Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Normal immunoglobulin (human)

Proprietary Product Name: Kiovig

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

November 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations 4

I. Introduction to product submission 6

Submission details 6

Product background 8

Regulatory status 10

Product Information 11

II. Registration timeline 11

III. Submission overview and risk/benefit assessment 12

Contents of the clinical dossier 12

Quality 13

Nonclinical 13

Clinical 13

Risk management plan 40

Risk-benefit analysis 40

Outcome 53

Attachment 1. Product Information 54

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ANOVA	Analysis of variance
ARTG	Australian Register of Therapeutic Goods
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
EMA	European Medicines Agency (European Union)
EU	European Union
FAS	Full analysis set
GBS	Guillain Barré syndrome
GCP	Good Clinical Practice
GS	Grip strength
IgG	Immunoglobulin G
INCAT	Improvement in inflammatory neuropathy case and treatment (Disability score)
ITP	Idiopathic thrombocytopenia
ITT	Intent-to-treat
IV	Intravenous
IVIg	Intravenous immunoglobulin
MNM	Multifocal motor neuropathy
MRC	Medical Research Council (United Kingdom)
MRI	Magnetic resonance imaging
NDS	Neurological Disability Scale
NNT	Number needed to treat
ODSS	Overall disability sum score
PID	Primary immunodeficiency disorder

Abbreviation	Meaning
SD	Standard deviation
SmPC	Summary of Product Characteristics (European Union)
US(A)	United States (of America)
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Product name:	Kiovig
Active ingredient:	Normal immunoglobulin (human)
Decision:	Approved
Date of decision:	20 July 2021
Date of entry onto ARTG:	23 July 2021
ARTG numbers:	131953, 131966, 131968, 131969, 131973, and 198488
, *Black Triangle Scheme:*[1]	No
Sponsor's name and address:	Takeda Pharmaceuticals Australia Pty Ltd Grosvenor Place, Level 39 225 George Street Sydney, NSW, 2000
Dose form:	Solution for injection
Strengths:	10% infusion; 1 g/10 mL; 2.5 g/25 mL; 5 g/50 mL; 10 g/100 mL; 20 g/200 mL; and 30 g/300 mL
Container:	Vial
Pack sizes:	Single vial (1 x 10 mL; 1 x 25 mL, 1 x 50 mL, 1 x 100 mL, 1 x 200 mL, and 1 x 300 mL)
Approved therapeutic use:	*Kiovig administered intravenously is indicated for the treatment of Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in adults.*
Route of administration:	Intravenous
Dosage:	Kiovig should be at room temperature during administration. Kiovig should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter and/or discoloration is observed. Only clear or slightly opalescent and colourless or pale yellow solutions are to be administered. Kiovig should only be administered intravenously

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

or subcutaneously. Other routes of administration have not been evaluated. The use of an in-line filter is optional.

The dose and dosage regimen are dependent on the indication. In replacement therapy the dosage may need to be individualised for each patient depending on the pharmacokinetic and clinical response. The dosage regimens are given as a guideline below.

For the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in adults:

Starting dose and frequency of injections:

2 g/kg bodyweight, in divided doses over 2 to 5 days.

Maintenance dose and frequency of injections:

1 g/kg bodyweight, over 1 to 2 consecutive days over 3 weeks.

The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

It is recommended that Kiovig be infused at an initial rate of 0.5 mL/kg/h. If the infusion at this rate and concentration does not cause the patient to have distress, the administration rate may be gradually increased.

This recommendation is based on the first infusion in a pivotal Phase III clinical study where Kiovig was infused at an initial rate of 0.5 mL/kg/h (0.8 mg/kg/min). The rate was gradually increased every 30 minutes to a rate of 5.0 mL/kg/h (8.9 mg/kg/min) if it was well tolerated. However, some patients completed the infusion before the maximum rate could be obtained. During subsequent infusions the initial rate and the rate of escalation were based on their previous infusion history; however, the maximum rate attained during the first infusion was used throughout the remainder of the study. A maximum tolerable infusion rate of up to 4 mL/kg/h was attained in majority (78.7%) of the patients, with a small proportion (19.7%) of patients achieving > 4 but < 6 mL/kg/h.

In general, it is recommended that patients beginning treatment with intravenous immunoglobulin or switching from one intravenous immunoglobulin brand to Kiovig be started at the lowest rate and then increased to the maximal rate if they have tolerated several infusions at intermediate rates of infusion. It is important to individualise rates for each patient.

In patients at risk for acute renal failure or thromboembolic adverse reactions, Kiovig should not be infused rapidly.

For further information regarding dosage, refer to the Product

	Information.
Pregnancy category:	B2 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Takeda Pharmaceuticals Australia Pty Ltd (the sponsor);[2] to register Kiovig (normal immunoglobulin, human) 10% infusion 1 g/10 mL, 2.5 g/25mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL, and 30 g/300 mL solution for injection (vial) for the following proposed extension of indications:

> *Kiovig administered intravenously is indicated for the treatment of Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).*

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare, acquired immune-mediated neuropathy primarily affecting adults. Chronic inflammatory demyelinating polyradiculoneuropathy is a chronic sensory and motor neuropathy with a relapsing and remitting or progressive course of more than 2 months. The neuropathy is characterised by proximal weakness (or weakness in the shoulders and hips), positive sensory symptoms (incoordination, numbness, tingling, or prickling sensations), areflexia (absence of deep muscle tendon reflexes) without wasting, and impaired sensation with a preferential loss of vibration or joint position sense. Muscle stretch reflexes are depressed and sensory loss is variable.

The estimated prevalence of CIDP in populations from the United Kingdom, Australia, Italy, Japan, and the United States of America (USA) is 0.8 to 8.9 per 100,000 with worldwide estimates of an annual incidence of 0.15 to 1.6 per 100,000 population. Chronic inflammatory demyelinating polyradiculoneuropathy is reported to occur more commonly in patients with diabetes mellitus, but this has not been rigorously tested, and CIDP can present in, and affect all ages, but is more common in older males. It is thought the disease is more likely to be progressive in the older age group and relapsing-remitting in younger patients. No specific predisposing factors for CIDP have been identified.

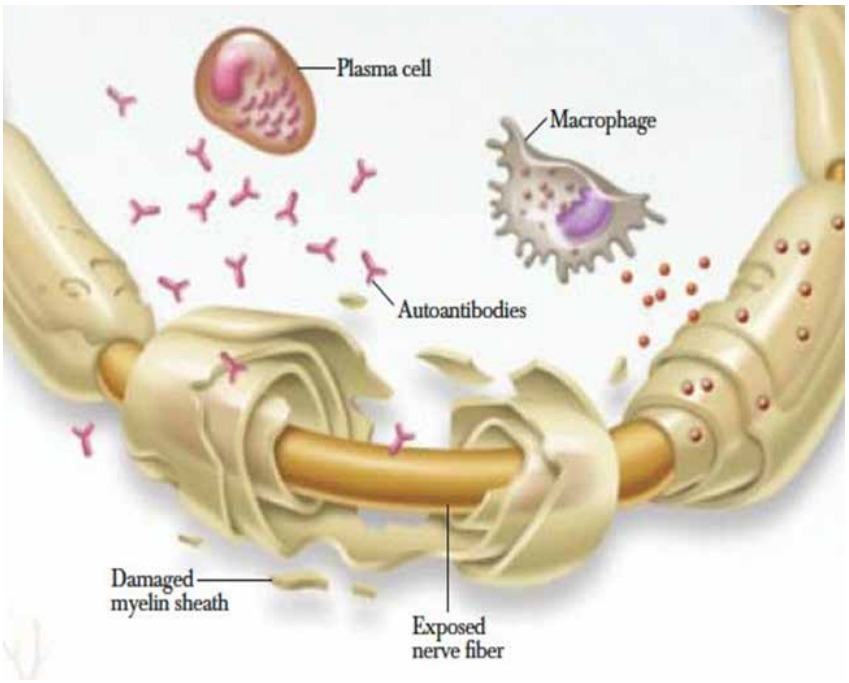
Patients may have mild to severe weakness and may require assisted ambulation or a wheelchair, however it is rare for patients to require respiratory support.
The overwhelming majority of patients with CIDP will have electrodiagnostic evidence of primary demyelination, including nerve conduction testing and electromyography looking

[2] Note, the original sponsor at the time of submission was Shire Australia Pty Ltd. During the timeframe in which this submission was considered for approval, the named sponsor for this submission changed to Takeda Pharmaceuticals Australia Pty Ltd. For clarity and ease of understanding, Takeda Pharmaceuticals Australia Pty Ltd has been used as throughout this AusPAR.

for very slow nerve conduction velocities, and magnetic resonance imaging (MRI) of the nerve roots looking for enlargement and signs of inflammation.

The precise pathophysiology of CIDP remains uncertain, however, demyelination resulting from phagocytosis of myelin by macrophages has been proposed to play an important role in the pathogenesis of CIDP with both B and T cell mechanisms are believed to be implicated. These mechanisms of immunopathogenesis are illustrated in Figure 1, below. Cellular immunity involvement is supported by evidence of T cell activation, crossing of the blood-nerve barrier by activated T cells, and expression of cytokines, tumour necrosis factor, interferons, and interleukins. Humoral immunity (also known as antibody-mediated immunity) is evidence by the demonstration of immunoglobulin and complement deposition on myelinated nerve fibres, and by passive transfer experiments that induce conduction block and demyelination by injecting serum or purified immunoglobulin from CIDP patients into rats.

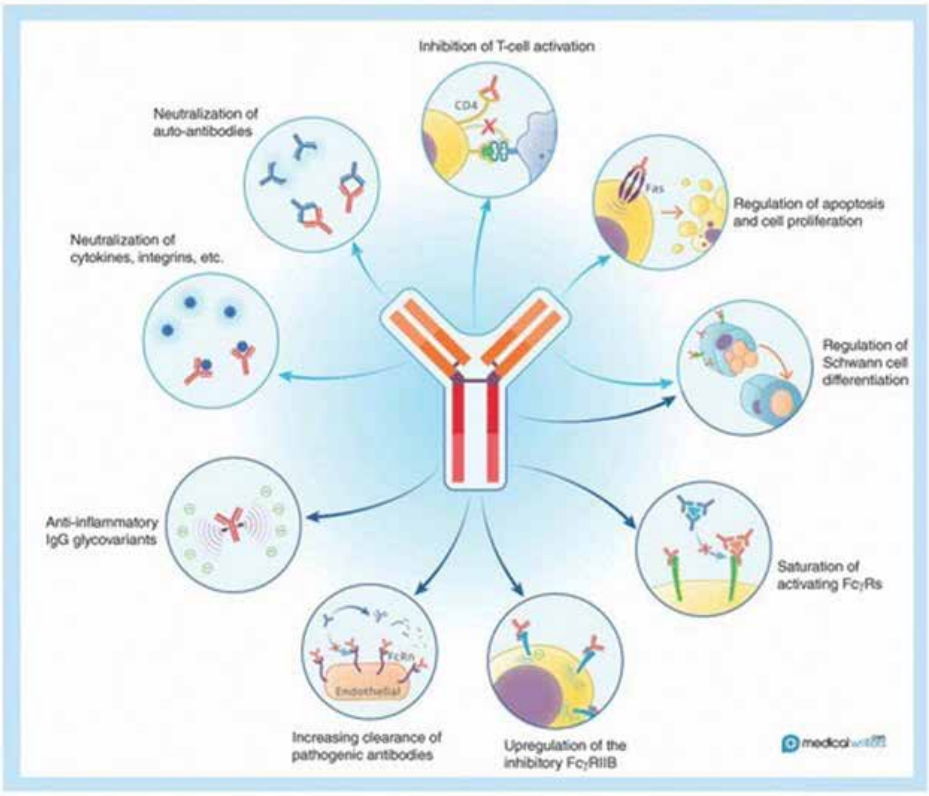
Figure 1: Illustration of the immunopathology of chronic inflammatory demyelinating polyradiculoneuropathy



Chronic inflammatory demyelinating polyradiculoneuropathy requires long-term treatment to prevent further disability. First-line treatment options include: intravenous immunoglobulins (IVIg), corticosteroids, and plasma exchange (plasmapheresis). The mechanisms by which intravenous immunoglobulins affect the activity of autoimmune diseases such as CIDP are multiple and complex. Some of the potential mechanisms are summarised in Figure 2, below. Second-line treatments and indicated when first-line treatments are inadequate and may require the use of immunosuppressants or other immunomodulatory agents such as azathioprine, cyclophosphamide, ciclosporin and methotrexate.

At the time of this submission, four branded human normal immunoglobulin products were registered on the Australian Register of Therapeutic Goods (ARTG), indicated for the treatment of CIDP: Gamunex, Intragam 10, Privigen and Hizentra.

Figure 2: Potential mechanisms of intravenous immunoglobulin activity in the treatment of autoimmune diseases



Regulatory status

Kiovig received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 11 August 2008, for intravenous (IV) replacement therapy for patients with primary immunodeficiency disorders (PID), and patients with symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. Kiovig was also registered at the same time, for immune modulation in idiopathic thrombocytopenia purpura (ITP), Guillain Barré syndrome (GBS) and Kawasaki disease.

On 8 January 2014, Kiovig was licensed in Australia for the treatment of multifocal motor neuropathy (MMN).

The subcutaneous route of administration for the treatment of PID was approved in Australia on 30 November 2011. Note, this current submission proposes the use of Kiovig in the treatment of CIDP via the IV route only.

Table 1: International regulatory statusshown below, outlines similar applications overseas along with their approved indications.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	November 2018	Approved; May 2019	*Immunomodulation in adults, and children and adolescents (0-18 years) in Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).*
Switzerland	March 2019	Approved; August 2019	*Immunmodulation in Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-02469-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	30 June 2020
First round evaluation completed	7 December 2020
Sponsor provides responses on questions raised in first round evaluation	29 January 2021
Second round evaluation completed	19 February 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 May 2021
Sponsor's pre-Advisory Committee response	18 May 2021
Advisory Committee meeting	18 June 2021
Registration decision (Outcome)	20 July 2021

Description	Date
Completion of administrative activities and registration on the ARTG	23 July 2021
Number of working days from submission dossier acceptance to registration decision*	229

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Contents of the clinical dossier

This is a literature based submission.

The TGA approved the methodology and search strategies, that the sponsor undertook in support of this literature based submission on 10 January 2020 (provided the search was not limited by date). No pre-submission meetings were undertaken between the sponsor and representatives of the TGA.

The sponsor's overall search identified 149 studies. Of these, 53 priority studies were identified by a primary and independent second researcher. Prioritisation for data extraction included:

- Studies investigating Gammagard/Kiovig (including single-arm studies); or
- Comparative studies looking at the effectiveness of other intravenous immunoglobulins which could be either placebo-controlled or compared intravenous immunoglobulins with other interventions (for example, plasma exchange, subcutaneous immunoglobulins or corticosteroids).

For this submission, 29 studies met the inclusion criteria for priority data extraction and were reported in 53 publications (some provided information on more than one study). The remaining 96 publications were considered lower or given no priority status.

For the evaluation of efficacy and safety, the following were submitted:

- 2 systematic reviews of all relevant randomised controlled trials, meta-analyses;
- 5 controlled studies: one main randomised control trial that assessed Kiovig and 4 main placebo-controlled randomised control trial studies (non-specific to Kiovig);
- 6 supportive studies in CIDP patients: 4 randomised control trials, and 2 uncontrolled clinical trials;
- 5 retrospective studies, of which one was for safety only;
- one periodic safety update review (dated 22 July 2019); and
- literature references.

No pivotal Phase III, or Phase II dose-finding, studies were included in the clinical dossier.

