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SCIENCE MEDICINES HEALTH

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Overview of comments received on "Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCIg/IMIg) rev 2"

Name of organisation or individual	General or Specific comment	Line from (line nr. or 0 for general comment)	Line to (line nr. or 0 for general comment)2	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
EuropaBio	General	0	0	If the CIDP indication is going to be extrapolated from the PID indication, then the SmPC of the product with the extrapolated CIDP indication must clearly state that the product has not been evaluated in clinical studies in CIDP in all relevant sections (including Posology and Pharmacodynamic properties sections).		The extrapolation of CIDP from PID is confirmed. Not agreed. The infomation reported in section 5.1 (product specific) is considered suffcient to inform on the clinical available data in specific therapeutic indications
EuropaBio	Specific	Line 73-76: This revision (2024) includes updates to the guideline to be consistent where applicable with the revised Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)(EMA/CHMP/BPWP/94038/2007 Rev. 6) 5 and the inclusion of the indication for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).		See correction in text, "5" should be deleted from text after "Rev. 6)"	Line 73-76: This revision (2024) includes updates to the guideline to be consistent where applicable with the revised Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)(EMA/CHMP/BPWP/94038/2007 Rev. 6) (5 should be deleted) and the inclusion of the indication for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).	Accepted. The text has been corrected.
EuropaBio	Specific	Line 214-215: Immunomodulation in adults, children and adolescents (0-18 years) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as maintenance therapy after stabilisation with IVIg.		These lines stand under the Heading "Replacement therapy in adults, children and adolescents (0-18 years) in:" - Additional heading for immunomodulatory therapy should be introduced.	Line 214-215: Immunomodulatory therapy in adults, children, and adolescents (0 to 18 years) in: Immunomodulation in adults, children and adolescents (0–18 years) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as maintenance therapy after stabilisation with IVIg.	Accepted. The text has been modified as follows: Immunomodulatory therapy in adults, children, and adolescents (0 to 18 years) in: Immunomodulation in adults, children and adolescents (0–18 years) in Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as maintenance therapy after stabilisation with IVIg.
EuropaBio	Specific	Line 254: <This medicinal product can be administered at regular intervals from once daily up to every other week.>		The safety of each other product for biweekly regimen of the high-dose indication CIDP should be demonstrated by post-marketing exposure, before other SCIG products can simply be extrapolated to biweekly dosing.	Line 254: < This medicinal product can be administered at regular intervals from once daily up to weekly.> "every other week" should be deleted from the text	Not agreed. The text at line 254 is related to replacement therapy; in this setting the administration every two weeks is widely supported by literature
EuropaBio	Specific	Line 271: ...cumulative monthly dose of the order of 0.2-0.4 g/kg (1.2 – 2.4 ml/kg). Each single dose may need to be…		The ml dose is incorrect as the SCIG on the markets might be differently concentrated.	Line 271: ...cumulative monthly dose of the order of 0.2-0.4 g/kg. Each single dose may need to be… "1.2 – 2.4 ml/kg" should be deleted from the text.	Accepted. The text has been updated.
EuropaBio	Specific	Line 297-298: The weekly dose can be divided into smaller doses and administered by desired number of times per week.For dosing every two weeks, the weekly dose should be doubled.		The extrapolation to the biweekly regimen for less concentrated SGIG is not appropriate without data due to high SC volumes to infuse in a high-dose CIDP indication.	Line 297-298: The weekly dose can be divided into smaller doses and administered by desired number of times per week. "For dosing every two weeks, the weekly does should be doubled." should be deleted from the text.	Partially agreed. The text has been updated as follows: "Generally, the dose should be administered at regular intervals. The weekly dose can be divided into smaller doses and administered by desired number of times per week. The intervals are at the discretion of the treating physician and patient preference (and may be up to two weeks) and the dose needs to be adjusted accordingly."
EuropaBio	Specific	Line 292-298: Treatment is initiated 1 week after the last IVIg infusion. The recommended subcutaneous dose is 0.2 to 0.4 g/kg body weight per week administered in 1 or 2 sessions over 1 or 2 consecutive days. The initial subcutaneous dose may be a 1:1 conversion from the previous IVIg dose (calculated as weekly dose). Example: a 1 g/kg IVIg dose given every 3 weeks would convert into a 0.33 g/kg dose given once a week. The weekly dose can be divided into smaller doses and administered by desired number of times per week. For dosing every two weeks, the weekly dose should be doubled.		Dosing for CIDP shoud be product-specific and supported by data from clinical trials. The highest dose should be supported by safety data.	The entire paragraph in line 292-298 should be deleted from the text - "Treatment is initiated 1 week after the last IVIg infusion. The recommended subcutaneous dose is 0.2 to 0.4 g/kg body weight per week administered in 1 or 2 sessions over 1 or 2 consecutive days. The initial subcutaneous dose may be a 1:1 conversion from the previous IVIg dose (calculated as weekly dose). Example: a 1 g/kg IVIg dose given every 3 weeks would convert into a 0.33 g/kg dose given once a week. The weekly dose can be divided into smaller doses and administered by desired number of times per week. For dosing every two weeks, the weekly dose should be doubled."	Not agreed on the basis of literature data. The text has been modified to reflect the role of treating physician and the importance of patient preference in the decision of treatment intervals.
