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12th June 2015

Re: Comments on the Assessment Report: Immunosuppressive therapy for kidney transplantation in children and adolescents (Review of TA99) [ID346]

Dear Meindert,

Sanofi welcomes the opportunity to provide comments on the Assessment Report produced by the Peninsula Technology Assessment Group (PenTAG) for the above appraisal.

We note that PenTAG did not identify any studies that evaluated Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) in children and adolescents. In our attached comments we have provided details of two non-randomised studies that have evaluated Thymoglobulin® in this patient population.

Although no Thymoglobulin studies were identified, PenTAG did present an analysis of cost-effectiveness that incorporated Thymoglobulin®. This was conducted by extrapolating the effectiveness estimates from the RCT evidence in adults that was synthesised for the review of TA 85 [ID 456]. We provided comments on the assessment report pertaining to adults on the 8th May 2015 and have reiterated the salient points from our response in our attached comments. Principally we are concerned that the analysis of adult RCT data involved the synthesis of data from three different induction therapies as if they were the same product; namely Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]). Thymoglobulin®, ATGAM® (lymphocyte immune globulin, anti-thymocyte globulin [Pfizer]) and ATG-Fresenius S® (rabbit anti-human T-lymphocyte immunoglobulin, [Neovii Biotech]) are different products, produced in different ways, by different manufacturers. Given the limitations of this analysis, we believe that using this data to inform the cost-effectiveness of Thymoglobulin® in children and adolescents is inappropriate.

Please let me know if you have any questions regarding our comments.

Yours Sincerely,

[redacted]
Sanofi

Sanofi – June 2015

Response to the Assessment Group Report: Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99)

Section/Page	Comment
Page 75, Table 7 Page 183, Table 55	**Thymoglobulin® licence** There is some confusion in the report as to whether Thymoglobulin® is licensed for use in children and adolescents. Table 7 states that Thymoglobulin is not licenced for use in children and adolescents whereas Table 55 states that it is licensed for use in children and adolescents. To clarify, although there is no specific paediatric indication for Thymoglobulin®, the licensed indication for Thymoglobulin® is not restricted to adults (Thymoglobulin® SmPC). The SmPC contains the following information regarding paediatric patients: *Paediatric Population* *Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made. Available information indicates that paediatric patients do not require a different dosage than adult patients.*
Section 1.4.1 Page 37	**We have identified two non-randomised studies that could help inform the clinical effectiveness of Thymoglobulin® in children and adolescents.** A retrospective comparison of low dose Thymoglobulin® versus basiliximab or no induction found no significant differences between the three regimens in terms of graft survival, acute rejection rate and GFR (Baron 2008). It should be noted that this study is limited by significant differences in baseline characteristics. A small non-randomised, prospective comparison of Thymoglobulin® versus basiliximab demonstrated that ATG induction significantly reduced the incidence of delayed graft function versus basiliximab (Vilalta 2009).
Table 79, Page 223	**Sanofi have previously provided comments on the assessment report for immunosuppressive therapies in adults. The network meta-analysis of RCT data from the adult assessment report has been used to inform a cost-effectiveness analysis in children and adolescents that includes Thymoglobulin®. Our concerns with the adult RCT data are reiterated below:** 1. The adult RCT data inappropriately includes four studies as Thymoglobulin® studies. Samsel (2008), Kyllönen (2007), and Sheashaa (2008) used ATG-Fresenius and Sollinger (2001) used equine-derived antithymocyte globulin (ATGAM), not Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]). Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATGAM are anti T and B lymphocyte immunoglobulin products derived from thymus lymphocyte immunisation, but rATG is rabbit derived whereas ATGAM is horse-derived. ATG-Fresenius is an anti-T-lymphocyte immunoglobulin product derived from rabbits immunised with Jurkat cells, a lymphoblastoid cell line. Both ATGAM and ATG-Fresenius differ inherently from Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]), and the three products cannot be considered interchangeable. The doses, activity and targets of the three products have been assessed seperately, and although they may be used in various induction protocols in a similar manner, there are numerous pieces of evidence to

	suggest that that they are not biosimilar products, and are in fact inherently different. The efficacy and safety of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATGAM have been compared in a prospective randomised double-blind single-site study (Hardinger 2008), in which significant outcome differences were identified, including the composite endpoint of freedom from death, graft loss or acute rejection at 10 years (in favour of Thymoglobulin). To our knowledge, there have been no randomised controlled studies that have directly compared the efficacy and safety of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATG-Fresenius for induction of kidney transplant patients, to discern similarity or otherwise. However, one randomised comparative study of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus ATG-Fresenius, assessing haematologic adverse effects at one month, has been reported in kidney transplant patients (Rostaing 2010). This study concluded that reduced platelet and reticulocyte counts occurred less frequently with Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]), accompanied by a reduced requirement for erythropoietin-stimulating agents versus ATG-Fresenius. Another recent publication demonstrated that Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATG-Fresenius differ significantly in terms of regulation of the intrarenal transcriptome (Urbanova 2012). Two retrospective series also have indicated significant differences in terms of white blood cell count recovery rates (Cicora 2013) and rates of delayed graft function and acute rejection (Chen 2015). Finally, in regard to the idea that Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) may benfically have immunomodulatory activity in addition to lyphocyte-depleting, Leitner 2010 determined that Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATG-Fresenius targets dendritic cell antigens with differential activity. All four non-Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) studies addressed in the assessment group's report have been incorporated into subsequent network meta-analyses for a variety of outcome measures.There is no rationale or justification provided in the assessment group's report for combining data from studies involving different lymphocyte-depleting products. The European Public Assessment report for paediatric studies of Anti-human T-lymphocyte immunoglobulin from rabbits states that although Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) and ATG-Fresenius have the same ATC code they actually constitute two different drug products (EMA 2014). Furthermore, please find the following quotation from an editorial piece (Mohty 2012); "Despite sharing some common properties, these different products are strictly different drugs, and have never been compared thus far in a controlled setting." A recent review (Hardinger 2012) also stated; "A recent meta-analysis of six randomized studies including 853 patients showed no differences between ATG and basiliximab for the outcomes including BPAR, delayed graft function (DGF), graft loss, and patient death [Liu 2010]. A major limitation to this meta-analysis was that authors included all preparations of ATG in the analysis". The Liu meta-analysis was not considered in the assessment group report. We believe that it is clearly incorrect to combine analyses from studies involving different products that are considered non-interchangeable. We therefore recommend that all relevant analyses should be rerun with the exclusion of Samsel (2008), Kyllönen (2007), Sheashaa (2008) and Sollinger (2001).