Guidance

The following TGA guideline and TGA-adopted EU guidelines are referred to in support of the clinical aspects of this application:

- EMA/CHMP/BPWP/94033/2007 rev. 4 Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (draft), 17 September 2020;[3]
- Literature-based submissions, Therapeutic Goods Administration, 27 May 2014;[4]
- CHMP/EWP/83561/2005 Guideline on clinical trials in small populations, 27 July 2006;[5] and
- CPMP/EWP/2330/99 Points to consider on application with (1) Meta-analyses and (2) One pivotal study, 31 May 2001.[6]

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacology

Pharmacokinetics

No new pharmacokinetic (PK) data were provided in this application.

With regard to the above, the approved PI reads:

> *'Normal immunoglobulin (human) is immediately and completely bioavailable in the recipient's circulation after IV administration. It is rapidly and nearly evenly distributed between plasma and extravascular fluid. After approx. 3 to 5 days, equilibrium is reached between the intra- and extravascular compartments. Kiovig has a median half-life of about 30 days in PID* [primary immunodeficiency disorder] *patients. PK values are comparable to other human immunoglobulins'.*

The Delegate stated that comparable data should have been provided by the sponsor to support the stated claim of Kiovig having comparable PK values.

[3] European Medicines Agency (EMA): EMA/CHMP/BPWP/94033/2007 rev. 4 Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (draft), 17 September 2020. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig_en-1.pdf
[4] TGA: Literature-based submissions. Therapeutic Goods Administration, Canberra. Available at: https://www.tga.gov.au/publication/literature-based-submissions
[5] European Medicines Agency (EMA) Guideline on clinical trials in small populations (CHMP/EWP/83561/2005: 27 July 2006).
[6] European Medicines Agency (EMA) Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99: 31 May 2001). https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-application-1meta-analyses-2one-pivotal-study_en.pdf

Pharmacodynamics

No new pharmacodynamics (PD) data were provided in this application. The precise mechanisms of action of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy are unknown, but the pleiotropic immune-modulating effects of immunoglobulin G (IgG) are assumed to be responsible for the therapeutic effect.

With regard to the above, the approved PI reads:

> *'IgG antibodies are protein molecules that are capable of specific interaction with molecules that are part of the membranes of infectious agents, foreign or abnormal cells, or toxic materials (antigens). Antibodies are produced by B- lymphocytes, often with the help of T-lymphocytes, macrophages or dendritic cells. Following an initial interaction, some B-cells differentiate to memory cells, which upon encountering with the same infectious agent later in life, are capable of rapidly reproducing and producing increased quantities of the IgG antibodies specific to the same infectious agent. Thus, the mode of action of IVIg* [intravenous immunoglobulin] *mimics the action of the normal plasma immunoglobulin in a healthy adult individual, having a broad spectrum of antibodies against infectious agents'.*

Dose finding studies

No studies were identified by the clinical evaluator as providing dosage selection information for the literature based submission studies in the dossier provided. The five main clinical studies reviewed in the appropriate section of the clinical evaluation report, did not include comparisons of intravenous immunoglobulin administered for more than one dose-regimen in either the (a) initial phase of treatment; or (b) maintenance phase of treatment.

The Delegate, to reiterate the clinical evaluator's overall conclusions on dose finding for the literature based submission, drew attention to the following from the clinical evaluation report:

> No formal dose finding studies were identified; the proposed starting and maintenance doses for use in CIDP in Australia are the same as those described in the European guideline;[3] and the core EU Summary of Product Characteristics (SmPC) for human normal immunoglobulin for IV administration. The posology in the guideline appears to be based on the ICE study by Hughes et al. (2008);[7] which is an acceptable approach since it was a generally well-designed, placebo-controlled, peer-reviewed randomised control trial, with the largest number of study subjects than any of the other submitted publications. It also incorporated a 3-weekly fixed-dose regimen in its assessment of IVIg as maintenance treatment. The brand of IVIg used in the ICE study was neither Kiovig nor Gammagard Liquid. If the brand had been Kiovig, or an equivalent product, the Hughes et al. (2008) study would have been considered pivotal in this literature based submission application.

[7] Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial [published correction appears in *Lancet Neurology* 2008 Sep;7(9):771]. *Lancet Neurology.* 2008;7(2):136-144.

Efficacy

Kuitwaard et al. (2010)[8]

This was the main randomised control trial (Kiovig-specific; active-controlled; maintenance treatment only).

The results for serum IgG from this study were published in Kuitwaard et al 2013).[9]

Study design

This was an investigator-initiated, multicentre, Phase lll, double-blind, randomised control trial conducted at three university-affiliated neuromuscular disease centres in the Netherlands. The trial consisted of 10 infusions in three stages:

1. a 3-week open-label period with one Gammagard S/D infusion (questionably 2 infusions rather than one);
2. an individualised 6- to 16-week double blind period with 4 blinded infusions of either Gammagard S/D or Kiovig infusions; and
3. an open label extension period with five Kiovig infusions (questionably 4 infusions rather than five).

Patients were treated either in hospital or at home as per pre-trial entry.

Objectives

The primary objective was:

> to compare the efficacy of two different IVIg brands (Kiovig versus Gammagard S/D) in the treatment of CIDP.

The secondary objective was:

> to compare the safety of Kiovig versus Gammagard S/D.

The objective in Kuitwaard et al., (2013)[9] was to determine the inter- and intra-variability of serum IgG in clinically stable, IVIg-dependent CIDP patients receiving fixed-dose maintenance treatment of IVIg, with variable frequency of dosing (as a possible biomarker to monitor the effect of IVIg treatment).

Inclusion criteria

The main inclusion criteria were:

- Age ≥ 18 years;
- Diagnosis of CIDP made by a consultant neurologist and fulfilling the American Academy of Neurology (AAN) clinical research criteria;
- Initial chronically progressive, stepwise progressive or recurrent weakness of all extremities, developing over at least 2 months, with reduced or absent tendon reflexes;
- Observed and documented clear improvement of muscle function after the first use of Gammagard S/D;
- Active CIDP defined by an overall disability sum score (ODSS) grade ≥ 2 and a Medical Research Council (MRC) grade ≤ 4 in at least one of the muscles assessed in the MRC

[8] Kuitwaard K, et al. Randomised controlled trial comparing two different intravenous immunoglobulins in chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Neurosurg Psychiatry. 2010 Dec;81(12): 1374-1379.
[9] Kuitwaard K et al. Serum IgG levels in IV immunoglobulin treated chronic inflammatory demyelinating polyneuropathy. Journal of Neurology, Neurosurgery and Psychiatry. 2013;84(8):859-861

sum score before start of the trial or following a reduction of IVIg dose sometime within the last 12 months before start of the trial;

- Ongoing intermittent treatment with IVIg (Gammagard S/D) leading to a stable condition. The individual dose must have been stable (within a 25% range of the total dose) for at least 8 weeks and unchanged within the last 4 weeks before start of the trial;
- Electromyography findings compatible with CIDP at least once during their illness.

Exclusion criteria

The main exclusion criteria were:

- Known hereditary neuropathy or severe concomitant diseases such as human immunodeficiency virus (HIV) infection, Lyme disease, chronic active hepatitis, congestive heart failure, systemic lupus erythematosus, drug- or toxin-induced neuropathy, vasculitis and malignancies;
- IgM paraprotein with anti-myelin-associated glycoprotein antibodies;
- Multifocal motor neuropathy, fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria;
- Atypical CIDP with pure sensory or persistent unifocal impairment or significant central nervous system involvement;
- Treatment with an IVIg brand other than Gammagard S/D during the previous 8 weeks.

The Delegate questioned if the requirement that prior treatment exposure to other IVIg products, except Gammagard S/D, be excluded in this comparative study indicates intrinsically, that IVIg products are not identical?

Study treatments

A group of active but stable CIDP patients being treated with a stable maintenance dosage of 5% freeze-dried IVIg (Gammagard S/D) at fixed frequency per individual, were randomised at an equivalent allocation ratio to receive either:

- 4 infusions of the same product at the stable maintenance dosage or;
- an equivalent dosage of a more concentrated 10% liquid IVIg preparation (Kiovig).

The frequency of dosing for each patient, whether on Gammagard S/D or Kiovig, was kept the same as per the treatment regimen prior to trial entry and remained constant throughout the whole trial, thus maintaining individually optimised fixed doses per patient.

The IVIg was given at a standard safe infusion rate although as previously alluded to, the dose-frequency amongst patients varied.

The clinical evaluation report states that:

- [in order to] establish the optimal regimen of IVIg, the dosage was increased to achieve maximal clinical response and the infusion frequency shortened when patients experienced end-of-dose symptoms and signs;
- regular attempts to decrease the dosage were made as recommended; and
- the ranges of actual dosages used during the double blind treatment period were not specified.

The Delegate questioned [if the points raised by the clinical evaluator, above] pose an issue relevant to determining the exact dosing instructional guide?

Randomisation and blinding methods

A computer-generated randomisation list was produced by a statistician, with block randomisation for each centre.

Patients and Investigators were blinded to drug allocation. A central pharmacist was responsible for reconstitution, packaging, labelling and distribution of trial medication during the double blind phase.

The 10% [Kiovig] solution was not diluted to a 5% solution as there were no stability data available. Due to different volumes of the preparations, nurses who were experienced in administering the IVIg could not be blinded to drug assignment, as the infusion speed had to be adjusted to ensure the integrity of the patient blind.

The infusion bag and the drip chamber were enclosed in a covering bag and a coloured infusion line was used to maintain the blind for the assessor and patient.

Participant flow

Screening was undertaken for 75 persons. Of these, 27 subjects were enrolled and randomised in the double blind phase: 13 Gammagard S/D and 14 Kiovig.

Twenty-six subjects completed double blind treatment phase. The latter is due to one subject in the Kiovig discontinuing treatment due to an adverse event.

Twenty-five subjects completed the open-label extension treatment phase. One subject in the Kiovig discontinued treatment due to an adverse event during double blind treatment.

Efficacy parameters and endpoints

Primary: a difference in the mean overall disability sum score (ODSS) change from Baseline between the two groups of ≤ 1 point was considered as equivalence.[10] The ODSS was recorded before every infusion.

Others: 1) immediately before infusions 1 and 2 (baseline open-label), 4 and 6 (blind phase), 8 and 10 (open-label extension phase), a neurological examination was undertaken, which included changes in the:

> *Vigorimeter*; Range 0 to 160: Higher scores indicate better muscle strength; Recorded before every infusion
>
> *Medical Research Council (MRC) sum score (6 muscles):* Range 0 to 60: Higher scores indicate better muscle strength;
>
> *Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score (ISS):* Range 0 to 20: Higher scores indicate more sensory deficits; and
>
> *Total serum IgG (g/L) measured by turbidimetry* (Kuitwaard et al, 2013): IgG levels were determined in serum samples obtained immediately before and 5 minutes after every infusion. The peak increase in serum IgG after IVIg (change in IgG) was defined as the IgG level after treatment minus the level just before treatment. The latter were used to assess for both inter- and intra-patient variability of serum IgG.

One week after each infusion, the patient completed the following questionnaires:

> *Fatigue severity scale* (FSS; Range 0 to 7: higher scores indicate more fatigue);
>
> *Short Form (36) Health Survey, Dutch language acute version 1 (SF-36*); All separate items range 0 to 100: Higher scores indicate better health or less bodily pain; and

[10] The two ODSS measurements, assessed immediately before infusion one (Gammagard) and two (first blinded infusion), were averaged and the mean value was taken as a baseline measurement. Range 0 to 12: Higher values indicate more limitations. This is reported by Merkies et al (2002) as a validated method in CIDP and GBS.

The Rotterdam handicap scale (RHS); Range: 9 to 6: High scores indicate less handicap.

Analysis of populations

The intent-to-treat (ITT) population was N = 27 patients (Gammagard S/D, N = 13 and Kiovig, N = 14).

The analysis of population in Kuitwaard et al., (2013) was N = 25 patients, representing those who completed the study.

The Delegate commented that these numbers are small for both Gammagard and Kiovig.

Sample size

The sample size calculation, based on historical data, showed a standard deviation (SD) of 0.84 for change in ODSS, over a stable period of 2 months. To exclude (that is, to detect) differences of >1 point in change in ODSS between the two different treatment arms, 11 patients were required in each treatment group ($\alpha = 0.05$; power 80%).

Statistical methods

The mean of ODSS changes from baseline for each of the 4 blinded infusions (infusions 3, 4, 5, 6) was compared using repeated measurements analysis of variance (ANOVA). The 95% confidence intervals (CI) for the difference in mean ODSS should not cross -1 and +1.

Inter- and intra-patient variability of serum IgG in Kuitwaard et al (2013) was assessed by coefficient of variation, calculated as the ratio of the SD to the mean x 100%.

The peak effect (change in IgG) of both preparations was compared using Wilcoxon matched-pairs signed-rank test. Correlation was tested with Spearman correlation coefficient (rs). Analysis was performed using SPSS v17.0. Two-sided p values < 0.05 were regarded significant.

Baseline data

Baseline clinical and demographic characteristics were generally similar between the 2 treatment groups for:

- Mean age (54.0 to 54.6 years);
- Baseline ODSS of 3 to 3.7
- Medical Research Council sum scores (53.6 to 54.6);
- Vigorimeter scores (86.8 to 89.3).

Regarding the above, the Delegate commented that it would appear that the patients only have mild to moderate symptoms at Baseline.

Patients in the Kiovig treatment arm compared to the Gammagard S/D treatment arm had:

- Higher percentage of males (86% versus 62%),
- Heavier subjects (85.6 versus 78.5 kg);
- Higher weekly median IVIg Gammagard S/D doses (14.6 versus 12.5 g/week);
- Lower mean dose-intervals of IVIg Gammagard S/D (15.5 versus 18.8 days);
- Higher baseline ODSS scores (3.7 versus 3.0).

The Delegate questioned, does that [the baseline data above] translate to the Kiovig group as being slightly sicker than the Gammagard S/D group?

All patients had at least moderate disability in their arms or legs at Baseline or following IVIg reduction during the 12 months before the trial started.

All patients had been treated successfully with maintenance IVIg Gammagard S/D before start of the trial (mean 5 years; Range 5 months to 13 years) and had active disease that required intermittent IVIg Gammagard S/D treatment, that is confirmed IVIg dependency.

Major protocol violations/deviations

One patient ceased blinded treatment after 1 infusion due to an adverse event (fatigue) and was then observed during the rest of the double blind phase with unblinded Gammagard S/D.

A second patient received double-dosage on alternate, that is, every other infusion. No further details were provided.

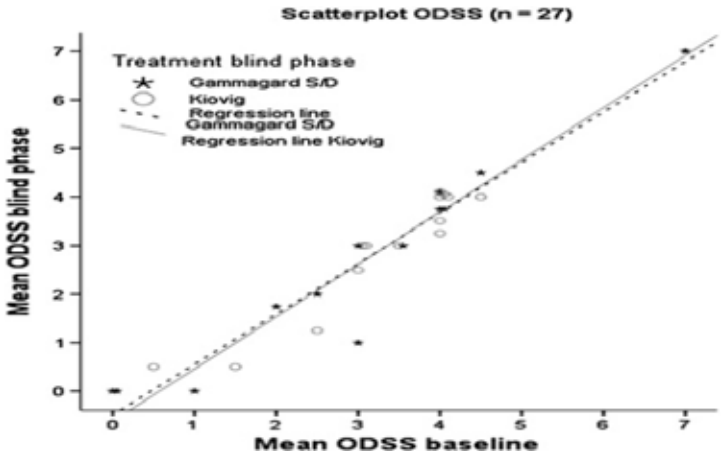
Efficacy outcomes

The following is a summary of the clinical evaluator's findings.

Primary outcome:

- Treatments were not significantly different for the primary outcome measure (full analysis set (FAS, ANOVA)):
  - difference 0.004 (Gammagard minus Kiovig), 95% confidence intervals (CI): -0.4 to 0.4; p = 0.98, using repeated measurements ANOVA. ODSS showed a similar distribution between treatments (as shown in Figure 3, below). This effect did not differ significantly between the 4 measurements in the blinded phase (p = 0.19).