IPOPI	Specific	269-276		We agree with this		No comment
IPOPI	Specific	302		We are missing a reference to obese/severely overweight individuals for which the dosage would need to be adjusted.		Not agreed. On the basis of literature evidence, no adjustments seems to be necessary in case of obesity. "Both SCIG and fSCIG successfully maintained trough values at or above the hypothetical protective threshold after switching from stable IVIG, irrespective of BMI or age. Differences in trough values between BMI groups and age groups (≤ 22%) may not warrant SCIG or fSCIG dose adjustments based on BMI or age alone; instead, the dosing paradigm should be guided by prior IVIG dose, individual IgG monitoring, and clinical findings" (Zhaoyang Li et al. Effects of Body Mass and Age on the Pharmacokinetics of Subcutaneous or Hyaluronidase-facilitated Subcutaneous Immunoglobulin G in Primary Immunodeficiency Diseases. Journal of Clinical Immunology (2023) 43:2127–2135)
Grifols	General	0	0	Grifols endorses the 2024 revision of Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCIg/IMIg) including updates to be consistent where applicable with the revised Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) and the inclusion of the indication for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In relation to the inclusion of "established" immunomodulatory indications for IVIgs other than CIDP, a substantial body of evidence confirms that SCIg is feasible, safe, and equally effective as IVIg in treating MMN. Therefore, Grifols recommends the inclusion of MMN as maintenance therapy after stabilisation with IVIg. Regarding method of administration, Grifols proposes to add specific recommendations on manual administration of SCIg, considering it offers an effective and well-tolerated alternative to administration by infusion pump. Overall, Grifols endorses the EMA updates and inclusions on the core SmPc for SCIg guidelines and proposes the inclusion of MMN and specific instructions for manual administration to advance in patients care. Specific comments for sections 4.1, 4.2 and 5.1 are provided below.		The extrapolation of therapeutic indication MMN is not agreed, due to the paucity of literature data available. Further clinical data are considerd necessay to establish the correct posology. Further data will be monitored.

Grifols	Specific	85		Inclusion in proposed guidance text of the references used for the rationale provided in this proposal.	1. Al-Zuhairy, A., Jakobsen, J., Andersen, H., Sindrup, S. H., & Markvardsen, L. K. (2019). Randomized trial of facilitated subcutaneous immunoglobulin in multifocal motor neuropathy. European Journal of Neurology, 26 (10), 1289-1295. 2.Al-Zuhairy, A., et al. (2021). Long-term follow-up of facilitated subcutaneous immunoglobulin therapy in multifocal motor neuropathy. Journal of the Neurological Sciences, 427, 117495. https://doi.org/10. 1016/j.jns.2021.117495 3.Alemany, A., et al. (2023). Subcutaneous anti-COVID-19 hyperimmune immunoglobulin for prevention of disease in asymptomatic individuals with SARS-CoV-2 infection: A double-blind, placebo-controlled, randomised clinical trial. eClinicalMedicine, 57, 101898. https://doi.org/10.1016/j.eclinm. 2023.101898 4.Bienvenu, B., et al. (2018). Rapid push vs pump-infused subcutaneous immunoglobulin treatment: A randomized crossover study of quality of life in primary immunodeficiency patients. Journal of Clinical Immunology, 38(4), 503-512. https://doi.org/10.1007 /s10875-018-0507-x 5.Braine, M. E., & Woodall, A. (2012). A comparison between intravenous and subcutaneous immunogobulin. British Journal of Nursing, 21(8), S21-S27. 6.Claytor, B., Polston, D., & Li, Y. (2025). Multifocal motor neuropathy: A narrative review. Muscle & Nerve, 71(5), 512-534. 7.Cocito, D., Merola, A., Peci, E., Mazzeo, A., Fazio, R., Francia, A., ... & Lopiano, L. (2014). Subcutaneous immunoglobulin in CIDP and MMN: a short-term nationwide study. Journal of Neurology, 261(11), 2159-2164. 8. Cowan, J., et al. (2021). Safety and tolerability of manual push administration of subcutaneous IgPro20 at high infusion rates in patients with primary immunodeficiency: Findings from the manual push administration cohort of the HILO study. Journal of Clinical Immunology. https://doi.org/10.1007/s10875-020-00876-6 9. Cozon, G. J. N., et al. (2018). In-depth interviews of patients with primary immunodeficiency who have experienced pump and rapid push subcutaneous infusions of immunoglobulins reveal new insights on their preference and expectations. Patient Preference and Adherence, 12, 423-429. 10 Eftimov, F., Vermeulen, M., de Haan, R. J., van den Berg, L. H., & van Schaik, I. N. (2009). Subcutaneous immunoglobulin therapy for multifocal motor neuropathy. Journal of the Peripheral Nervous System, 14(2), 93-100.11.Gentile, L., Russo, M., Rodolico, C., Arimatea, I., Vita, G., Toscano, A., & Mazzeo, A. (2021). Long-term treatment with subcutaneous immunoglobulin in multifocal motor neuropathy. Scientific Reports, 11(1), 9216. 12.Hadden, R. D. M., & Marreno, F. (2015). Switch from intravenous to subcutaneous immunoglobulin in CIDP and MMN: improved tolerability and patient satisfaction. Therapeutic Advances in Neurological Disorders, 8(1), 14-19. 13.Harbo, T., Andersen, H., Hess, A., Hansen, K., Sindrup, S. H., & Jakobsen, J. (2009). Subcutaneous versus intravenous immunoglobulin in multifocal motor neuropathy: a randomized, single-blinded cross-over trial. European Journal of Neurology, 16(5), 631-638. 14. Harbo T, Andersen H, Jakobsen J. Long-term therapy with high doses of subcutaneous immunoglobulin in multifocal motor neuropathy. Neurology. 