2. Lack of consideration of immunological risk status.

It is our understanding that in clinical practice Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) is predominantly used in patients with a moderate/high immunological risk status, where a powerful immunospuppresant may be most justified. Use of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) in this setting is supported by the 2009 KDGIO guidelines and a more recent review by Hardinger (2013).

Randomised trials of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus no induction or placebo in populations selected according to higher immunological risk have not been performed. However, one randomised trial has shown a lower rate of acute rejection for Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus basiliximab induction in patients at moderate to high immunological risk (Brennan 2006). Although studies of daclizumab (another IL-2 receptor antagonist) are not in scope for this appraisal, it should be noted that comparisons of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) with daclizumab are consistent with the Brennan findings (Noël 2009). Three other studies in lower risk patients found no significant benefit of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) versus IL-2 receptor antagonist induction (Lebranchu 2002; Mourad 2004; Abou-Ayache 2008). The benefits of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) are therefore likely to be concentrated in moderate or high-risk populations.

The Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) studies included in the assessment group's report recruited patients with different immunological risks, potentially resulting in different outcomes. Of the five Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) studies included in the report, two studies recruited patients with low/medium immunological risk (Lebranchu 2002; Mourad 2004) , one study selectively recruited high risk patients (Brennan 2006) and two studies were non-selective (Charpentier 2001; Charpentier 2003).

3. The dose of Thymoglobulin® used in some of the included studies no longer reflects clinical practice.

Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) is a potent immunosuppressing agent, used as induction therapy to suppress acute rejection of kidney transplants. However, the implications of over-suppression are potentially increased infection and malignancy rates. Therefore, it is important to balance safety and benefits by appropriate dosing. It is understood that the high cumulative dose (12.5 mg/kg) of Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) used in Charpentier (2001) and Charpentier (2003) is no longer used in kidney transplantation, as the increased risk may not be offset by the benefits. Based on pharmacodynamic studies (Büchler 2013; Kho 2012), a cumulative Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) dose of 6 mg/kg is generally considered appropriate for induction therapy related to kidney transplantation. For example, the large ongoing SAILOR study is currently administering a total dose of only 5 mg/kg (Ekberg 2014). Thus, these early studies in which a dose of 12.5 mg/kg was utilised no longer reflect current practice.

Given the dose-dependency of possible side effects related to Thymoglobulin® (rabbit anti-human thymocyte immunoglobulin, [Sanofi]) induction, that could potentially affect graft survival, such as post-transplant lymphoproliferative disease (Marks 2011; Hertig 2015), infection and malignancy, outcomes of

	Charpentier (2001) and Charpentier (2003) should not be considered relevant to current practice. **Conclusion** Although we acknowldege that there is a paucity of evidence in children and adolescents, given the above issues with the adult RCT data as it stands, we believe it is inappropriate to use this data to inform a cost-effectiveness analysis.
Section 6.2.72. Page 229,Table 84	**The dose of Thymoglobulin® used in the economic model is likely to be higher than that used in clinical practice.** ***Dosing in adult patients*** The study by Brennan *et al* is from 2006. Since then Thymoglobulin® dosing has been declining and is now frequently lower than 6.5 mg/kg. Examples from randomized trials include: - The large ongoing randomized SAILOR study is currently administering a total Thymoglobulin® dose of only 5 mg/kg (Eckberg 2014), reflecting contemporary practice. - A recent randomized trial compared standard-dose Thymoglobulin® versus low-dose Thymoglobulin® in adult kidney transplant patients (Grafals 2014). In that study, the standard-dose was 3.75 mg/kg – markedly lower than the 6.5 mg/kg used in Brennan et al (2006). In the low-dose arm, a total dose of 2.25 mg was found to be equally effective. - Another controlled prospective study has successfully administered a single 1.5 mg/kg dose of Thymoglobulin® and observed similar outcomes to basiliximab induction (Patel 2014). - An earlier randomized trial applied a minimum total Thymoglobulin® dose of 3 mg/kg (maximum 6 mg/kg) with successful outcomes (Goggins 2003). The assumed dose of 6.5 mg/kg, even in adult patients, derived from a single RCT undertaken in 2006, no longer appears relevant. ***Dosing in children*** Retrospective analyses that included more than 20 patients have reported a Thymoglobulin® total dose of 5.1 mg/kg (Baron 2008) or planned doses of 5 mg/kg (Ellis 2007) or 7.5 mg/kg (Warejko 2014). It is likely that the dose of 6.5mg/kg used in the economic model is higher than would be used in clinical practice.

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