Figure 3: Kuitwaard et al, (2010) Scatterplot overall disability sum score



Source: Figure 3, Kuitwaard et al (2010)

- No pre-specified or reported post hoc estimation for the subgroup analysis (SGA) of the primary endpoint.
- For the sensitivity analysis (SAs) of the primary endpoint, the ODSS score in the patient who received 1 blinded treatment in the double blind phase instead of 4 treatments was the same as after non-trial medication, that is, no change in ODSS.

Others:

No clinically relevant differences were reported between treatments for secondary measures (detailed in the table below).

Table 3: Kuitwaard et al, (2010) Results for the secondary outcomes

	Difference (Gammagard minus Kiovig)	95% CI	p Value
MRC sum score	−0.58	−1.9 to 0.7	0.37
Vigorimeter	0.54	−4.0 to 5.0	0.81
ISS	0.59	−0.7 to 1.8	0.33
FSS	0.18	−1.9 to 0.6	0.33
RHS	0.74	−0.2 to 1.6	0.12
SF-36			
Physical functioning	−2.1	−4.5 to 0.28	0.08
Role-physical	1.8	−3.6 to 7.2	0.50
Bodily pain	−2.8	−6.6 to 6.1	0.93
General health	−1.9	−4.8 to 1.0	0.19
Mental component summary	1.5	−2.4 to 5.4	0.43

Source: Table 2, Kuitwaard et al (2010)

For serum IgG (Kuitwaard et al, 2013):

- the intra-patient variability of the pre-treatment serum IgG levels, post-treatment levels and peak increase in serum IgG shortly after Kiovig (change in IgG) was low (mean coefficient of variation = 3%, 4%, 10%);
- the inter-patient variability of serum IgG between patients treated with the same dose and interval was low in pre-treatment, post-treatment and change in IgG level (mean coefficient of variation = 13%, 11%, 20%) after Kiovig;
- Gammagard infusion was reported to have similar low variability in IgG levels for intra- and inter-patient variability, but no results were provided;
- post-treatment IgG levels and change in IgG levels for Kiovig were related to the IVIg dosage administered per infusion ($rs = 0.405$, $p < 0.05$; $rs = 0.78$, $p < 0.001$), but not to the infusion frequency;
- total dosage per infusion required to reach a stable clinical state and change in IgG did not correlate with age, sex, bodyweight, lean body mass, muscle strength, disability or sensory dysfunction; and
- change in IgG after Gammagard infusion was less than after Kiovig (median 6.1 g/L versus 6.8 g/L, $p < 0.001$).

The Delegate questions, from the above, is Kiovig stronger?

Clinical evaluator's conclusions for the Kuitwaard et al., (2010) study

The following is a summary, adapted by the Delegate, of the clinical evaluator's overall conclusions on clinical efficacy for a Kiovig-specific; active-controlled; maintenance treatment study:

- the study population was generally representative of CIDP (middle-aged males);
- patients were still IVIg dependent since most had at least moderate disability in arms or legs at baseline or following IVIg reduction during the previous 12 months. Patient selection minimised the probability of recruitment of IVIg-refractory patients;
- the efficacy endpoints were generally acceptable. This publication used ODSS (reported in the literature as a validated method) to assess disability, whereas most other recent CIDP publications used the more widely studied and validated INCAT disability score;

- the sample size and power calculations and the statistical methods used were generally acceptable;
- the treatments used were not strictly interchangeable since there were differences in IgG subclasses and excipients, as well as differences in manufacturing processes;
- changes in serum IgG after Gammagard infusions were smaller than after Kiovig infusions (median 6.1 g/L versus 6.8 g/L, $p < 0.001$), which may, in part, be attributed to the lower IgG content in Gammagard (95%) compared to Kiovig (around 100%);
- this evaluator did not agree with the sponsor, that the Phase III study by Kuitwaard et al., (2010) with the additional data presented in the Kuitwaard et al (2013) publication was pivotal. While this evaluator accepts that the Kuitwaard et al (2010) clinical study, is the only head-to-head randomised clinical trial identified in the literature search that assessed Kiovig in CIDP, from a regulatory perspective it failed to meet many criteria listed in the TGA-adopted guideline to assess pivotal studies in an application.[4] In particular the Kuitwaard et al (2010) study:
  - did not assess acute/unstable CIDP, so loading dose regimens could not be assessed, only maintenance dose regimens;
  - information about treatment optimisation prior to randomisation, including up- and down-titration of IVIg doses was not provided;
  - relapse and/or withdrawal effects were not evaluated;
  - no comparison versus placebo were undertaken to account for underlying disease course, so efficacy of long-term Kiovig treatment was difficult to interpret;
  - no data were available for nerve conduction outcomes;
  - the estimated size of the treatment benefit, in terms of both statistical and clinical significance, was not adequately undertaken (as there was no comparison versus placebo or the underlying disease course);
  - the study may have lacked internal consistency since no analyses of pre-specified sub-populations were undertaken. However, robustness of the primary results was demonstrated by the results from secondary efficacy outcome measures;
  - the external validity of the study results may have been adversely impacted, since no information on ethnicity and body mass index were reported. Also, the study did not assess IVIg in paediatric populations (≤ 18 years old);
  - no results of 'centre effects' were presented. It is unclear from the data whether subjects were recruited equally across participating centres or whether one centre dominated;
  - the internal validity of the results may have been adversely affected, since the differences in baseline demographic and disease characteristics between the treatment groups indicated there may have been a suboptimal randomisation process in treatment assignation. In addition, the blinding of treatment assignation was suboptimal and prone to introduce bias; and
  - very limited safety data were presented.

The Delegate is in agreement with the clinical evaluator's conclusions, as listed above.

The clinical evaluator also concluded that:

> Although a stable maintenance dose of approx. 1g/kg, which is generally consistent with the EU guideline for maintenance treatment in CIDP, was used, the IVIg dose-interval varied between patients. Four IVIg infusions were administered over 6 to 16 weeks with a mean duration of 10 weeks. Hence, each infusion, on

average, was administered every 2.5 weeks, with some patients receiving IVIg every 1.5 weeks and others every 4 weeks. On balance, these infusions were administered in general agreement with the EU guideline (every 3 weeks) and equivalence between the 2 IVIg preparations was adequately demonstrated. Since only 2 different IVIg brands were compared, conclusions about equivalence can only be drawn between these 2 products, not other commercial brands of IVIg.

While serum IgG levels were constant before and after serial IVIg infusions, the study population had stable CIDP and received a constant maintenance dose of IVIg. These results suggest steady-state had been achieved. The study design did not allow for investigation of severe or unstable disease and corresponding changes in serum IgG levels, or in treatment-naive or non-responsive CIDP patients, or by CIDP subtype (chronic progressive, chronic relapsing) or by age-group (adults versus paediatrics); No explanation why CIDP patients required different dosages in their IVIg maintenance treatment was provided. For these reasons, the study is not considered generalisable to other study populations. However, the results provide evidence of maintenance of effect of Kiovig in adult patients with stable CIDP.

The Delegate questioned if serum IgG levels were constant, or was this relatively. The Delegate also queried if steady-state had been achieved.

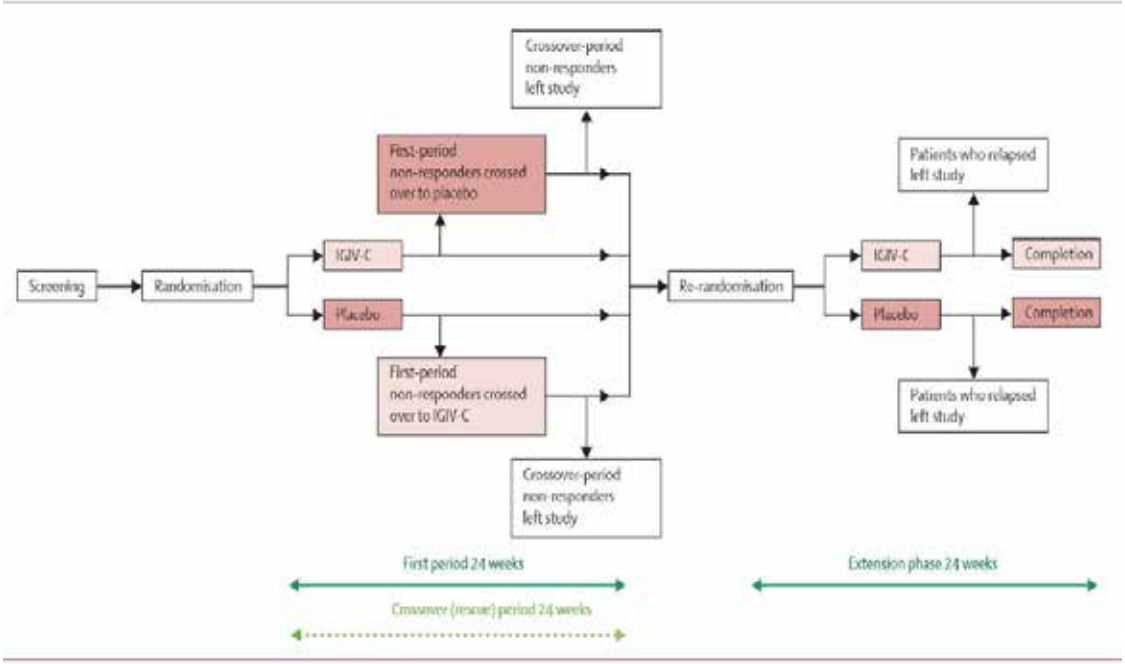
Hughes et al. (2008)

This is a placebo-controlled randomised control trial that investigated IVIg (not specific to Kiovig) in CIDP.[7]

Study design

Hughes et al., (2008);[7] is a randomised, double blind, placebo-controlled, response-conditional (rescue), cross-over multicentre study. Patients who showed an improvement in inflammatory neuropathy case and treatment (INCAT) disability score during treatment were re-randomised into a 24-week extension phase. Patients 18 years or older were recruited. The following figure provides an overview of the study design.

Figure 4: Hughes et al, (2008) Study design



Source: Figure 1 (Hughes et al, 2008)

The Delegate stated that it would appear that the above design implicitly points to the fact that a significantly high placebo response was expected.

Objectives

The primary objective was to establish whether 10% intravenous caprylate-chromatography purified immune globulin (Gamunex) has short-term and long-term benefits in CIDP patients.

The clinical evaluators overall conclusions on clinical efficacy for this study (abbreviated by the Delegate was that:

> The Hughes et al., (2008);[7] study was well designed (particularly the use of a rescue cross-over period to allow for ethical practice) and conducted, appeared to be Good Clinical Practice (GCP) compliant and was generally consistent with the clinical guideline on IVIg.[3]

Regarding the above, the Delegate believed that crossing over from 'active to placebo arm' (in the first period of the study) due to lack of response, does not really constitute an acceptable ethical clinical practice.

The efficacy endpoints (including the validated INCAT disability scale), statistical methods, sample size and power calculations were acceptable. The inclusion and exclusion criteria were acceptable, and the study population generally representative of the target (adult) population.

The results demonstrated both a statistically significant treatment effect of IVIg Gamunex versus placebo treatment, which was also clinically meaningful (number needed to treat (NNT) = 3.The study results had good internal consistency, with generally supportive results from pre-specified subgroup, sensitivity and secondary efficacy analyses (other than compound muscle action potential amplitude).

It was unclear whether particular subtypes of CIDP or treatment-naivety might affect treatment outcomes. It is also unclear from the data whether centre effects were investigated, since the distribution of subject recruitment by centres (and by country) was not reported in detail. Over-recruitment in one or more centres and/or one or more countries has potential to introduce bias into the results, but on balance, the study results appeared valid, robust and generalisable to adults with CIDP.

Most IVIg infusions were given over 2 to 4 days for the 2 g/kg loading dose followed by a maintenance infusion dose of 1.0 g/kg for 1 to 2 days every 3 weeks. The loading and maintenance doses, as well as the periods of infusion, and dose-interval in maintenance treatment were generally consistent with the EU guideline;[3] and indeed, this guideline may actually be based on results from this study, which is often referred to as the 'ICE' study.

The ICE study is the largest published trial in treating CIDP with IVIg, using the commercial brand Gamunex. The level of evidence is high and if Kiovig had been the brand of IVIg used, then this evaluator would have considered this study as pivotal. It is generally consistent with the requirements of one Phase III pivotal study for regulatory purposes;[6] and although it had relatively small subject numbers, the design was also generally consistent with the guideline in small populations.[5]

Short-term improvement in adjusted INCAT disability score in response to IVIg Gamunex was significantly greater than placebo. These results were supported by significant improvements in objective measures of GS, MRC sum score and ISS score, which in turn can be expected to lead to better functionality for patients. Patients who continued to receive IVIg in the extension phase had significantly longer time to relapse than placebo-treated patients (p = 0.011; number needed to harm = 3). These results support IVIg Gamunex as a first-line treatment option in adults with CIDP.

The Delegate is essentially in agreement with the clinical evaluator without the need for further elaboration. The outcome of the assessed study article is not exactly new and has not yielded substantial evidence to definitely and unequivocally, support the basic tenet of the current submission given that:

- Gamunex is already indicated for CIDP on the ARTG;
- placebo and not Kiovig was the comparator in the randomised control trial;
- there are differences in IgG subclasses and excipients, as well as differences in manufacturing processes; and
- there is no way of drawing conclusions about equivalence of Kiovig to Gamunex, either therapeutic or biologic, from this randomised control trial.

To approve Kiovig for the CIDP indication with the above deficiencies at this stage will be quite inappropriate. A deferral option will be preferred as the latter will allow the commercial sponsor of Kiovig to generate adequate and supportive comparable or bridging data for the proposed CIDP indication for Kiovig. The deferral preference is even more appropriate, given that there are already a host of other different Immunoglobulin, normal (human) products, such as Gamunex, Hizentra, Intragam and Privigen on the ARTG for CIDP indication.

Hahn et al. (1996)[11]

This was a prospective two-period, double blind, placebo-controlled, cross-over study in IVIg-naïve patients recruited at neuromuscular clinics in two Canadian institutions between 1990 and 1994. The study comprised two identical 28-day periods with a variable washout period.

Patients were randomised to receive approx. 0.4 g/kg 5% IVIg (in 9 to 11% mannose) or placebo (10% dextrose) infusions on 5 consecutive days within a 28 day period, before cross-over. All infusions were given in hospital or at an outpatient treatment centre.

The clinical evaluators overall conclusion, abbreviated by the Delegate, was:

The study design qualified it for a Level II rating, although numbers of patients were small. The cross-over period enabled each patient to act as their own control. This design is generally expected to lead to a more precise estimate of the treatment effect in each individual patient and is therefore a strength of this design. There were more female subjects than males, which contrasts with most other published studies submitted in this application.

The primary efficacy measures (Neurological Disability Scale (NDS), Grip Strength (GS) and Clinical Grading (CG)) were not directly comparable with the more stringent INCAT disability scale used by Hughes et al. (2008).[7] Inter-observer agreement was tested before the study began for the 3 primary measures of efficacy and was found to be very good. This is a positive feature and provides evidence of good internal validity.

In the primary efficacy analysis, baseline values for NDS and CG were lower in the sham treatment arm compared to the IVIg treatment arm, and GS was higher in the sham treatment arm compared to the IVIg treatment arm. These differences can be explained when the first treatment period was analysed separately. This analysis showed good balance between baseline characteristics across the treatment groups, which is indicative of an adequate randomisation process. Hence, a significant carry-over effect appeared to have occurred and the 28-day washout period between treatments was inadequate i.e. clinical response to treatment lasted longer than 28 days in many instances. Similar observations were made in respect of the secondary efficacy endpoints. This 'cross-over

[11] Hahn AF et al. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. Brain. 1996; 119(4): 1067-1077.

effect' does not support (that is, line up properly with) a 3-weekly IVIg pulse maintenance dose-regimen as proposed in the EU guideline directly after the loading dose.[3]

The loading dose of IVIg used in this study was consistent with the proposed dose-regimen, even though Kiovig was not the brand of IVIg used. The 3-weekly pulse maintenance treatment with IVIg in the open label treatment period appeared to provide clinical benefit in some subjects for up to 3 years, while others benefited from variable dosing and dosing frequency based on predicted deterioration in function. Although based on small numbers of subjects, these results suggest some patients might benefit from individualisation of doses and dosing- intervals once the patient has been stabilised on treatment. However, it is unclear from the publication what criteria were applied when making dose-adjustments.