2010 Oct 12;75(15):1377-80. doi: 10.1212 /WNL.0b013e3181f735ce. PMID: 20938030. 15. Herraets, I. J. T., Bakers, J. N. E., van Eijk, R. P. A., Goedee, H. S., van der Pol, W. L., & van den Berg, L. H. (2019). Human immune globulin 10% with recombinant human hyaluronidase in multifocal motor neuropathy. Journal of Neurology, 266(11), 2734-2742. 16.INGID European Nursing Guideline Committee.(2016). European Nursing Guidelines for Immunoglobulin Administration (Version 7). Retrieved from INGID European-Nursing-Guideline-Immunoglobulin-Administration-V7-20160623.docx.pdf 17.Jovanovich, E., & Karam, C. (2015). Human immune globulin infusion in the management of multifocal motor neuropathy. Degenerative Neurological and Neuromuscular Disease, 6, 1-12. 18.Katzberg, H. D., Rasutis, V., & Bril, V. (2016). Subcutaneous immunoglobulin for treatment of multifocal motor neuropathy. Muscle & Nerve, 54(5), 856-863. 19.Keith, P. K., et al. (2022). Transitioning subcutaneous immunoglobulin 20% therapies in patients with primary and secondary immunodeficiencies: Canadian real-world study. Allergy, Asthma & Clinical Immunology, 18(1), 709. 20.Misbah, S. A., Baumann, A., Fazio, R., Dacci, P., Schmidt, D. S., Burton, J., & Sturzenegger, M. (2011). A smooth transition protocol for patients with multifocal motor neuropathy going from intravenous to subcutaneous immunoglobulin therapy: an open-label proof-of-concept study. Journal of the Peripheral Nervous System, 16(2), 92-97. 20. Patel, N. C., et al. (2015). Subcutaneous immunoglobulin replacement therapy with Hizentra® is safe and effective in children less than 5 years of age. Journal of Clinical Immunology, 35(6), 558-565. 22.Racosta, J. M., Sposato, L. A., & Kimpinski, K. (2017). Subcutaneous versus intravenous immunoglobulin for chronic autoimmune neuropathies: A meta-analysis. Muscle & Nerve, 55(6), 802-809. 23.Shapiro, R. (2010). Subcutaneous immunoglobulin therapy by rapid push is preferred to infusion by pump: A retrospective analysis. Journal of Clinical Immunology, 30(3), 301-307. 24.Shapiro, R. (2013). Subcutaneous immunoglobulin (16 or 20%) therapy in obese patients with primary immunodeficiency: a retrospective analysis of administration by infusion pump or subcutaneous rapid push. Clinical and Experimental Immunology, 173(3), 365-371. 25.Shapiro, R. S. (2013). Subcutaneous immunoglobulin therapy given by subcutaneous rapid push vs infusion pump: a retrospective analysis. Annals of Allergy, Asthma & Immunology, 111(1), 51-55.	Partially Agreed. Publications on use in MMN and on use of different devices are not pertinent. Other literature references on immunodeficiencies and on CIDP have been added.
Grifols	Specific	214-215		-The mainstay of MMN treatment is IVIg or SCIg. Other treatments that have been studied, such as corticosteroids and plasma exchange, are not recommended due to their potential to exacerbate weakness. (Jovanovich 2015) -A substantial body of evidence confirms that SCIg is feasible, safe, and equally effective as IVIg in treating MMN. This conclusion is supported by data from retrospective and prospective observational studies (Brain and Woodall, 2012; Cocito, 2014; Hadden and Moreno, 2015; Gentile, 2021), prospective open-label studies (Eftimov, 2009; Misbah, 2011; Katzberg, 2016; Herraets, 2019), randomized single-blinded studies (Harbo, 2009; Al-Zuhairy, 2019), and a meta-analysis encompassing five studies (Racosta, 2017). -SCIg has been shown to be as effective as IVIg in maintaining muscle strength and functional status in MMN patients. Studies indicate no significant differences in muscle strength outcomes between SCIg and IVIg (Racosta, J. M. 2017; Cocito, D. 2014; Gentile, L. 2021) -Long-term follow-up studies (up to 96 months) have shown that SCIg can maintain or even improve strength and motor functions in MMN patients [Gentile 2021]. Another study demonstrated stable muscle strength and functional scores over a 2-year period [Harbo 2010]. -SCIg has been found feasible and effective for long-term maintenance treatment, with patients maintaining their strength and functional status over extended periods [Al-Zuhairy 2021]. -SCIg is associated with fewer systemic adverse effects compared to IVIg, with a 28% reduction in the relative risk of moderate and/or systemic adverse effects [Racosta 2017]. Local skin reactions are generally mild and transient [Harbo 2010] . -MMN patients stable with IVIg benefit from switching to SCIg due to fewer systemic side effects, no need for venous access, greater convenience, autonomous administration, and reduced economic burden. (Claytor 2025)	<*Proposed text added*> Immunomodulation in adults, children and adolescents (0–18 years) in: - chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as maintenance therapy after stabilisation with IVIg. <*- multifocal motor neuropathy (MMN) as maintenance therapy after stabilisation with IVIg. *>	Extrapolation to MMN not agreed. See response to the comment above
Grifols	Specific	299		Including specific posology text for MMN.	<*Proposed text added*> <*Immunomodulatory therapy in MMN Treatment is initiated 1 week after the last IVIg infusion. The recommended initial subcutaneous dose may be a 1:1 conversion from the previous IVIg dose (calculated as weekly dose). The weekly dose can be divided into smaller doses and administered by desired number of times per week. The dosing and intervals may have to be adapted according to the individual course of the disease.*>	Extrapolation to MMN not agreed. See response to the comment above
