S.P.A. *	AT	Ig VENA "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	2-00321
KEDRION S.P.A. *	DE	Ig VENA "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	PEI.H.03409.01.1
KEDRION S.P.A. *	IT	Ig VENA "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	025266141 025266154 025266166

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
						025266178
KEDRION S.P.A. *	IT	KeYven "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	037253010 037253022 037253034 037253046
KEDRION S.P.A., former Hardis *	IT	VENITAL	50g/l	Solution for infusion	Human normal immunoglobulin	037254012 037254024 037254036 037254048
KEDRION S.P.A. *	MT	IG VENA N I.V. "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	MA128/00301
KEDRION S.P.A. *	PL	IG VENA "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	12908
KEDRION S.P.A. *	PT	IG VENA "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	5016407 5016415 5016423 5016373
KEDRION S.P.A. *	RO	IG VENA "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	8213/2006/01 8214/2006/01 8215/2006/01 8216/2006/01
KEDRION S.P.A. *	ES	IG VENA "KEDRION"	50g/l	Solution for infusion	Human normal immunoglobulin	8213/2006/01 8214/2006/01 8215/2006/01 8216/2006/01
Octapharma Benelux S.A./N.V.,	BE	Octagam	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	1474 IS 1 F12 1474 IS 2 F12 1474 IS 3 F12
Octapharma (IP)-Ltd.	CZ	Octagam	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	75/123/98-C
Octapharma AB/ Octapharma Nordic AB	DK	Octagam infusionsvæske, opløsning, 50mg/ml	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	15986
Octapharma France S.A.S.	HU	Octagam 5% infúzió, 100ml	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	OGYI-T-9697/02 (100ml)

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance	Marketing Authorisation Number
Octapharma France S.A.S.	HU	Octagam 5% infúzió, 200ml	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	OGYI-T-9697/03 (200ml)
Octapharma France S.A.S.	HU	Octagam 5% infúzió, 50ml	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	OGYI-T-9697/01 (50ml)
Octapharma (IP)-Ltd. Octapharma AB	LV	Octagam - Solution for infusion 10g/200ml	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	04-0296 (200ml)
Octapharma (IP)-Ltd. Octapharma AB	LV	Octagam - Solution for infusion 1g/20ml	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	04-0293 (20ml)
Octapharma (IP)-Ltd. Octapharma AB	LV	Octagam - Solution for infusion 2.5g/50ml	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	04-0294 (50ml)
Octapharma (IP)-Ltd. Octapharma AB	LV	Octagam - Solution for infusion 5g/100ml	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	04-0295 (100ml)
Octapharma GmbH Octapharma Benelux S.A./N.V.	NL	Octagam, infusievloeistof	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	RVG 18396
Octapharma AG	NO	Octagam infusjonsvæske 50mg/ml Octapharma™	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	8241
Octapharma (IP)-Ltd.	RO	Octagam	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	6345/2006/01 (50 ml)
Octapharma (IP)-Ltd.	RO	Octagam	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	6345/2006/02 (100 ml)
Octapharma (IP)-Ltd.	RO	Octagam	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	6345/2006/03 (200 ml)
Octapharma AB / Octapharma Nordic AB	SE	Octagam	50 mg/ml	Solution for infusion	Human Normal Immunoglobulin (IVIG)	12065 (50ml, 100ml, 200ml, 500ml)