The study results indicate that there may have been a correlation (albeit not statistically significant) between disease course and response to treatment. In particular, patients with chronic progressive CIDP (56%) may be less responsive to IVIg treatment than the chronic relapsing form of CIDP (71%). The former group were more heterogeneous than most of the patients with relapsing subtype, who were treated during an acute relapse or within 12 months of onset of disease and hence were more likely to respond to treatment. The chronic progressive subtype achieved maximal benefit at 6 weeks (range: 3 weeks to 18 months), whereas the relapsing subtype appeared to have a reproducible benefit that continued to improve with pulse therapy. These results may be considered hypothesis generating, but this area needs further examination since if there becomes a clear association between CIDP subtype and response to IVIg treatment, the subtype of CIDP may give rise to differences in treatment approach rather than the current EU guideline;[3] and the dose-regimens proposed in this application.

Notwithstanding the differences in design and efficacy endpoints between this study and the Hughes et al., (2008) study;[7] the overall results demonstrated that IVIg was an effective treatment versus placebo in adults with CIDP.

The Delegate, again, is essentially in agreement with the clinical evaluator on the outcome findings without the need for further elaboration, favouring IVIg over placebo or sham treatment in adults with CIDP. The latter however, does not add substantial evidence perse to support the basic tenet of the current submission given that:

- the unidentified bio-characteristics of the particular commercial IVIg used in the study;
- the ARTG status of the unidentified IVIg is unknown;
- placebo and not Kiovig was the comparator in the randomised control trial;
- there are differences in IgG subclasses and excipients, as well as differences in manufacturing processes; and
- there is no way, of drawing conclusions about equivalence of Kiovig to the referenced IVIg, either therapeutically or biologically, from this randomised, placebo controlled study.

The Delegate commented that Kiovig's approval at this stage for CIDP, not specifically based on comparable trials with another IVIg, especially one of those listed on the ARTG for CIDP, is tantamount to abductive reasoning.

Mendell et al. (2001)[12]

This is a randomised, double blind, placebo-controlled, multicentre, investigator-initiated study conducted over a 3-year period in the USA.

[12] Mendell JR, et al. Randomized controlled trial of mg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. Neurology. 2001;56(4):445-449.

Evaluations were performed at Baseline, Days 10, 21 and 42 (endpoint of double blind period). There was no extension or follow-up period.

The primary objective was to determine the efficacy of IVIg in patients with untreated CIDP.

The clinical evaluator's overall conclusions on clinical efficacy, abbreviated by the Delegate, were:

The results of this study are less convincing than the Hughes et al., (2008) and Hahn et al., (1996) studies, since the assessment appeared to be less rigorous overall. The choice of primary outcome measure (average muscle score (AMS)) may not be directly comparable to clinical response observed with scores on the validated and more stringent INCAT and Rankin scales. Nevertheless, the trial demonstrated that IVIg was effective versus placebo, and the primary analysis results were generally supported by most secondary efficacy results (Hughes Disability Functional Scale (HDFS) and some neurophysiological measures). These results provided assurance the study had reasonable internal validity, although no sensitivity analyses of the primary efficacy analysis were undertaken.

One important limitation in the study design was that the 6-week trial did not allow for a full evaluation of long term treatment effect of IVIg, or permit an evaluation on relapse following study drug discontinuation.

The randomisation process was suboptimal (block randomisation to participating centres), which led to an imbalance in the number of subjects allocated to each treatment arm. However, this imbalance is not expected to adversely affect the primary efficacy results.

Although the brand of IVIg used in this study was not Kiovig, the loading dose (1 g/kg on Days 1 and 2, that is 2 g/kg in total) and the follow-up dose (1 g/kg on Day 21) were generally consistent with the proposed dose-regimens.

Notwithstanding the study limitations, particularly the short duration, the results provided good evidence of a treatment benefit from IVIg in adults with CIDP who are treatment-naïve.

The Delegate noted the identified study deficiencies as per the clinical evaluator, without the need for further elaboration. Apart from the latter, any favourable benefit associated with the IVIg treatment over placebo in adults with CIDP is neither a panacea nor absolute evidence to granting Kiovig the proposed CIDP indication.

Furthermore:

- Pasteurized Gammar IV is not listed on the ARTG;
- placebo and not Kiovig was the comparator;
- there are differences in IgG subclasses and excipients, as well as differences in manufacturing processes; and
- there is no way, of drawing conclusions about the equivalence of Kiovig to the referenced IVIg (Pasteurized Gammar IV), either therapeutically or biologically from this study.

Vermeulen et al., (1993)[13]

This is a randomised, double blind, placebo-controlled, multicentre trial conducted in the Netherlands pre-August 1992.

[13] Vermeulen M et al. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: A double blind, placebo-controlled study. Journal of Neurology Neurosurgery and Psychiatry. 1993;56(1):36-39.

The primary objective was to investigate whether high-dose IVIg for 5 consecutive days had a beneficial effect in newly diagnosed CIDP, who had received no prior therapy.

The clinical evaluator's overall conclusion on clinical efficacy, abbreviated by the Delegate was:

- The results of this study are less convincing than the Hughes et al., (2008) study;[7] since the assessment appeared to be less rigorous overall. The choice of primary outcome measure (Rankin scale), while a validated method is not as stringent as the Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score (ISS) disability scale. However, the INCAT disability scale had not been validated at the time this study was conducted.
- The number of patients who were treated with IVIg was also considerably less than in the Hughes et al (2008) study.
- Unlike the other main studies submitted in support of the application for IVIg in CIDP, the study results did not demonstrate a treatment benefit of IVIg treatment over placebo treatment. The authors explored in detail reasons to explain their findings and concluded that the results were attributed to the methods used for assessment.
- The selection of patients according to established criteria did not appear to have been undertaken. The 1991 AAN criteria for CIDP diagnosis were published at the time the study results were analysed and the authors did not make reference to this or any other clinical guideline or consensus statement. Since the study population were those with newly diagnosed CIDP and who had received no prior therapy, it is important to establish how the participants were diagnosed (definite or probable CIDP) and why they had not received prior treatment for their condition. The majority of patients were also categorised as chronic relapsing. It is unclear from the published article whether patients had active or static CIDP. It is possible, particularly for new onset CIDP patients with relapsing CIDP that many of the patients might have been in remission as a natural consequence of the natural course of the disease and hence would not have benefited from treatment.
- Although the loading dose used by the authors is consistent with the proposed loading- dose, the short duration of the double blind phase of the study did not allow for investigation of maintenance, that is, follow-up treatment. Some patients received open-label IVIg, but no further details on dose or frequency of dosing were provided. Lack of placebo control during the open label treatment period may have introduced bias into the results, which could have skewed the results in either direction.
- An imbalance in the baseline disease characteristics between the treatment groups, for example, 86.7% of patients had a remitting course in the IVIg group versus 61.5% in the placebo group, suggested there might have been a problem in the randomisation process, which again might have introduced bias and confounding into the study results.

The Delegate commented that regardless of the causes for the failure of this study to demonstrate a treatment benefit of IVIg treatment over placebo treatment as assessed by the clinical evaluator, the study is nonetheless a testimony to the fact that Kiovig's approval at this stage for CIDP requires well-designed trial as per acceptable guideline depicting efficacy and safety in CIDP. The use of abductive reasoning should not be applied for this regulatory task/purpose.

Furthermore, the IVIg used in the placebo controlled study is not Kiovig and it is stated that the IVIg preparation contained 99% IgG, 1% immunoglobulin A (IgA) and traces of immunoglobulin M (IgM). IgG subclasses: IgG1 57.5%, IgG2 23.8%, IgG3 9% and IgG4 5.5% and at least 95% of IgG was monomeric.

Other studies

Other studies, including retrospective data set, in CIDP patients using IVIg included:

- Dyck et al. (1994)[14]
- Hughes et al. (2001)[15]
- Nobile-Orazio et al. (2012)[16]
- Thompson et al. (1996)[17]
- Jann et al. (2009)[18]
- Nemni et al. (1994)[19]
- Gallia et al. (2016)[20]
- Vucic et al. (2007)[21]
- Ellrichmann et al. (2017)[22]
- Williams et al. (2018; abstract and poster only)[23]

The following are the clinical evaluator's overall conclusions on clinical efficacy for other studies, including retrospective data, abbreviated slightly by the Delegate:

- 6 other additional studies to claim efficacy of IVIg in CIDP were provided:
  - 2 randomised control trials lacking placebo control (Dyck et al, 1994 and Hughes et al, 2001);
  - 2 studies without any control, that is, uncontrolled (Nemni et al, 1994 and Jann et al, 2009);

[14] Dyck PJ et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Annals of neurology. 1994;36(6):838-845
[15] Hughes R et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. Annals of Neurology. 2001;50(2):195-201
[16] Nobile-Orazio E et al (2010). Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. Lancet Neurol 11: 493-502
[17] Thompson N et al (1996). A novel trial to study the effect of intravenous immunoglobulin in CIDP J Neurol 243:280-285
[18] Jann S et al. Intravenous immunoglobulin is effective in patients with diabetes and with chronic inflammatory demyelinating polyneuropathy: Long term follow-up. Journal of Neurology, Neurosurgery and Psychiatry. 2009;80(1):70-73
[19] Nemni R et al. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating neuropathy not responsive to other treatments. Journal of neurology, neurosurgery, and psychiatry. 1994;57 Suppl (Suppl):43-45
[20] Gallia F et al. Efficacy and tolerability of different brands of intravenous immunoglobulin in the maintenance treatment of chronic immune-mediated neuropathies. Journal of the Peripheral Nervous System. 2016;21(2):82-84.
[21] Vucic S et al. Long-term effects of intravenous immunoglobulin in CIDP. Clinical Neurophysiology. 2007;118(9):1980-1984
[22] Ellrichmann G et al. Two years' long-term follow up in chronic inflammatory demyelinating polyradiculoneuropathy: Efficacy of intravenous immunoglobulin treatment. Therapeutic Advances in Neurological Disorders. 2017;10(2):91-101
[23] Williams T et al. Real-world use of IVIG in U.S. regional healthcare plans. Journal of Managed Care and Specialty Pharmacy. 2018; 24: S103. (abstract)

- 2 studies that were placebo-control randomised control trials. Nobile-Orazio et al, (2012) compared intravenous methylprednisolone versus IVIg and Thompson et al. (1996). These 2 studies were both included as primary evidence in the Eftimov et al., (2013) meta-analysis;[24] (discussed later in this section (efficacy)) but were not considered main studies in the clinical evaluation report.

The Delegate comments that:

For a previously stated reason, that is, non-use of Kiovig, and, regardless of the use of placebo or not, any efficacy outcome from neither the two randomised control trials without placebo nor the 2 studies with placebo control can supersede the requirement for well-designed trial, as per acceptable guideline, depicting efficacy and safety of Kiovig in adults CIDP patients.

The Delegate agrees with the clinical evaluator that the Nobile-Orazio et al. study comparing IVIg (not Kiovig) to intravenous methylprednisolone, has little relevance to this application.

The Thompson et al. study design was suboptimal and subsequent early termination/cessation as per the clinical evaluator.

Many different efficacy measures were used across studies, which made data comparisons difficult. While most efficacy measures were validated for general CIDP populations, evidence of validation in some comparisons is unclear, for example, the Rankin scale in CIDP populations refractory to plasma exchange and/or corticosteroids.

The study designs, including study duration and follow-up periods differed across studies, as well as the IVIg brands administered and the loading and maintenance dose-regimens used.

Few studies provided sample size and statistical power calculations. The numbers of patients who received IVIg (not Kiovig) in each study was small and ranged from 7 to 24 patients. Several smaller studies most probably lacked power to demonstrate differences in effect between treatment comparisons. Hence, caution should be exercised in the interpretation of these results.

None of the studies used Kiovig or Gammagard brands of IVIg. Sandoglobulin was used in three studies.

Four retrospective studies (Gallia et al., 2016; Vucic et al., 2007; Ellrichmann et al., 2017; and Williams et al., 2018) were also included. In those retrospective studies:

- There was limitation due to lack of study control and lack of pre-specified primary and secondary endpoints. Those features have potential to introduce bias and over-estimate treatment effect.
- Subject numbers were mostly small (n = 6 to 21) and hence, caution should be exercised in the interpretation of the retrospective data. Furthermore, some data e.g. Williams et al were only presented in an abstract and a poster.
- While Vucic et al., and, Williams et al., used Gammagard in the studies, and Gallia et al., used Kiovig in the study, results were not generally presented by the specific IVIg brand. The brand of IVIg used in the study by Ellrichmann et al. study was not specified.
- Loading doses were administered in each study, of which only the regimen by Gallia et al., (2 g/kg over 4 days) was fully consistent with the proposed loading-dose regimen.

[24] Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD001797.

The loading-dose regimen used in the Vucic et al., study was also consistent with the proposed dose (0.4 g/kg over 5 days), except three loading doses were administered before maintenance treatment was initiated. The studies by Ellrichmann et al., (approximately 1 g/kg) and by Williams et al., (1.4 to 1.5 g/kg) used lower dose-regimens than proposed in this application and the EU. It is noted, that Kiovig was not administered to new patients in the Gallia et al., study and so none of the study subjects received a loading dose of Kiovig.

- The maintenance IVIg doses used across the four [4] retrospective studies were generally consistent with the proposed regimen: Gallia et al., 1 g/kg; Vucic et al., 0.4 to 2.0 g/kg/4 weeks; Ellrichmann et al., approximately 1 g/kg; and Williams et al., approximately 1.1 g/kg. In contrast, the dose-intervals between IVIg infusions varied across studies. Only the studies by Vucic et al., (4-weekly) and Williams et al., (approximately 22 days) were consistent with the proposed dose-interval of every 3-weeks. Both Gallia et al., (3 to 8-weekly infusions) and Ellrichmann et al., (mean 6.9 weeks per infusion) used variable dose-intervals based on clinical response.

Pooled analysis

For the pooled analysis, two meta-analyses were provided for evaluation:

- Eftimov et al (2013); and
- Eftimov et al (2009).[24]

Only significant differences between the meta-analyses were presented in the clinical evaluation report.

The clinical evaluator, in the clinical evaluation of these analyses, came to the following conclusions.

- Both meta-analyses were generally well conducted with low heterogeneity reported for the primary outcome measure in each study, between the five placebo-controlled randomised control trials. However, deficiencies that limit the usefulness of the results include:
  - subgroup and sensitivity analyses were not undertaken to demonstrate robustness of the primary results, due to insufficient subject numbers and data;
  - no analyses of treatment effect (including heterogeneity), or author comment, in respect of:
    - dose or dose-interval;
    - IVIg brand;
    - age-group (particularly paediatric populations);
    - CIDP subtype (chronic progressive or chronic relapsing); and
    - CIDP diagnosis category (definite or probable).
  - each trial used different disability scales and definitions of significant improvement and so the clinical relevance from each study in relation to other results remains unclear;
  - the authors of each meta-analysis referred to an anonymous 1982 WHO (World Health Organization)[25] publication in relation to the source (and inferred brand) of IVIg used, which was not considered important provided the IVIg preparation was

[25] World Health Organisation. Appropriate uses of human immunoglobulin in clinical practice: memorandum from an IUIS/WHO meeting. *Bulletin of the World Health Organisation* 1982; 60: 43-7

produced according to WHO guidelines. This publication pre-dated the clinical trial studies submitted in support of this application, as well as many international registrations of IVIg for CIDP populations.