Grifols	Specific	317-328		Regarding the "Methods of administration" section, to enhance patients' choice and assist physicians in guiding patients for home treatment, Grifols proposes providing specific recommendations on device-assisted infusion and manual administration of SCIg. Adding specific instruction on manual administration is based on: - Facilitating instructions regarding SCIg administration options can lead to better individualization and optimization of treatment, and is essential for the effective patient administration of SCIg at home. -Both, manual and pump administration methods are effective, safe and show comparable patient satisfaction. Individual patient medical situation, preferences and quality of life should be considered when choosing the administration method. (Keith PK, et al. 2022 ; Cozon GJN, et al. 2018; Bienvenu B, et al. 2018, Warnatz K, et al. 2022) -Studies using manual administration for the delivery of SCIg therapies have demonstrated the efficacy, safety, and tolerability in adults and paediatric patients with PIDs (Cowan et al. 2021; Patel et al. 2015; Shapiro 2010; Shapiro 2013; Shapiro 2013; Walter et al. 2020; Warnatz et al. 2022) -Clinical trials (Bienvenu B, et al. 2018; Cowan J, et al. 2021; Warnatz K, et al. 2022; Alemany A, et al. 2023) have shown that manual administration of SCIg at an infusion speed of 1-2 mL/min is well tolerated. This practice is recommended by the European Nursing Guidelines for Immunoglobulin Administration [https://ingid.org/resources/nursing-guidelines/]. Published 2016. Accessed May 5, 2025. -Manual administration of SCIg avoids technical and logistical requirements associated with infusion pump use, permitting easier infusion at home [https://www. fda.gov/medical-devices/infusion-pumps/examples-reported-infusion-pump-problems]. Accessed 28 Mar 2025.	<*Proposed text added*> Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. <*The healthcare professional must select the appropriate mode of infusion (device-assisted or manual administration), based on patient's individual medical situation and preferences. Infusion devices appropriate for subcutaneous administration of immunoglobulins can be used.*> The patient must be instructed in the use of syringe driver, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions. {{Invented} name} may be injected into sites such as abdomen, thigh, upper arm, and lateral hip. More than one <*device*> can be used simultaneously. The amount of product infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 ml. In adults, doses over 30ml may be divided according to patient preference. There is no limit to the number of infusion sites. <*{{Invented} name} can be infused using: •an infusion device, or •by manual administration using a syringe. Device-assisted infusion:*> It is recommended to use an initial administration speed of {XX} ml/h/infusion site. If well tolerated (see section 4.4), the infusion speed can be enhanced by {YY} mL/kg/hr every subsequent infusion. The recommended maximum speed is {ZZ} mL/kg/hr. <*Manual administration infusion: {{Invented} name} may be administered using a syringe at a single infusion site. If administration with additional {{Invented} name} is required, a new sterile injection needle should be used and the infusion site changed. The infusion speed should be adjusted for each patient's tolerance. The recommended maximum infusion speed is 1.0-2.0 ml/min/site.*>	Not agreed. The infusion devices are not part of packaging and are not specific for single medicinal product; instruction on the better device for single patient will be provided by the treating physician and this is explained by the senterence: "The patient, healthcare professional or caregiver must be instructed in the use of a infusion device, the infusion techniques,..." already reported in the text.
Grifols	Specific	531-532		"…for extravascular administration, …" is missing in the draft core SmPC (rev. 2). This text should be included according to the ATC classification. It is included in the current core SmPC (rev. 1).	<*Proposed text added*> Pharmacotherapeutic group: immune sera and immunoglobulins, immunoglobulins, normal human, <*for extravascular administration,*> ATC code: J06BA01	Disagreed, according to the SmPC guideline the 2nd together with the 3rd or 4th ATC level should be included.
Takeda	General	0	0	Takeda supports the EMA's proposed SCIG label review as a positive step towards accelerating access to essential therapies and alleviating supply constraints, particularly in areas of limited availability. While we fully endorse efforts to streamline processes that enhance efficiency and reduce costs, maintaining the highest efficacy and safety standards remain paramount. Any changes must ensure patient safety, including considering and addressing the distinct needs of the unique patient populations. 1. The draft guideline proposes that if efficacy has been proven in primary immunodeficiency syndromes (PIDs), no further studies are required to demonstrate efficacy in secondary immunodeficiency syndromes (SIDs). Takeda agrees with this proposal as PID and SID share clinical manifestations that lead to severe infections due to hypogammaglobulinemia, necessitating replacement therapy, and several studies provide evidence of the efficacy and safety of SCIG in SID [Blau IW, et al. Expert Rev Clin Immunol. 2016;12(7):705-711; Benbrahim O, et al. Hematology. 2019; 24(1):173-182; Borte M, et al. J Clin. Immunol. 2023 Aug; 43(6):1259-1271; Vacca A, et al. Clin Immunol. 2018; 191:110-115; Visentin A, et al. Curr Oncol. 2022; 30(1):274-283].		No comment.