– since the meta-analyses primarily included studies that did not investigate the Kiovig brand of IVIg, the results of these meta-analyses are considered supportive (not pivotal) of confirmatory effect of IVIg treatment in adults with CIDP.

Regarding the pooled analyses and the clinical evaluator's evaluation, the Delegate made the following comments:

- Unfortunately, the various IVIg used in the pooled /meta- analytical data, which predated the referenced anonymous WHO publication, would have been significantly different in terms of the manufacturing processes, as well as in the IgG subclasses and excipients in a modern world of competitive, manufacturing pharmaceutical edge.
- [Regarding the WHO] the above therefore further highlights, the importance of ensuring that the data analysed and upon which, the proposed CIDP Kiovig indication is based, utilised Kiovig for the greater content.
- [Regarding the last bullet point above, the conclusions are] indicative of the need for a well-designed trial specifically using Kiovig.

Clinical evaluator's overall conclusion regarding efficacy

The clinical dossier included four main placebo-controlled randomised control trials that investigated both loading and maintenance dose-regimens of IVIg, and one main study by Kuitwaard et al., (2010);[8] that investigated maintenance treatment of Kiovig versus the closely related product, Gammagard S/D. The main studies comprised 315 patients with CIDP. The dossier also included six studies regarding the use of IVIg in CIDP, four retrospective studies in CIDP (3 included Kiovig or its equivalent brand) and two meta-analyses in CIDP.

Only the Kuitwaard et al., (2010);[8] study specifically examined the efficacy and safety of Kiovig for the proposed indication. However, the authors only investigated Kiovig in a relatively clinically stable population, that is, as maintenance treatment. This study was not considered pivotal for an extension of indications application based on the criteria specified in the relevant guideline. Therefore, the evaluator considered it reasonable, to review the main studies in detail and, evaluate the other studies as well, including those that specifically did not use Kiovig or Gammagard, in order to better examine the evidence for the use of IVIg in CIDP:

- particularly given the relatively low prevalence and incidence of CIDP in the general population; and
- in case, the sponsor's extrapolation of clinical data from those other brands to Kiovig be sufficiently justified to support registration.

The study by Hughes et al., (2008);[7] would have been considered pivotal if Kiovig had been used. This study comprised of 117 patients, 59 of whom, were exposed to IVIg in accordance with the proposed dose-regimen (acute and maintenance treatment) and the EU guideline.[3] The design and conduct were generally consistent with the guideline on pivotal studies.[6] The available evidence also suggested the dosing recommendations in the EU guideline were based on the Hughes et al (2008) study, commonly referred to as the ICE study.

Despite some variability in the IVIg infusion periods and dose-intervals for maintenance treatment used in the main placebo-controlled randomised control trials and the Kuitwaard et al. (2010) study, the dose-regimens used for loading and maintenance dosing were generally consistent with the proposed regimens and the EU guideline.[3] Most other and retrospective studies also generally supported the proposed dose-regimens. Several

studies adopted a dose-individualisation approach during the maintenance phase of treatment, in which subjects had their dose adjusted based on clinical response and, the interval between dosing adjusted on anticipated/predicted clinical deterioration. To dose at the minimum effective dose that produces a treatment benefit and maintenance of function was reasonable.

Comparable efficacy of IVIg to high-dose oral prednisolone, intravenous methylprednisolone and plasma exchange was reported in several other studies, as well as some improvement in function for patient's refractory to corticosteroids and/or plasma exchange. It was beyond the scope of the clinical dossier to claim equivalence of IVIg against other recognised first-line treatments in CIDP. However, notwithstanding that, these small studies lacked statistical power to demonstrate equivalent efficacy, and other study limitations, the results support IVIg as a possible first-line treatment option in adults with CIDP or as an alternative (short-term) treatment option for patients, who are unable to tolerate corticosteroids, or when plasma exchange is not readily available. Further trials are needed to compare long-term benefit of IVIg with that of plasma exchange or corticosteroids.

Despite some variability in primary outcome measures used in the main placebo-controlled studies, the study results consistently demonstrated efficacy of IVIg versus placebo treatment. Treatment differences were both statistically significantly different and clinically meaningful. The number need to treat to derive a clinical benefit was three, both in the Hughes et al (2008) study;[7] and the pooled analysis in the meta-analyses. In the Hughes et al (2008) study the number needed to harm was also 3, with the time to relapse demonstrated to be longer in IVIg-treated subjects compared to placebo-treated subjects.

IVIg improved disability for at least 2 to 6 weeks versus placebo. However, except for Hughes et al (2008), no study investigated long-term IVIg treatment (and relapse). Hughes et al (2008); [7] demonstrated a maintenance of treatment effect for at least 24 weeks, and possibly up to 48 weeks. Results from some other and retrospective studies suggested a treatment benefit of up to 5 years with intermittent IVIg dosing. However, the latter studies were generally small and lacked placebo control

Only limited efficacy data were obtained from the meta-analyses that were not already covered in individual study analyses. Included studies were generally of moderate or high quality, albeit limited by subject numbers, in part due to the relative rareness of CIDP in the general population. The design and conduct of the meta-analyses were generally compliant with literature based study submission requirements detailed in the TGA-adopted guideline for meta-analyses.[6] On balance, the Eftimov et al., (2013) results are considered the strongest available confirmatory evidence to support short-term (up to 6 weeks) efficacy of IVIg in adults with CIDP.[24]

Most study participants in the submitted studies were adults (aged 18 years and older). Those studies that included paediatric subjects provided few details on the numbers of subjects and their ages upon study commencement. On this basis, no recommendation for approval of Kiovig in paediatric populations with CIDP can be made at the time of the first-round report. The issue of a paediatric indication was the subject of clinical question [inclusion is beyond the scope of the AusPAR].

Dose-response relationships of IVIg were not reported in any of the submitted publications, or discussed in the meta-analyses. Hence, the minimal effective dose of IVIg in CIDP populations does not appear to have been established. Since the proposed IVIg dose-regimen is considered a relatively high-dose exposure (particularly in the loading dose phase of treatment), this may result in high rates of adverse events.

The evidence presented appears contradictory in respect of whether IVIg treatment by CIDP subtype (chronic progressive or chronic relapsing) results in a different treatment benefit. Although no statistically significant differences were reported in studies that

reported results by CIDP subtype, some study results suggested patients with relapsing disease might be generally over-treated using a 3-weekly pulse maintenance regimen. Further study is required.

The choice of validated efficacy endpoints in the CIDP studies appeared broad. Further studies are needed to identify more appropriate outcome measures for trials in CIDP.

In the Kuitwaard et al., (2010) publication,[8] equivalence was demonstrated in maintenance treatment between Kiovig and Gammagard S/D in a stable CIDP population. Equivalence in this study was primarily based on the ability to carry out everyday functions measured using a validated disability scale (the Overall disability sum score (ODSS)). However, since only two different IVIg brands were compared, conclusions about equivalence can only be drawn between these two products, not other commercial brands of IVIg. The sponsor did not provide adequate justification as to how the results from this study involving Kiovig, could be extrapolated to other commercial brands of IVIg used in other publications for CIDP, with particular reference to differences in composition (including IgG subclasses and IgA content), bioavailability and manufacturing/purification processes that may affect efficacy and tolerability. This was the subject of a clinical question to the sponsor [inclusion of this is beyond the scope of this AusPAR].

Despite the limitations from evaluating the evidence from a literature based submission application, the evidence consistently supported the efficacy of IVIg in the short-term (up to 6 weeks) treatment of adults with CIDP. However, the available evidence for the Kiovig brand alone does not support the application. The evidence of a treatment benefit in paediatric populations and the generalisability of the overall results from studies that did not administer the Kiovig brand of IVIg was the subject of a clinical question to the sponsor [inclusion is beyond the scope of this AusPAR].

Safety

Clinical evaluator's overall conclusions regarding safety

The clinical dossier included safety data from four main studies (including three placebo-controlled randomised control trials), four other studies, two retrospective studies and pooled safety data from two meta-analyses. Kiovig was administered to at least 58 patients across studies, and 556 patients with CIDP received IVIg (irrespective of brand).

Of note, approximately 90% of patients in the main (controlled) studies received the proposed loading dose of 2 g/kg and approx. 69% patients received the proposed maintenance dose of 1 g/kg. Most study participants were adults. It is unclear from the published reports how many participants were under 18 years of age, what doses of IVIg they received (loading and maintenance doses) and their experience of adverse events.

Although the long-term safety data provided in this application were generally limited, given the rareness of the condition being treated (CIDP); and the lack of reporting of safety data per se in many of the published studies, this clinical evaluator considers that the requirement of a minimum 12 months' duration specified in the TGA-adopted EU guideline for medicinal products for long-term use, has been adequately met.[26]

The frequency and pattern of IVIg-related adverse events and IVIg-related adverse drug reactions were generally consistent across studies, and generally consistent with the draft PI. Adverse events associated with IVIg treatment tended to be mild to moderate in severity, transient, non-serious and non-severe. Very few adverse events or adverse drug reactions led to study-drug discontinuation.

[26] Clinical Investigation of Medicinal Products for Long-Term Use: Directive 75/318/EEC as amended (last revised: February 1987). https://www.tga.gov.au/sites/default/files/vol3cc6aen.pdf

The incidence of serious adverse events across studies were generally low (6%) and similar to placebo-treated subjects (7%). Similarly, the frequency of serious adverse events per infusion was low (0.8%) and generally similar to placebo (1.9%). Serious adverse events were often transient and not considered treatment related. These findings are important since the dose-regimens proposed (2 g/kg for loading dose and 1 g/kg maintenance dose) are considered as a high-dose regimen. From the published data, it was not possible to determine whether there were significant trends for adverse event incidence by dose administered or dosing interval, and whether there were also time-dependent changes in adverse event rates (increased or decreased) with long-term exposure.

Of the four deaths reported across the published clinical studies in regard of this application, none was considered IVIg-related by the study authors (or by the sponsor). One of the two deaths in the Nobile-Orazio et al., (2012) study was due to 'cardiac arrest'.[16] The relationship between IVIg exposure and this death cannot be excluded based on the available evidence.

The safety data presented in the published studies, albeit limited, were generally consistent with the known safety profile of Kiovig and IVIg in general. Incidence of adverse events, adverse drug reactions, serious adverse events, severe adverse events and deaths were low and generally similar to rates in placebo-treated patients. No new safety signal was identified from this evaluation. The safety risk in paediatric populations with CIDP were not characterised in this application.

Conclusions regarding the clinical evaluation

The clinical evaluator's assessment of the benefit-risk balance is summarised here, along with the Delegate's assessment and conclusions.

Clinical evaluator's recommendation

The clinical evaluator's final assessment of benefits, risks and the benefit-risk balance of Kiovig for the treatment of CIDP follow, along with the Delegate's commentary.

Benefits

The following is the clinical evaluator's assessment of this submission, adapted from the clinical evaluation report, followed by the Delegate's commentary.

After consideration of the sponsor's responses to clinical questions, the clinical evaluator considered the benefits of Kiovig in the proposed usage are as follows:

> The results from the main clinical studies and the Eftimov et al., (2013) meta-analysis,[24] may beindirectly considered generalisable to Kiovig in CIDP based on (a) acceptance of IVIgs as first-line treatment in CIDP, as a class effect, by the National Blood Authority in Australia; (b) international consensus, including international regulatory jurisdictions, of 'equivalence between IVIgs inCIDP,' with Level of evidence Category 1 (based on similar literature-based applications to this application).
>
> The sponsor's clarification that it is not seeking an indication for the treatment of CIDP in the paediatric population;
>
> The overall effect of these changes is a more positive benefit-risk balance.

The Delegate commented with following:

> It will be an assumption, to apply the generalisability and class effect principle to the sponsor's proposed Kiovig's extension of indication of CIDP. In that case, the sponsor would not have needed to submit a Category 1 extension of indications submission [that is, a full data package supporting the extension of indications]

> and, should simply just have added CIDP to Kiovig's already approved and listed indications.
>
> The Delegate is not convinced that the submitted literature-based submission provided Category 1 level evidence of equivalence between IVIgs in CIDP, when head tohead IVIg trials were mostly not involved. Only the Kuitwaard et al. (2010) study compared Gammagard S/D with Kiovig and that was in a maintenance treatment study only.[8] Therefore, the talk of international consensus, including international regulatory jurisdictions, of 'equivalence between IVIgs in CIDP' based on the literature based submssion, does not really hold firm.

Risks

After consideration of the responses to clinical questions, the risks of Kiovig in the proposed usage are as follows:

> No international regulatory jurisdiction or expert panel, as well as the National Blood Authority in Australia, has identified any concern, in regards to either efficacy or safety, forany particular IVIg brand in the treatment of CIDP, including Kiovig.
>
> No clear CIDP-specific adverse drug reactions have been identified nationally or internationally at the time of the second-round evaluation.
>
> The sponsor clarified that it is not seeking an indication for the treatment of CIDP in the paediatric population;
>
> The overall effect of these changes is a more positive benefit-risk balance.

In response to the clinical evaluators evaluation of risks, the Delegate commented with the following:

> The Delegate has not sighted any extensive data in support of the above statement [first paragraph] in regard of Kiovig.
>
> It is worth noting Health Canada's statement regarding the use of IVIg in CIDP: 'if IVIg is to be used in the long-term management of CIDP, the patient should be under the care of a qualified expert with specialised knowledge of CIDP and a systematic approach be taken to determine the minimal effective dose'.
>
> The role of National Blood Authority in Australia is simply to provide an adequate, safe, secure and affordable supply of blood products, blood related products and blood related services. It does not engage in clinical trials documenting efficacy and safety of any blood product per se.

Clinical evaluator's assessment of benefits-risks balance

The benefit-risk balance of Kiovig, given the proposed usage, is favourable. This conclusion hasbeen reached by the clinical evaluator for the following reasons:

> The sponsor clarified that it is not seeking an indication for the treatment of CIDP in thepaediatric population.
>
> No international regulatory jurisdiction or expert panel identified any concern, in regards toeither efficacy or safety, for any particular IVIg brand in the treatment of CIDP. Also, the National Blood Authority in Australia recommends use of IVIg (including Kiovig) as first-linetreatment in patients with CIDP. Based on extensive data from the National Blood Authority website, considerable volumes of Kiovig have been imported into Australia over the past 10 years, and much of that for use in CIDP patients (adults and paediatrics), without any new safety signals identified. Also, this data may highlight the medical need for locally produced IVIg.

The safety profile of Kiovig has been well characterised from clinical experience in ITP and PID, with no clear CIDP-specific adverse drug reactions identified to date. Many of the adverse drug reactions identified from Kiovig exposure are predictably related to dose administered and infusion rates. Hence, if the PI advice is followed and dose-adjustment is made on an individual basis to achieve a beneficial treatment effect, at the minimum effective dose for that patient, risk of occurrenceof infusion- and/or dose-related adverse drug reactions should be mitigated.

The clinical data package was comprehensive as practicably possible, notwithstanding the limitations of a literature based submission. Many international regulatory jurisdictions have approved CIDP treatment based on literature based submission applications, including the EU, using a similar approach and dataset to that provided in this application. Similarly, in Australia Intragram 10NF was approved in 2011 based on a similar literature based submission application to this application.

Of the branded IVIg products specified across the clinical studies submitted in support of this application, several related to the Sandoglobulin brand, while none mentioned Intragram 10. The clinical data package submitted in support of this application differed from the Intragram 10 application by use of more current publications (including guidelines), provided a detailed comparison of IVIg products approved for CIDP in Australia, as well as providing brand-specific clinical data in support of its application. In particular, the Kuitwaard et al (2010) publication was the only published study of a direct head-to-head comparison of two brands of IVIg (Kiovig versus Gammagard S/D) in CIDP (maintenance) treatment.[8] Furthermore, Gammagard (equivalent brand to Kiovig) was used in the retrospective studies by Vucic et al.;[21] and Williams et al.;[23] and Kiovig was used in the study by Gallia et al.;[20] however, results from these publications were not presented by IVIg brand, which limits their usefulness.

It is accepted that brands of IVIg are not identical since IVIg is sourced from thousands of human donors. The standard pharmacopeia monograph specifications reflect this fact and therefore provide an acceptable range of IgG subclass values, which in turn closely resembles

normal human plasma. There appears to be an expectation that different branded products of IVIg that meet the accepted specifications will have 'equivalence of efficacy'. The Kuitwaard et al (2010) publication is the only published article that demonstrated equivalence between Kiovig and Gammagard S/D (as maintenance treatment only in CIDP). Despite differences in IgG content between Kiovig (approximately 100%) and Gammagard S/D (95%) treatments, and differences in formulation excipients and their manufacturing processes, no clinically meaningful differences were observed between treatments for the primary and secondary efficacy endpoints;

While the evidence to support Kiovig in an acute/induction phase of treatment is limited, there is no clear reason to expect that there would be a concern during initiation of Kiovig treatment, beyond the predictable adverse effects listed in the PI in respect of dose- administration and infusion-rates.

Although long-term efficacy and safety data for Kiovig in CIDP treatment is limited, the advice provided in the PI helps to mitigate risk of longer-term Kiovig treatment by recommendation of treatment based on the clinical need of the patient and their responsiveness to treatment. Risks associated with long-term treatment of Kiovig have to be weighed against the established risks associated with long-term

corticosteroid treatment, or the availability of long-term access to facilities that provide plasma exchange.

The published clinical data provided by the sponsor is as fully comprehensive and current as practicably possible. The data package also included some supportive studies using the Kiovig (or equivalent) brand, in accordance with scientific advice provided in Section 2.6. National and international expert consensus has not identified any additional concerns from use of IVIg in CIDP in terms of both efficacy and safety. On balance, the clinical evaluator considers, taking the totality of the information provided in the clinical dossier into consideration, that the sponsor has 'adequately justified' extrapolation of the available published clinical data to the proposed indication, as outlined in the EU Guideline. Hence, the benefit-risk balance is favourable for Kiovig for the proposed indication.

Based on the evaluation of the clinical data, and the sponsor's response to the first-round evaluation, the clinical evaluator recommends approval of Kiovig for Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

This recommendation differs from the first-round recommendation for the following reasons:

- The published clinical data provided by the Sponsor is as fully comprehensive and current as practicably possible;
- Clinical data supported Kiovig use in the maintenance of effect in the treatment of adult CIDP. There is no indication that Kiovig would not be efficacious in the induction (initial) phase of treatment;
- International and national guidelines and expert consensus indicate that there are no clinically meaningful differences between brands of IVIg, in terms of efficacy or safety for use of IVIg in CIDP;
- The safety profile of Kiovig has been reasonably well characterised in ITP and PID, using data derived from robust controlled clinical trials. The safety concerns listed in the Summary of Safety Concerns in the RMP are primarily class effects of IVIgs. No new safety signals have been identified specifically in IVIg treatment in CIDP. Any rare adverse events that may be specific to treatment of CIDP patients should become clearer during routine post-market surveillance monitoring activities.

Delegate's comments on the clinical evaluation

In relation to the clinical evaluator's assessment (above), the Delegate commented that:

The National Blood Authority raw data showed graph, not recommendation, depicting IVIg utilisation in CIDP without any particular reference/recommendation to Kiovig.

While the National Blood Authority website documents the vast importation of various IVIgs to Australia, the Delegate is unable to locate the statement 'and much of that (Kiovig) for use in CIDP patients (adults and paediatrics), without any new safety signals identified' ascribed to the website.

Regarding adverse drug reactions, the Delegate commented that it is hardly surprising that there are no clear CIDP-specific Kiovig adverse drug reactions identified to date, given the scanty specific clinical data which exist on the use of Kiovig in CIDP despite, the purported registration of Kiovig in several countries.

The Delegate commented that they were in agreement with the clinical evaluator concerning the limitations associated with this particular literature based submission.

It is noted that the approval of Intragam 10NF in Australia was based on a literature based submission similar to the current submission, and, similar to submissions in the EU and other international regulatory jurisdictions. However, the Intragam 10NF situation was about a decade ago and on-going regulatory actions, demand moving forward for the sake of achieving better overt efficacy and safety outcomes.

The Delegate suggested there may be upcoming level I trials regarding the use of Kiovig in CIDP, for example a proposed Phase III efficacy, safety and tolerability clinical study of Hyqvia/HyQvia and Gammagard Liquid/Kiovig in CIDP; with a US National Library of Medicine: Clinical Trials.gov identifier of NCT02549170; and studies seeking a larger cohort population to confirm the use of Kiovig in CIDP, for example, N.Nikolov et al. 2016, '10% liquid human immunoglobulin (Kiovig) for immunomodulation in autoimmune disorders'; Immunotherapy, Vol 8, No 8.

The Delegate commented pointing out that Intragram 10 and *not* Sandoglobulin is listed on the ARTG. Contrary to what is stated, only a comparison of IVIg products for CIDP in Australia in terms of excipient composition was provided. There was no actual head to head comparable clinical trial study provided with respect to ARTG listed IVIgs.

The Delegate stated that they believe that there was quite a limitation of brand-specific clinical data in the submission. The Delegate could only recognise Gammagard S/D (not on the ARTG) and Gamunex Kuitwaard et al (2010) publication was a direct head-to-head comparison of two brands of IVIg (Kiovig versus Gammagard S/D) in CIDP, maintenance, *not acute*, treatment only.

The acknowledgement that the different brands of IVIgs are not identical is noted. Any expectation that the different branded products of IVIg that meet the accepted specifications will have 'equivalence of efficacy', that is, therapeutic equivalence (and safety) based on accepted standard pharmacopeia monographs, may be an assumption. A well-designed comparable study of Kiovig with a listed ARTG IVIg for the CIDP indication will have been more convincing /decisive.

This statement from the National Blood Authority website 'Products available under current contracts will continue to be available and patients already receiving ongoing treatment with particular Ig products are not expected to be required to switch product brands' will seem to be mooting that IVIgs are strictly *not* interchangeable generics (in contrast with biosimilars in the Australia context).

It is not factual to state that the evidence to support Kiovig in an acute/induction phase of CIDP treatment is limited when in fact, there is virtually none.

The Delegate stated that, again, long-term efficacy and safety data for Kiovig in CIDP treatment is not just limited but actually absent.

The Delegate provided scientific advice on two issues pertaining to the clinical dossier in pre-submission correspondence with the sponsor dated 15 June 2020 (Issue 1) and 25 June 2020 (Issue 2):

> Issue 1: In the absence of a bridging study or insufficient published Kiovig-specific efficacy and safety data to support the extension of indications application in its entirety, use of non-Kiovig data would be acceptable, provided the IVIg brand was specified in the publication. For the latter, robust rationale for inclusion of each publication wasrequired, since all IVIgs are not identical. UnspecifiedIVIg data were not acceptable for an extension of indications.

It would appear that the sponsor did not satisfactorily resolve Issue 1 above prior to submitting the application, as the bulk of the IVIg brand used in the submitted non-Kiovig publication data was not specified. The hope was that the specification and/or identification of those IVIgs would turn out to be those listed on the ARTG, being used in reputable publications. The inclusion of each publication was also not robustly justified.

> Issue 2: The Delegate advised the sponsor that a deficiency in a previously approved literature based submission application for CIDP treatment negated its use as a precedent in this literature based submission application.

Despite the above advice, the sponsor has cited a 'precedent of the TGA approval in March 2011 of the application filed by CSL Behring to extend the indication of Intragram 10NF to CIDP.' The sponsor stated that the application was 'supported by a LBS [literature based submission] without a bridging study or brand-specific data,' as well as reference to an National Blood Authority publication.

As previously stated, the sponsor did not provide adequate detailed justification to extrapolate efficacy and safety data from established indications as suggested in the EU guidance document. The strength of the justification provided is weak:

> *'The EU CIDP indication was mainly based on literature data and, multiple countries had CIDP approved as an indication based on the same literature data package'.*

Kuitwaard et al. (2010) publication was a direct head-to-head comparison of two brands of IVIg (Kiovig versus Gammagard S/D) in CIDP, maintenance, *not acute*, treatment only.

Despite the sponsor's claim of Kiovig being registered and used widely for CIDP in Europe and other countries except the USA, the submitted published clinical data were far from being specifically related to Kiovig.

There was no specific data submitted the on initiation of Kiovig for CIDP treatment, unlike the robust controlled clinical trials submitted for both ITP and IDP as stated by the clinical evaluator.

The EU guideline simply states that 'If the efficacy [of an IVIg] in primary immunodeficiency disorders (PID) and in ITP is established, then an extrapolation to GBS, Kawasaki disease, MMN and CIDP might be possible without the need to perform separate clinical trials in these indications, if adequately justified' (evaluator's emphasis). For Kiovig however, the sponsor did not provide adequate detailed justification to extrapolate efficacy and safety data from established indications, as suggested in the EU guidance document referred to by the sponsor. The Delegate notes, the sponsor has no proposal for a bridging study.

Health Canada's statement regarding the use of IVIg in CIDP was that : 'if IVIg is to be used in the long-term management of CIDP, the patient should be under the care of a qualified expert with specialised knowledge of CIDP and a systematic approach be taken to determine the minimal effective dose'.

The role of National Blood Authority in Australia is simply to provide an adequate, safe, secure and affordable supply of blood products, blood related products and blood related services. It does not engage in clinical trials documenting efficacy and safety of any blood product per se;

There are available literature documenting that all brands of IVIg are neither equal nor equally tolerated:

§ Stiehm ER. Lessons from Kawasaki Disease: All Brands of IVIg are not Equal. The Journal of Pediatr. 2006; 48:6-8.

§ Feldmeyer L, Benden C, Haile SR, et al. Not All Intravenous Immunoglobulin Preparations are Equally Well Tolerated. Acta Derm Venereol. 2010; 90(5):494-7.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[27]

Risk-benefit analysis

Delegate's considerations

As per the sponsor, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare, acquired immune-mediated sensory and motor neuropathy. CIDP has a relapsing-remitting or progressive course of more than 2 months and it is characterised by proximal weakness, positive sensory symptoms, areflexia without wasting, and impaired sensation with a preferential loss of vibration or joint position sense.

Chronic inflammatory demyelinating polyradiculoneuropathy can affect all ages, but is more common in older males. The disease is thought to be more likely progressive in the older age group and relapsing-remitting in younger patients. No specific predisposing factors for CIDP have been identified. Patients may have mild to severe weakness and, may require assisted ambulation or a wheelchair.

As per the clinical evaluation report, the estimated prevalence of CIDP in populations from the United Kingdom, Australia, Italy, Japan, and the United States of America (USA) is 0.8 to 8.9 per 100,000, with worldwide estimates of an annual incidence of 0.15 to 1.6 per 100,000 population.

The sponsor stated that the treatment options for CIDP include:

- First line:
  - Intravenous immunoglobulins (IVIg),
  - Corticosteroids,
  - Plasma exchange.
- Second-line, when first-line treatments are inadequate:
  - Immunosuppressants or other immunomodulatory agents such as azathioprine, cyclophosphamide, ciclosporin and methotrexate.

In Australia, four branded human normal immunoglobulin products (Gamunex, Intragam 10, Privigen and Hizentra) are indicated for CIDP. Of these, Intragam 10 was approved in March 2011 for the treatment of CIDP, via a literature based submission.

Further, the sponsor stated that Kiovig's safety and efficacy in idiopathic thrombocytopenia purpura (ITP) and primary immunodeficiency disorders (PID) have been established, based on relevant clinical data (biological, pharmacokinetics, efficacy

[27] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

and safety data) leading to the granting of a marketing authorisation for these indications in Australia (2008). Based on those facts, it is claimed by the sponsor that the key elements required for licensing in the proposed indication (of CIDP), are in line with the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration and, are considered sufficient. The latter then implies that no efficacy/safety data are required for the proposed CIDP indication, as such data were already provided for both ITP and PID indications!

The application to register Kiovig for the CIDP indication was a literature based submission (literature based submission). The Delegate agrees with the CE, that the efficacy and safety data package in the submitted clinical dossier for the proposed extension of indication for the use of Kiovig in CIDP was not generally comprehensive. For a start, the literature based submission did not include comparisons of IVIgs administered for more than one dose-regimen, for either initiation or maintenance treatment.

The main pivotal study (Kuitwaard et al. 2010);[8] was an investigator-initiated, multicentre, Phase III, double-blind, randomised, active (Gammagard S/D, n = 13) controlled trial, in the maintenance treatment of CIDP with Kiovig (n = 14). It would appear that patients only had mild to moderate symptoms at baseline. The study neither included data for initiation of Kiovig in CIDP populations nor investigated withdrawal or relapse effects. Apart from being a maintenance as opposed to initiation treatment trial, the requirement for inclusion in the trial is that there should be no prior treatment exposure to other IVIg products, except Gammagard S/D. That aspect of the trial gives the intrinsic implication that IVIg products are not identical.

Although in order to establish the optimal regimen of IVIg in the trial, the dosage was increased to achieve maximal clinical response and, the infusion frequency shortened when patients experienced end-of-dose symptoms and signs, the ranges of actual dosages used during the double blind treatment period were not specified.

The primary objective was to compare the efficacy of two different IVIg brands (Kiovig versus Gammagard S/D) in the maintenance treatment of CIDP. The secondary objective was to compare the safety of Kiovig versus Gammagard S/D.

Comparable maintenance treatment of CIDP with either Kiovig or Gammagard S/D, was not significantly different regarding the primary outcome measure and no clinically relevant differences were reported between treatments for secondary measures. Since only the two different IVIg brands (Kiovig versus Gammagard S/D) were compared, conclusions about (possibly therapeutic) equivalence in maintenance treatment can only be drawn between these two products and, no other commercial brands of IVIg. As stated by the clinical evaluator, the sponsor did not provide adequate justification as to how the results from this study involving Kiovig, could be extrapolated to other commercial brands of IVIg used in other literature based submission publications for CIDP, with particular reference to differences in composition (including IgG subclasses and IgA content), bioavailability and manufacturing/purification processes that may affect efficacy and tolerability. In the Australia context, the relevance/significance of the study is even debatable given, that Gammagard S/D is not listed on the ARTG.

Included in the literature based submission were prospective data on placebo versus IVIgs in the initiation treatment of IVIg naïve CIDP patients. The drawback from the assessment perspective of the application is that the referenced IVIgs were not specifically Kiovig. Except for Gamunex (on the ARTG) and Pasteurised Gammar IV (not on the ARTG), the other referenced IVIgs in the literature based submission have not been identified.

The findings from those literature based submission prospective data, except one, suggested that the referenced IVIgs demonstrated statistically significant treatment effect over placebo, in patients not previously exposed to IVIg. The Vermeulen et al., (1993);[13]

study article for whatever reason, did not demonstrate a treatment benefit of IVIg over placebo.

The Delegate believes that the outcome of the assessed study articles is unsurprising and, has not yielded substantial evidence to; support definitely and unequivocally the basic tenet of the current submission for Kiovig, given that:

- the submission is about Kiovig and not Gamunex which is already indicated for CIDP on the ARTG;
- placebo and not Kiovig was the comparator in the literature based submission data;
- there is no way of drawing conclusions about equivalence of Kiovig to Gamunex or any other IVIg in the literature based submission, therapeutic- or biologic-wise;
- the ARTG status of the unidentified referenced IVIg is unknown; the identified 'Pasteurized Gammar IV' is not listed on the ARTG; and
- the unidentified bio-characteristics of the various commercial IVIg referenced in the literature based submission and the fact, that there are differences in IgG subclasses and excipients, as well as differences in manufacturing processes.