Takeda	General	0	0	2. The core SmPC does not explicitly list the putative immunomodulatory mechanisms by which IGs exert their effect in autoimmune disorders, even though there is published evidence that consistently points to certain mechanisms for anti-inflammatory and immunomodulatory effects of IG. Takeda is concerned that the current MoA-agnostic language in the core SmPC may falsely lead to the conclusion that IG treatment is used without a mechanistic rationale and therefore may impact access to IG therapies by appropriate patients. Takeda proposes the EMA establish a smaller MoA working group to develop a concise and evidence-based standard MoA statement for the immunomodulatory actions of IGs. Please see the Supporting Evidence section / topic on Mechanisms of immunomodulatory actions.		The MoA working group has not been considered necessary. The text on MoA has been revised and implemented. Please see response to comment below.
Takeda	General	0	0	3. The current draft core SmPC describes the dose, dose range, dosing interval and administration characteristics only for conventional SCIG (cSCIG). This draft does not differentiate between cSCIG and recombinant human hyaluronidase (rHuPH20)-facilitated SCIG (fSCIG) [Ponsford M, et al. Clin Exp Immunol. 2015; 182(3):302-13; Wassermann, RL, Immunol Allergy Clin N Am. 2019; 39(1):95–111]. As cSCIG and fSCIG differ in important aspects – including bioavailability, dose, dosing interval and administration time – it would be beneficial to ensure these differences are clear within the core SmPC. In her presentation at the EMA Workshop on 05 March 2025, Dr. Maria Pia Cicalese emphasized that, although "the common active component of IG products is IgG, IgG concentrations and formulations can vary significantly", and the "various approved IG products are not interchangeable" [Ness S., Am J Manag Care. 2019; 25(suppl 6):S98-S104]. Takeda proposes to acknowledge the specifics on dosing and administration for facilitated SCIG in the core SmPC. Please see the Supporting Evidence section / topic that shows that cSCIGs and fSCIGs are not considered interchangeable.		The physician chooses the better therapeutic option, on the basis of the charachteristics of the specific product (reported in its SmPC as product specific) and of the patient, without the necessity to add further distinctions in the CoreSmPC. Adding a note on non interchangeability of products can lead to problems in case of necessity of switch of therapy, such as for example in case of shortages.
Takeda	General	0	0	4. The draft guideline states that where the efficacy in PIDs is established, then an extrapolation to maintenance therapy for CIDP after stabilization with IVIG might be possible without the need to perform separate clinical trials in this indication, if adequately justified. Both IVIG and SCIG have been extensively studied in PID and CIDP and both exhibit proven efficacy and safety. Takeda understands that extrapolation from PID to CIDP without the need for further clinical studies could facilitate SCIG development and patient access. However, there are fundamental differences in pathophysiology, dosing and treatment response behavior between these two distinct diseases that deserve further consideration. It may even be beneficial to consider what questions an extrapolation in the other direction – from CIDP to PID – would raise. Additionally, Takeda would like to highlight the critical role that clinical evidence plays in benefit-risk assessment, cost-effectiveness appraisal and reimbursement decisions by HTA bodies and payers. While it is understood that such considerations fall outside of scope of regulatory evaluation, regulatory and HTA research questions are often distinct yet overlapping. Takeda proposes that studies should be designed to address the evidence needs of both decision makers simultaneously – and, in this way, provide data that clarify and confirm SmPC indications, helping to facilitate access to the right treatments for the right patients at the right time. Considering the fundamental differences between PID and CIDP and to assist downstream access decisions, Takeda proposes the consideration of options for a simplified clinical pathway for SCIG development for CIDP. One such option could be open-label, single arm efficacy, safety and tolerability studies for label extension, where success for efficacy is determined against a fixed threshold based on the published placebo rates in recent clinical trials. This approach – which could be considered an option midway between direct extrapolation and a randomized, placebo-controlled trial – would be expected to facilitate generation of data relevant to treatment safety, tolerability and efficacy. Furthermore, the additional clinical data would potentially demonstrate discreet benefits for distinct patient sub-populations across the different, non-interchangeable cSCIG / fSCIG options, enabling more informed HTA evaluations, broader options for patients alongside timely patient access. Please see the Supporting Evidence section / topic on extrapolation from PID into maintenance therapy for CIDP.		Not agreed; further simplified clinical studies are nor considered necessary due to the available literature that support the use of IVIG, SCIG and FSCIG in CIDP. See response to comment above.