Given all that is stated above, to approve Kiovig for the CIDP indication at this stage may be quite inappropriate. A deferral option will be preferred, as the latter will allow the commercial sponsor of Kiovig to generate adequate and supportive comparable or bridging data for the proposed CIDP indication for Kiovig. The deferral preference is even more appropriate, given that Kiovig is not particularly filling a clear unmet medical need for a novel treatment to treat CIDP, as there are, already a host of other different Immunoglobulin, normal (human) products, such as Gamunex, Hizentra, Intragam 10 and Privigen on the ARTG for CIDP indication.

The approval of Kiovig at this stage for CIDP, based on non-specifically comparable trials with another IVIg, especially one of those listed on the ARTG for CIDP, tantamount to abductive reasoning. The sponsor may wish to provide reference to the appropriate TGA's guideline in support of such a reasoning. It is certain however, that prescription drugs do not get on the ARTG simply based on probability premise as opposed to factual data evidence!

Furthermore, regardless of the causes for the failure of the previously mentioned literature based submission study to demonstrate a treatment benefit of IVIg over placebo as assessed by the clinical evaluator, the study is nonetheless a testimony to the fact that Kiovig's approval for CIDP requires well-designed trial as per acceptable guideline, depicting efficacy and safety in CIDP. The doctrine of abductive reasoning illustrated above is strictly not applicable to this regulatory task/purpose.

Apart from the limitations of retrospective data in general, the included retrospective data in the submitted literature based submission do not add external validity to the current application, due to the comparison of non Kiovig IVIg brands with either placebo, immunomodifier such as mycophenolate or no control at all.

Unfortunately, the various IVIgs used in the pooled /meta- analytical data, which predated the referenced anonymous WHO publication; would have been significantly different in terms of the manufacturing processes, as well as in the IgG subclasses and excipients in a modern world of competitive, manufacturing pharmaceutical edge. The latter therefore further highlights, the importance of ensuring that the data analysed and upon which, the proposed CIDP Kiovig indication relied utilised Kiovig for the greater content.

The clinical evaluator stated, post first round evaluation, that:

> 'most study participants in the literature based submission were adults (aged 18 years and older) and, the few studies that included paediatric subjects provided scanty details on the numbers of subjects and their ages upon study commencement. On that basis, the clinical evaluator opined that no recommendation for approval of Kiovig in paediatric populations with CIDP could be made (the sponsor in its response to TGA questions has proposed to include a statement in the PI on the line of no paediatric data were available in support of the CIDP indication and; clarified that it is not seeking an indication for the treatment of CIDP in the paediatric population).
>
> No dose-response relationships of IVIg were reported, in any of the submitted publications or discussed in the meta-analyses. Hence, the minimal effective dose of IVIg in CIDP populations does not appear to have been established.
>
> Based on the limited Kiovig data available, and the fact that the Kuitwaard et al., (2010) publication;[8] was not considered pivotal, the application to approve an extension of indications of Kiovig to the proposed indication cannot be recommended at this time, in the absence of a robust justification. Most of the published studies included in the clinical dossier investigated other brands of IVIg. No bridging study was included in the application and the justification for extrapolation of clinical data (efficacy and safety) from the other brands of IVIg was insufficient. However, from the publications, IVIg treatment consistently demonstrated a statistically significant and clinically meaningful benefit over placebo in CIDP, in the main studies and the Eftimov et al (2013) meta-analysis.[24] Despite variation in primary outcome measures used across the main randomised control trials, there was good study homogeneity and consistency in demonstration of improved clinical function after patients had received a 2 g/kg IVIg loading dose followed by at least one IVIg maintenance dose.

The Delegate is in agreement with the clinical evaluator on the above, especially given that:

- the commercial production of the various IVIgs is not identical;
- while IVIgs may have 'flavours' of being biosimilars, they are never generics;
- commercial IVIgs may exhibit variations in IgG subclass active ingredients;
- IVIgs are often associated with different excipients; and
- there are available literature documenting that all brands of IVIg are neither equal nor equally tolerated.[28,29,30]

It will be preferred that a determination on whether or not Kiovig should be approved for the proposed indication of CIDP, is not made until a well-designed study, specific to Kiovig on CIDP, is submitted by the sponsor and evaluated by the TGA.

A set of TGA questions were posed to the sponsor following the first round of clinical evaluation.

In response to a question, enquiring as to whether Kiovig was approved for CIDP based on literature based submission, conventional clinical trial data or a combination of both, the

[28] Stiehm ER. Lessons From Kawasaki Disease: All Brands Of IVIg Are Not Equal. The Journal of Pediatrics 2006;148:6-8.
[29] Skvaril F, Gardi A. Differences among available immunoglobulin preparations for intravenous use. The Pediatric Infectious Disease Journal. 1988; 7: S43-S48
[30] Feldmeyer L, Benden C, Haile SR, Boehler A, Speich R, French LE, Hofbauer GF (2010). Not all intravenous immunoglobulin preparations are equally well tolerated. Acta dermato-venereologica, 90(5), 494–497.

sponsor confirmed that, conventional clinical data were not used in any overseas applications for the CIDP indication. It went on that following European Medicines Agency (EMA) approval, based on updated EU guidelines and the core Summary of Medicine Characteristics (SmPC) for IVIg, to extend the indication of Kiovig to CIDP, overseas submissions utilised the same literature based submission data package submitted to the EMA.

Acceptability of the above sponsor's response by the clinical evaluator has drawn the following comments from the Delegate:

- The implication is that the Kiovig approval for CIDP indication in the EU was based on adductive reasoning. That is, once an IVIg product has approval for an indication, for example, the CIDP indication, all other IVIgs can reach for that same indication without each particular IVIg brand having to specifically demonstrate its efficacy/safety data for that indication.
- Given the existing literature debate on the sameness or not of all IVIgs, the above approach will essentially be skewed towards the acceptance that every biological IVIg is the same/similar, regardless of the differences in their IgG subclass, industrial manufacturing processes and excipients.
- If the current submission on Kiovig is approved for the proposed CIDP indication, simply based on the aforesaid principle of IVIg sameness, then it is debatable as to whether or not any prospective IVIg sponsor, should bother at all to submit a full application dossier for an Extension of Indications-type submission. Maybe, a simple dossier for a new generic product-type submision for any indication previously approved for an IVIg will suffice. However, the current Australian Regulatory Guidelines for Biologicals;[31] do not strictly consider biological medicines like IVIgs as generic 'interchangeable' products.

In response to a question enquiring about equivalence between commercial brands of IVIg and as to whether the sponsor is intending to submit a bridging study, the sponsor confirmed that it did not intend to submit a bridging study in support of the application. Given the latter response by the sponsor, the clinical evaluator requested a detailed response to justify the (questionably therapeutic) 'equivalence of Kiovig' to other commercially available IVIgs, particularly in Australia, for both acute treatment and for maintenance treatment in CIDP. Responding, the sponsor referred to this aspect of EU guideline;[3] 'if the efficacy in PID and ITP is established, then an extrapolation to CIDP might be possible with adequate justification'. The crux of the matter and as mooted by the clinical evaluator, is that the sponsor did not provide adequate detailed justification to extrapolate efficacy and safety data from established indications as suggested in the EU guidance document, or provide a bridging study. Instead, the sponsor's justification was that the CIDP indication in EU was based on similar literature based data and that 'multiple countries' had CIDP approved as an indication based on 'the same literature data package'. It is noteworthy that the only comparable overseas regulatory country to Australia is Switzerland.

Further, the sponsor cited a precedence that the TGA approved in March 2011, an application by CSL Behring, to extend the indication of Intragam 10NF to CIDP stating that the application was 'supported by a literature based submission without a bridging study or brand-specific data'.

It is now obvious that the sponsor is using a TGA's precedent as the required justification.

[31] Australian regulatory guidelines for biologicals (ARGB; 2020).
Available at: https://www.tga.gov.au/publication/australian-regulatory-guidelines-biologicals-argb

With the above in mind and in conjunction with the other previously stated generalisability of IVIg commercial products, the advice of the ACM will be sought regarding:

- Non-approvability at this point in time of Kiovig for the CIDP indication based on assumed sameness copy-cat approach for IVIgs, given that:
  - the universal, standard generic approach does not extend to biologics;
  - the sponsor neither submitted clinical nor biologic data comparing Kiovig to any IVIg listed on the ARTG;
  - there was no proper justification provided, even as required by the sponsor's own stated guidelines, except to base the justification on a TGA's precedent; however, two wrongs do not make a right;
  - the divided literature opinion on the interchangeability of IVIgs;
  - IVIgs differences with respect to IgG subclass, industrial manufacturing processes and excipients.
- Non-approvability at this point in time of Kiovig for the CIDP indication based on Kiovig being currently approved for both ITP and PID given that:
  - it is customary and universal for a proposed extension of indications of a product to be based on adequate clinical data for the extension of indications.

It is worth mentioning, that there is no urgency to fast tract Kiovig approval for the proposed CIDP indication for now given, that there are other IVIgs listed on the ARTG for CIDP. If, however, the advice for approval is contemplated as it is without either bridging comparable study or Kiovig specific data, then it becomes intrinsically futile, for the TGA to continue requesting for the usual data gamut of dossier in future:

- when a sponsor either wishes to register an extension of indications for its commercial brand of IVIg:
  - if that proposed extension of indications is already approved for an existing IVIg brand, whether or not that particular brand is on the ARTG; or
  - if the proposed brand of IVIg already has approval for other indications, for example, ITP and PID.

If approval is granted, then it is recommended that a class statement be generated pointing out that IVIgs, as biological products, are neither generics nor interchangeable.

Further to the issue of Kiovig's equivalence to other commercially available IVIgs, the sponsor stated that IV administration delivers normal human immunoglobulin directly into the systemic circulation to exert its therapeutic effect and it is highly unlikely, excipients used as stabilisers in the finished product would markedly alter the pharmacokinetics of IgG. The Delegate's comments on the latter are:

- IV administration is generally assessed for the purpose of bioavailability (relative versus absolute bioavailability) and *not* equivalence per se;
- the statement 'it is highly unlikely excipients used as stabilisers in the finished product would markedly alter the pharmacokinetics of IgG' is an assumption. The sponsor has not provided valid data to further its veracity, especially given that excipients may not be entirely inactive and may play role in pH modification, carrier/transporter activity etc. that may have significant pharmacokinetic outcomes.

The Delegate acknowledges the sponsor's statement that the:

- different excipients in various IVIgs will depict different side-effects; and
- IVIgs do not have identical distribution of IgG subclasses 1 to 4. However, the sponsor's claim that the IVIgs used in the literature based submission were compiled in terms of commercial manufacturing and purification as per standard pharmacopeia monographs, to ensure batch to batch consistency in product quality, was neither supported by the usually submitted quality data nor bridging data with a currently approved ARTG IVIg;
- The sponsor's confirmation that different IVIgs contain different amounts of IgA is noted.

Regarding manufacturing and purification processes, the sponsor claimed, 'irrespective of differences in the manufacturing steps and purification processes, different brands of IVIg on the Australian market are manufactured to meet the same quality specifications that control for critical finished product parameters'. The Delegate's response is to the crux of the matter:

- there was neither a bridging data linking the IVIgs used in the literature based submission to IVIgs listed on the ARTG nor absolute comparable head to head data of Kiovig with the IVIgs used in the literature based submission; and
- there is no specific reference to using the IVIgs listed on the ARTG in the literature based submission and, no quality data on quality control was submitted for the IVIgs used in the literature based submission.

The sponsor also wrote about Australian Guidelines and in particular, about the National Blood Authority's consideration of IVIg in CIDP treatment as a class effect and, then went on about the importation of various IVIgs, including those on the ARTG, into Australia by the National Blood Authority. The Delegate's assessment is that unfortunately, the issue under consideration is about registering Kiovig for CIDP based on the data provided. It is not about importing Kiovig for an unapproved indication, which does not necessarily attract data scrutiny about efficacy/safety.

With reference to the stance of comparable International regulatory authorities on Kiovig, it is worth noting that:

- Kiovig per se does not appear to be registered in the USA and Canada; and
- Canada's position on the use of IVIg for CIDP appears to be clarified, that short-term use in acute-onset or relapse of CIDP with caution on long-term use.

After assessment of the sponsor's responses to clinical questions, the clinical evaluator, in the second round of evaluation changed the previous benefits assessment of Kiovig in CIPD as follows:

- The results from the main clinical studies and the Eftimov et al., (2013);[24] meta-analysis may be indirectly considered generalisable to Kiovig in CIDP based on (a) acceptance of IVIgs as first-line treatment in CIDP, as a class effect, by the National Blood Authority in Australia; (b) international consensus, including international regulatory jurisdictions, of 'equivalence between IVIgs in CIDP,' with Level of evidence Category 1 (based on similar literature based submission applications to this application, in Australia);

To the above, the Delegate makes the following comment:

- It will be an assumption, to apply the generalisability and class effect principle to the sponsor's proposed Kiovig's extension of indication to CIDP. In that case, the sponsor would not have needed to submit a full dossier for an extension of indications

submission and should have simply just have added CIDP to Kiovig's already approved and listed indications.

- This Delegate is not convinced that the submitted literature based submission provided Category 1 level evidence of (questionably therapeutic) equivalence between IVIgs in CIDP, when head-to-head IVIg trials were mostly not involved. Only the Kuitwaard et al., (2010);[8] compared Gammagard S/D with Kiovig and, that was in a maintenance treatment study only. Therefore, the talk of international consensus, including international regulatory jurisdictions, of 'equivalence between IVIgs in CIDP' based on the literature based submission, does not really hold firm.

After reviewing the sponsor's responses to post-first round clinical questions, the clinical evaluator for the second round assessment, changed the previous risks of Kiovig in CIPD as follows:

- No international regulatory jurisdiction or Expert panel, as well as the National Blood Authority (NBA) in Australia, has identified any concern, in regards to either efficacy orsafety, for any particular IVIg brand in the treatment of CIDP, including Kiovig;

To the above, the Delegate makes the following comments:

- No extensive data was sighted in support of the above statement in regard of Kiovig;
- It is worth noting Health Canada's statement regarding the use of IVIg in CIDP:

  If IVIg is to be used in the long-term management of CIDP, the patient should be under the care of a qualified expert with specialised knowledge of CIDP and a systematic approach betaken to determine the minimal effective dose;

- The role of the National Blood Authority in Australia is simply to provide an adequate, safe, secure and affordablesupply of blood products, blood related products and blood related services. *It does not engage in clinical trials documenting efficacy and safety of any blood product per se.*

For the second round benefit -risk balance, the clinical evaluator considers the latter as now favourable based on these rationales:

- From the extensive data from the National Blood Authority website, considerable volumes of Kiovig have beenimported into Australia over the past 10 years, and much of that for use in CIDP patients (adults and paediatrics), without any new safety signals identified;
- The safety profile of Kiovig has been well characterised from clinical experience in ITP andPID, with no clear CIDP-specific adverse drug reactions identified to date;
- There were limitations to Kiovig's literature based submission for CIDP but, a similar application for Intragam10NF was approved in 2011 based on a similar literature based submission application to this application;

To the above, the Delegate makes the following comments:

- The National Blood Authority raw data showed a graph, not a recommendation, depicting IVIg utilisationin CIDP without any particular reference/recommendation to Kiovig;
- While the National Blood Authority website documents the vast importation of various IVIgs to Australia, the Delegate is unable to locate the statement 'and much of that (Kiovig) for use in CIDP patients (adults and paediatrics), without any new safety signals identified' ascribed to the website;
- It is hardly surprising that there are no clear CIDP specific Kiovig adverse drug reactions identified to date, given the very scanty specific clinical data (trial or

literature), available on the useof Kiovig in CIDP despite, the purported registration of Kiovig for CIDP in several countries;

- It is noted, that the approval of Intragam 10NF in Australia was based on literature based submission similar to the current Kiovig application in Australia and that, Kiovig for CIDP was approved in theEU and other international regulatory jurisdictions (the bulk of which are not comparable jurisdictions to Australia). However, the Intragam 10NF situation was about a decade ago and modern regulatory actions, demand moving forward for the sake ofachieving better overt efficacy and safety outcomes;

The Delegate also wished to highlight there may be:

- Studies seeking larger cohort population to confirm the use of Kiovig in CIDP for example, N.Nikolov et al.; 2016, '10% liquid human immunoglobulin (KIOVIG) for immunomodulation in autoimmune disorders'; Immunotherapy,Vol 8, No 8;
- Upcoming Level I trials regarding the use of Kiovig in CIDP, for example, proposed Phase III Efficacy, Safety and Tolerability: Clinical Study of Hyqvia/HyQvia and Gammagard Liquid/Kiovig in CIDP (US National Library of Medicine: Clinical Trials.gov identier:NCT02549170).