Takeda	General	0	0	5. The draft guideline states that other possible indications cannot be granted without relevant specific clinical data. However, MMN shares several similar pathophysiological characteristics with CIDP and there is consistent evidence that IG treatment offers substantial efficacy in MMN. As MMN is a very rare condition with few treatment options, the potential to bring a safe and efficacious treatment to MMN patients more quickly should be considered Takeda proposes an extrapolation to maintenance therapy for MMN is considered if the efficacy in CIDP is established with proprietary clinical data, without the need to perform separate clinical trials in MMN. The use of IGs in MMN is evaluated as appropriate, given the high unmet medical need due to disease burden and the lack of alternative treatments, and the high therapeutic value IGs offer in MMN in terms of efficacy, safety and practicality [Kołtan S., Kostera-Pruszczyk A., Styczyński J., Hus I., Więsik-Szewczyk E., Heropolitańska-Pliszka E., Pac M., Lipowska M., Jahnz-Różyk K., Szepietowski J., Czajkowski R., Pastuszczak M., Grywalska E., Roliński J., Drabko K., Młynarski W., Kluszczyński T., APPROPRIATE USE OF IMMUNOGLOBULINS IN POLAND - Key Considerations and Treatment Paradigms. J Health Policy Outcomes Res [Internet] 2025 [cited 2025 May 20]. Available from: https://jhpor.com/article/2438-appropriate-use-of-immunoglobulins-in-poland---key-considerations-and-treatment-paradigms]. Please see the Supporting Evidence section / topic on extrapolation of efficacy in CIDP to MMN.		An extrapolation to manteinance therapy in MMN is not agreed. See response to comment above.
Takeda	General	0	0	Supporting Evidence and Recommendations for Consideration Topic – Mechanisms of immunomodulatory actions Takeda proposes to provide the putative mechanisms of immunomodulatory actions of IG in the core SmPC. •Despite a wealth of evidence from independent investigators, the exact immunomodulatory MoA of IG therapy is generally considered unknown. •The core SmPC does not explicitly list putative immunomodulatory mechanisms by which IGs exert their effect in autoimmune disorders such as CIDP. Takeda is concerned that the current MoA-agnostic language in the core SmPC may lead to the conclusion that IG treatment is used without a mechanistic rationale. •The MoA of IG is not a black box; published evidence consistently points to certain mechanisms for anti-inflammatory and immunomodulatory effects of IG. •While the relative contribution of each mechanism in each clinical condition is not fully known, Takeda is concerned that a blanket approach that ignores the accumulated evidence on immunomodulatory MoA of IG could be misleading. Takeda proposes the EMA establish a smaller MoA working group to develop a concise and evidence-based standard MoA statement for immunomodulatory actions of IGs. Examples for known MoAs include: 1.Interaction with/blocking of Fc receptors on phagocytic cells in the spleen and liver such as splenic macrophages. 2.Inhibition of dendritic cell differentiation and maturation. 3.Reduction of proinflammatory subsets of peripheral blood monocytes (CD14+CD16++) and suppression of cytokine production by these cells. 4.Suppression or neutralization of cytokines by specific antibodies in the IVIG. 5.Blockade of leukocyte adhesion molecule binding to the vascular endothelium. 6.Blockade of Fas ligand-mediated apoptosis by anti-Fas antibodies. 7.Supply of anti-idiotypic antibodies directed against idiotypes on circulating autoantibodies. 8.Effects on the complement system, including: 1) Supply of an alternate binding site or "sink" for the complement component C3b, diverting it from binding to targets for complement activation, 2) Solubilization and clearance of immune complex deposits and/or inhibition of the binding of active complement components such as C4b and membrane attack complex to target tissues. 9.Expansion of FoxP3+ Tregs and downregulation of the Th17 pathway. 10.Induction of inhibitory Fc-gamma-RIIB receptors on effector macrophages leading to sialylation of the glycan component in the CH2 domain of the IgG molecule. Supporting Evidence and Recommendations for Consideration Topic – cSCIGs are not considered interchangeable. •We would like to underline that, overall, the updates to the core SmPC for SCIGs and the guidelines on clinical investigation of SCIGs should not imply that these treatments are interchangeable. •It has been noted, by multiple well-respected policy-making bodies world-wide (reference 1), that there are intrinsic product differences and the variations in patients' biology and specific disease state – and therefore distinct SCIG brands are considered not interchangeable from a medical perspective and should not be treated as such by regulators or policy makers. •This is due to differences in SCIG manufacturing processes, in the pharmaceutical properties and in final-product formulations (eg, pH, osmolality, IgA content, sodium content, and stabilizer) [Ness S., Am J Manag Care. 2019; 25(suppl 6):S98-S104], which can affect safety and tolerability in some patients and need to be considered by the prescribing physician to avoid potential health-associated risks to the patient. In addition, regarding extrapolation into other disease areas with different pathophysiology like CIDP, these product differences may substantially impact the dose at which the product is efficacious – underscoring the need for the extrapolation to be supported by specific studies. •Unlike monoclonal antibody therapies, different IG products cannot be considered "biosimilar" to each other. Therefore, having a diverse range of IG products with different tolerability profiles allows the prescribing physicians to select the right product for their patients to have the best possible treatment outcome.		The text on MoA has been revised and implemented. Please see response to comment below.
Takeda	General	0	0	fSCIG and cSCIG differ in key areas relevant to patient safety and outcomes. To meet the diverse and broad needs of patients who require treatment with IGs, there have been innovations in the range of products made available, including intravenous immunoglobulin (IVIG), conventional subcutaneous immunoglobulin (cSCIG), and recombinant human hyaluronidase (rHuPH20)-facilitated SCIG (fSCIG) (Ponsford M, et al. Facilitated subcutaneous immunoglobulin (fSCIG) therapy--practical considerations. Clin Exp Immunol. 2015 Dec; 182(3):302-13). •cSCIG and fSCIG differ in: •Bioavailability •Dose •Dosing interval •Duration of infusion time •It is critical to ensure patients have access to the full range of therapies, as evidenced by a survey conducted by the International Patient Organization for Primary Immunodeficiencies (IPOPI) (reference 2) – within which patients identified unmet treatment gaps and improvement areas in the traditional IVIG and cSCIG treatment options in terms of time, site of care, frequency of dosing, needle sticks and side effects of treatment. •By combining aspects of both IVIG and cSCIG, fSCIG offers an alternative that addresses many of these gaps and supports the need to include an additional section on dosing and administration for facilitated SCIG into the core SmPC. •In addition, analyses in different markets have indicated that fSCIG is more cost-effective compared to IVIG and cSCIG. For example, the Danish Medicines Council completed a cost analysis comparing different SCIGs for treating PID, SID and CIDP, which found that fSCIG was the most cost-effective choice among the evaluated SCIG treatments – including the lowest treatment-related costs for both initiating and maintaining treatment. Reference 1: Resolution CM/Res(2015)2 on Principles Concerning Human Normal Immunoglobulin Therapies for Immunodeficiency and Other Diseases (Adopted by the Committee of Ministers on 15 April 2015 at the 1225th meeting of the Ministers' Deputies) Reference 2: International Patient Organisation for Primary Immunodeficiencies. 2012. IPOPI PID Patient Needs and Outlooks Survey.		The Comment was taken into consideration. Anyway the addition of a specification it the the text of CoreSmPC is referred only to classic ScIg is not agreed (please see response to comment below)
Takeda	General	0	0	Supporting Evidence and Recommendations for Consideration Topic - Extrapolation from PID into maintenance therapy for CIDP Extrapolation from PID to CIDP could create concerns given there are fundamental differences in the pathophysiology, dosing, dose-response relationship, and inter- and intra-patient variability in treatment response to IGs across these two disorders. Takeda would suggest minimum clinical requirements to evaluate a "CIDP dosing regimen" to ensure patient safety. Takeda wishes to bring the following salient issues to the attention of the Agency to optimize SCIG development and access: The effective dose for replacement and immunomodulatory treatments shows considerable variation. The typical dose for replacement therapy (PID/SID) hovers around 0.4 g/kg/month to 0.6 g/kg/month with low inter- and intra-individual variability. In contrast, maintenance treatment of CIDP requires a much higher dose and dose range than PID. For instance, the median dose was 1.1 g/kg/month in the recent CIDP trial with an upper boundary of the dose range of 2.3 g/kg/month. Twenty-five percent of the study subjects received a dose >1.51 g/kg/month (the upper quartile). Wide dose range in CIDP (0.3 to 2.3 g/kg/month) indicates high interindividual variability in treatment response in CIDP. Unlike PID, which requires a relatively constant replacement maintenance dose, intra-patient variability in IgG dose is also high in CIDP leading to frequent dose adjustments depending on response to treatment in clinical practice. Based on PID data, it is difficult to develop a treatment algorithm that is safe, tolerable and effective in CIDP that is also tailored to individual patient variability – especially given the multiple CIDP sub-types. In Takeda's opinion, determination of a safe, tolerable and effective dose and dosing regimen requires a dedicated and standalone clinical study in CIDP. One such option could be open-label, single arm efficacy, safety and tolerability studies for label extension where success for efficacy is determined against a fixed threshold based on the published placebo rates in recent clinical trials. In conclusion, Takeda proposes a standalone safety and tolerability study of SCIG as a maintenance treatment for CIDP.		Not accepted, there is sufficient literature to support the use of IVIG, SCIG and FSCIG in CIDP. See response to comment above.
Takeda	General	0	0	Supporting Evidence and Recommendations for Consideration Topic - Extrapolation of efficacy in CIDP to MMN. MMN is a very rare disorder of autoimmune etiology that generally presents before the age of 50. [Cats EA, van der Pol WL, et al. Neurology. 2010;75(9):818–25]. oMMN is approximately 10 times less frequent than CIDP. The overall prevalence is estimated at 0.4-0.6 per 100,000 people, with limited information on the incidence of MMN, making drug development for this indication extremely challenging. oA trial in MMN would be unfeasible due to the need for very long observation times owing to slow progression of disease. MMN shares similar pathophysiological characteristics with CIDP. [Allen JA, Clarke AE, Harbo T. A Practical Guide to Identify Patients with Multifocal Motor Neuropathy, a Treatable Immune-Mediated Neuropathy. Mayo Clin Proc Innov Qual Outcomes. 2024 Jan 8;8(1):74-81]. Studies have shown that nerve dysfunction may be located at the nodes of Ranvier leading to failure of action potential conduction. oConduction block and paranodal demyelination are common. oAnti-GM1 antibodies are associated with both MMN and CIDP and may play a role in pathophysiology. Dose and dosing interval of IG therapy are similar between MMN and CIDP. MMN responds to IG, but not to corticosteroids or plasma exchange. [Allen JA, Clarke AE, Harbo T. A Practical Guide to Identify Patients with Multifocal Motor Neuropathy, a Treatable Immune-Mediated Neuropathy. Mayo Clin Proc Innov Qual Outcomes. 2024 Jan 8;8(1):74-81]. oMMN may worsen with corticosteroids or plasma exchange. oAccumulated evidence in the literature based on observational studies and an RCT consistently indicate that IG treatment offers substantial efficacy in MMN and is therefore considered to be the gold standard treatment for MMN. Takeda proposes that if the efficacy in CIDP is established with proprietary clinical data, an extrapolation to maintenance therapy for MMN might be considered without the need to perform separate clinical trials MMN.		The extrapolation to manteinance therapy for MMN is not agreed. See response to comment above.