A claim by the clinical evaluator , having initially acknowledged that the majority of the IVIgs listed in the literature based submission studies relate to the Sandoglobulin brand and none to Intragam 10 (on the ARTG), that the literature based submission package submitted in support of the Kiovig application differed from the Intragam 10 literature based submission application by:

- using more current publications [including guidelines];
- providing a detailed comparison of IVIg products approved for CIDP in Australia. The clinical evaluator went on to say that in particular, the Kuitwaard et al (2010)[8] publication was the only published study of a direct head-to-head comparison of two brands of IVIg (Kiovig versus Gammagard) in CIDP maintenance treatment. Furthermore, that Vucic et al.;[21] and Williams et al.[23] used Gammagard in their retrospective studies while, Kiovig was used in the study by*Gallia et al*. However, results from these publications were not presented by IVIg brand, which limits their usefulness);
- providing brand-specific clinical data in support of the application.

To the above, the Delegate makes the following comments:

- It is worth commenting that Intragam 10 and *not* Sandoglobulin is listed on the ARTG;
- Contrary to what is stated, only a comparison of IVIg products for CIDP in Australia in terms of excipient composition was provided. Even then, as previously mentioned, therewere differences in the various IVIg excipients. There was no actual head to head comparable clinical trial study provided with respect to ARTG listed IVIgs;
- The Delegate believes that there was quite a limitation of brand-specific clinical data in thesubmission. The Delegate can only recognise Gammagard S/D (not on ARTG) and Gamunex (on the ARTG);
- To reinforce, Kuitwaard et al. (2010)[8] publication was a direct head-to-head comparison oftwo brands of IVIg (Kiovig versus Gammagard S/D) in CIDP, maintenance, *not acute,* treatment only.
- While it is accepted that the brands of IVIg are not identical since IVIg is sourced from thousands of human donors, the standard pharmacopeia monograph specifications reflectthis fact and therefore provide an acceptable range of IgG subclass values, which in turn closely resembles normal human plasma. There appears to be an expectation

that thedifferent branded products of IVIg that meet the accepted specifications will have'equivalence of efficacy'.

To the above, the Delegate makes the following comments:

- The acknowledgement that the different brands of IVIgs are not identical is noted. Any expectation, that the different branded products of IVIg that meet the accepted specifications will have 'equivalence of efficacy' that is, therapeutic equivalence (and safety) based on accepted standard pharmacopeia monograph sounds like an assumption. Well-designed comparable study of Kiovig with a listed ARTG IVIg for the CIDP indication will have been more convincing /decisive;
- This statement from the National Blood Authority website: 'Products available under current contracts will continue to be available and patients already receiving ongoing treatment with particular Ig products are not expected to be required to switch product brands' will seem to be mooting that IVIgs are strictly *not* interchangeable biological medicine generics (in contrast to biosimilars in the Australia context).
- While the evidence to support Kiovig in an acute/induction phase of treatment is limited, there is no clear reason to expect that there would be a concern during initiation of Kiovigtreatment.

To the above, the Delegate makes the following comments:

- It is not factual to state that the evidence to support Kiovig in an acute/induction phaseof CIDP treatment is limited when in fact, there is virtually none.
- Although long-term efficacy and safety data for Kiovig in CIDP treatment is limited, the advice provided in the PI helps to mitigate risk of longer-term Kiovig treatment by recommendation of treatment based on the clinical need of the patient and their responsiveness to treatment.
- Again, long-term efficacy and safety data for Kiovig in CIDP treatment is not just limited but actually absent;
- With respect to the above, it is worth noting the Health Canada's statement regarding the use of IVIg in CIDP:

  If IVIg is to be used in the long-term management of CIDP, the patient should be under the care of a qualified expert with specialised knowledge ofCIDP and a systematic approach be taken to determine the minimal effective dose;

The clinical evaluator stated that the literature based submission studies provided by the sponsor is as fully comprehensive and current as practicably possible. The latter also included some supportive studies using the Kiovig (or equivalent) brand, in accordance with scientific advice provided in Section 2.6. On balance, the clinical evaluator considers, taking the totality of the information provided in the clinicaldossier into consideration that the Sponsor has 'adequately justified' extrapolation of the available published clinical data to the proposed indication, as outlined in the EU Guideline. Hence, the benefit-risk balance is favourable for Kiovig for the proposed indication.

To the above, the Delegate makes the following comments:

- The Delegate provided scientific advice on two clinical issues in the submission assessment form correspondence (*Response to questions*) to the sponsor, dated15 June 2020 (Issue 1) and 25 June 2020 (Issue 2):

  Issue 1: In the absence of a bridging study or insufficient published Kiovig-specific efficacy and safety data to support the extension of indications application in its entirety, use of non-Kiovig data would be acceptable, provided the IVIg brand was specified in the publication. For the latter, robust rationale for inclusion of each

publication was required, since all IVIgs are not identical. Unspecified IVIg data were not acceptable for an extension of indication;

- It now appears that the sponsor did not satisfactorily resolve *Issue 1* above prior to submitting the application, as the bulk of the IVIg brand used in the submitted non-Kiovig publication data was not specified. The hope was that the specification/identification of those IVIgs would turn out to be those listed on the ARTG and being used, in reputable publications. The inclusion of each publication was also not robustly justified.

  Issue 2: The Delegate advised the sponsor, that a deficiency in a previously approved literature based submission application for an IVIg (Intragam 10NF) CIDP treatment indication negated its use as a precedent in this literature based submission application.

- Despite the above advice, the sponsor has cited a 'precedent of the TGA approval in March 2011 of the application filed by CSL Behring to extend theindication of Intragam 10NF to CIDP.' The Sponsor stated that the application was 'supported by a literature based submission without a bridging study or brand- specific data,' as well as reference to a National Blood Authority publication.

As previously stated, the sponsor did not provide adequate detailed justification to extrapolate efficacy and safety data from established indications as suggested in the EU guidance document. The strength of the justification provided below is considered inferential and does not fulfil the stipulated detailed extrapolation justification:

- The EU CIDP indication was mainly based on literature data and, multiple countrieshad CIDP approved as an indication based on the same literature data package.

Recommendation regarding authorisation as per the clinical evaluator (first round) was:

- Clinical data supported Kiovig use in the maintenance of effect in the treatment of adult CIDP. There is no indication that Kiovig would not be efficacious in the induction (initial) phase of treatment;
- International and national guidelines and expert consensus indicate that there are no clinically meaningful differences between brands of IVIg, in terms of efficacy or safety for use of IVIg in CIDP;
- The safety profile of Kiovig has been reasonably well characterised in ITP and PID, usingdata derived from robust controlled clinical trials. The safety concerns listed in the Summary of Safety Concerns in the RMP are primarily class effects of IVIgs. No new safety signals have been identified specifically in IVIg treatment in CIDP. Any rare adverse events that may be specific to treatment of CIDP patients should become clearerduring routine post-market surveillance monitoring activities.

To the above, the Delegate makes the following comments:

- Despite the sponsor's claim of Kiovig being registered and used widely for CIDP in Europe and other countries except the USA, the submitted published clinical data were far from being specifically related to Kiovig;
- There was no specific data submitted on the initiation of Kiovig for CIDP treatment, unlike the robust controlled clinical trials submitted for both ITP and PID, as stated by the clinical evaluator;
- The EU guideline simply states that: '*If the efficacy* [of an IVIg] *in primary immunodeficiency disorders (PID) and in ITP is established, then an extrapolation to GBS, Kawasaki disease, MMN and CIDP might be possible without the need to perform separate clinical trials in these indications, if adequately justified*' (evaluator's emphasis). For Kiovig however, the sponsor did not provide adequate detailed

justification to extrapolate efficacy and safety data from established indications, as suggested in the EU guidance document referred to by the sponsor. The Delegate notes that the sponsor has no proposal for a bridging study);

- Health Canada's statement regarding the use of IVIg in CIDP was that: '*If IVIg is to be used in the long-term management of CIDP, the patient should be under the care of a qualified expert with specialised knowledge of CIDP and a systematic approach be taken to determine the minimal effective dose;*
- The role of National Blood Authority in Australia is simply to provide an adequate, safe,secure and affordable supply of blood products, blood related products and blood related services. It does not engage in clinical trials documenting efficacy and safety of any blood product per se;
- There are available literature documenting that all brands of IVIg are neither equal nor are equally tolerated:
  - Stiehm ER. Lessons from Kawasaki Disease: All Brands of IVIG are not Equal. The Journal of Pediatr. 2006; 48:6-8.
  - Skvaril F, Gardi A. Differences among available immunoglobulin preparationsfor intravenous use. Pediatr Infect Dis J. 1988; 7: S43-S48.
  - Feldmeyer L, Benden C, Haile SR, et al. Not All Intravenous Immunoglobulin Preparations are Equally Well Tolerated. Acta Derm Venereol. 2010; 90(5):494-7.

Proposed wording for the extension of indication

As per the sponsor:

> *Kiovig administered intravenously is indicated for:*
>
> *Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).*

As per the Delegate:

> *Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in adults*.

The rationale for this, is: Lack of paediatric data (as accepted by the sponsor).

Deficiency of the data

Essentially lack of a bridging comparable study of Kiovig with an IVIg listed on the ARTG for the CIDP indication in the absence of a Level 1 class, adequate clinical data for the proposed CIDP extension of indication.

Conditions of registration

If contemplated: non-interchangeability with the other IVIg products.

Outstanding issue

The sponsor did not provide adequate detailed justification to extrapolate efficacy and safety data from established indications for the proposed extension of indications to include CIDP, as suggested in the EU guidance document referred to by the sponsor. Apart from the latter, any favourable benefit associated with the IVIg treatment over placebo in adults with CIDP is neither a panacea nor absolute evidence to granting Kiovig the proposed CIDP indication, at this point in time.

The literature based studies do not satisfactorily contain Kiovig specific data for the proposed CIDP extension of indication and the sponsor did not submit any bridging data to that effect.

The Delegate will greatly appreciate the expert's advice of the Advisory Committee on Medicines (ACM) in this regard, for future guidance on IVIg submissions.

Proposed action

Taking the gamut of the previously mentioned comments into account, the Delegate is proposing the following options regarding the application:

- Non-approvability at this point in time of Kiovig for the CIDP indication until either a bridging comparable study of Kiovig with an IVIg listed on the ARTG for the CIDP indication is at hand or Level 1 class, adequate clinical data for proposed CIDP extension of indication is submitted;
- Approvability now of Kiovig for the CIDP indication with the qualification that, like other IVIgs, Kiovig as a biological product is neither a generic nor interchangeable with the other IVIgs. The latter can be made out like a class statement.

The Delegate opined that there is no urgency to fast tract Kiovig approval for the proposed CIDP indication now given, that there are other IVIgs listed on the ARTG for CIDP. If however, the advice for approval is being contemplated in the absence of either a bridging comparable study or Kiovig specific data, then the advice of ACM is sought as to the need for TGA to continue requesting for the usual gamut of data dossier in future:

- when a sponsor either wishes to register an extension of indications for its commercial brand of IVIg;
- if that proposed extension of indications is already approved for an existing IVIg brand, whether or not that particular brand is on the ARTG or;
- if the proposed brand of IVIg already has approval for other indications for example, ITP and PID.

Advisory Committee considerations[32]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Consideration of non-approvability/approvability of Kiovig now, given the outstanding issues raised.

The ACM acknowledged that the literature based submission under consideration had limited data on the use of Kiovig and was lacking a pivotal study.

However, on balance the ACM were of the view that the application is approvable, stating that the safety and efficacy of IVIg in CIDP is well established and noting that other IVIg products have been approved by the TGA for the treatment of CIDP. The ACM advised that it is acceptable to extrapolate evidence from an immunomodulatory indication to CIDP,

[32] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

and were of the opinion that the extrapolation has been adequately justified by the sponsor as per the EMA guideline on the clinical investigation of human normal immunoglobulin for intravenous administration.[3] The ACM commented that the EMA guideline implies recognition of a class effect of IVIgs in CIDP and other immunomodulatory indications. The ACM were also of the view that the safety of Kiovig has been established by wide post-marketing experience.

2. If approvable now, consideration of:

a. Probable class statement requirement on non-interchangeability of IVIg products.

The ACM emphasised that blood products are quite different from traditional drug products in the way they are manufactured, supplied and used. The ACM advised that in current clinical practice in Australia, IVIg products are used interchangeably based on National Blood Authority recommendations and funding, availability, and preference of the prescriber.

The ACM discussed the difference between the terms 'interchangeable' and 'equivalent', and emphasised that while IVIg products are interchangeable they are not considered to be equivalent, and have different side effect profiles.

The ACM were of the view that a class statement on the non-interchangeability of IVIg products is not required. If such a class statement were to be implemented by the TGA, the ACM advised that the wording would have to be carefully considered to account for current clinical practice in Australia. Potential wording for the PI could include:

> *'While IVIgs are interchangeable, they are not therapeutically equivalent in terms of efficacy and safety profiles.'*

b. The requirement / necessity for the sponsor to produce data in similar situation for an IVIg product on the ARTG, going for extension of indication.

The ACM advised that they are satisfied that the EMA guideline has been fulfilled by the current submission;[3] and that further data is not required from the sponsor for approval of the product. The ACM acknowledged that this could set a precedent for future extension of indication applications for other IVIg products, however 'adequate justification' (as per the EMA guideline) would need to be provided with each submission and considered by the TGA on a case-by-case basis, and would ideally include product-specific data.

c. Slight modification of the proposed indication to:

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in adults.

The ACM agreed that a CIDP indication is appropriate.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for a chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) indication.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Kiovig (normal haemoglobin, human) 1 g/10 mL, 2.5 g/25mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL, and 30 g/300 mL solution for injection (vial) indicated for the following extension of indications:

> *Kiovig administered intravenously is indicated for the treatment of Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in adults.*

As such, the full indications at this time were:

Kiovig administered intravenously is indicated for:

1. *Replacement therapy indications*

   – Primary immunodeficiency disorders (PID);

   – Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

2. *Immunomodulation indications*

   – Idiopathic thrombocytopenia purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count;

   – Guillain Barré Syndrome;

   – Kawasaki Disease;

   – Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in adults.

   – Multifocal Motor Neuropathy (MMN).

Kiovig administered subcutaneously is indicated for:

1. *Replacement therapy indications*

   – Primary immunodeficiency disorders (PID).

Specific conditions of registration applying to these goods

This approval does not impose any requirement for the submission of periodic safety update reports (PSUR). You should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed. You are reminded that sections 29A and 29AA of the Therapeutic Goods Act 1989 provide for penalties where there has been failure to inform the Secretary in writing, as soon as a person has become aware, of:

(a) information that contradicts information already given by the person under this Act;

(b) information that indicates that the use of the goods in accordance with the recommendations for their use may have an unintended harmful effect;

(c) information that indicates that the goods, when used in accordance with the recommendations for their use, may not be as effective as the application for registration or listing of the goods or information already given by the person under this Act suggests;

(d) information that indicates that the quality, safety or efficacy of the goods is unacceptable.

Attachment 1. Product Information

The PI for Kiovig approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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