Takeda	Specific	65-66		Please see Takeda Position, item #3, and Supporting Evidence section / topic on non-interchangeability of SCIg. We thus recommend to add the proposed text into the guideline for further clarification.	SCIg are not considered interchangeable. Differences in SCIg manufacturing processes, in the pharmaceutical properties and in final-product formulations (eg, pH, osmolality, IgA content, sodium content, and stabilizer) can affect safety and tolerability in some patients and need to be considered by the prescribing physician to avoid potential health-associated risks to the patient.	Not agreed. Please see comment above to item 3
		214-215		Inclusion of the immunomodulatory therapy in CIDP should remain a selectable component of the core SmPC, not a default text.	<Immunomodulation in adults, children (…) as a maintenance therapy after stabilisation with IVIG.>	Not agreed, since maintenance therapy in CIDP is extrapolated on the basis of efficacy in PID
Takeda	Specific	216		Please see Takeda Position, item #5, on MMN. Takeda proposes an extrapolation to maintenance therapy for MMN is considered if the efficacy in CIDP is established with proprietary clinical data, without the need to perform separate clinical trials in MMN. •MMN is a very rare disorder of autoimmune etiology that generally presents before the age of 50.[Cats EA, van der Pol WL, et al. Neurology. 2010;75(9): 818–25] •MMN is approximately 10 times less frequent than CIDP. The overall prevalence is estimated at 0.4-0.6 per 100,000 people, with limited information on the incidence of MMN, making drug development for this indication extremely challenging. •A trial in MMN would be unfeasible due to the need for very long observation times owing to slow progression of disease. •MMN shares similar pathophysiological characteristics with CIDP. [Allen JA, Clarke AE, Harbo T. A Practical Guide to Identify Patients with Multifocal Motor Neuropathy, a Treatable Immune-Mediated Neuropathy. Mayo Clin Proc Innov Qual Outcomes. 2024 Jan 8;8(1):74-81] •Studies have shown that nerve dysfunction may be located at the nodes of Ranvier leading to failure of action potential conduction. •Conduction block and paranodal demyelination are common. •Anti-GM1 antibodies are associated with both MMN and CIDP and may play a role in pathophysiology. •Dose and dosing interval of IG therapy are similar between MMN and CIDP. •MMN responds to IG, but not to corticosteroids or plasma exchange. [Allen JA, Clarke AE, Harbo T. A Practical Guide to Identify Patients with Multifocal Motor Neuropathy, a Treatable Immune-Mediated Neuropathy. Mayo Clin Proc Innov Qual Outcomes. 2024 Jan 8;8(1):74-81] •MMN may worsen with corticosteroids or plasma exchange. •Accumulated evidence in the literature based on observational studies and an RCT consistently indicate that IG treatment offers substantial efficacy in MMN and is therefore considered to be the gold standard treatment for MMN. Rationale for dose recommendation. 1.Induction: IVIg (2 g/kg given over 2–5 days) should be the first line treatment (level A) 2.Maintenance: The frequency of IGF maintenance therapy should be guided by the response. Typical treatment regimens are 1 g/kg every 2–4 weeks or 2 g /kg every 1–2 months. [EFNS MMN guidelines Journal of the Peripheral Nervous System 15:295–301 (2010)]	<Maintenance therapy to improve/maintain muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN)>	Extrapolation to MMN not agreed. See response to the comment above

Takeda	Specific	299		Please see Takeda Position, item #5, on MMN. Takeda proposes an extrapolation to maintenance therapy for MMN is considered if the efficacy in CIDP is established with proprietary clinical data, without the need to perform separate clinical trials in MMN. •MMN is a very rare disorder of autoimmune etiology that generally presents before the age of 50.[Cats EA, van der Pol WL, et al. Neurology. 2010;75(9): 818–25] •MMN is approximately 10 times less frequent than CIDP. The overall prevalence is estimated at 0.4-0.6 per 100,000 people, with limited information on the incidence of MMN, making drug development for this indication extremely challenging. •A trial in MMN would be unfeasible due to the need for very long observation times owing to slow progression of disease. •MMN shares similar pathophysiological characteristics with CIDP. [Allen JA, Clarke AE, Harbo . T. A Practical Guide to Identify Patients with Multifocal Motor Neuropathy, a Treatable Immune-Mediated Neuropathy. Mayo Clin Proc Innov Qual Outcomes. 2024 Jan 8;8(1):74-81]. •Studies have shown that nerve dysfunction may be located at the nodes of Ranvier leading to failure of action potential conduction. •Conduction block and paranodal demyelination are common. •Anti-GM1 antibodies are associated with both MMN and CIDP and may play a role in pathophysiology. •Dose and dosing interval of IG therapy are similar between MMN and CIDP. •MMN responds to IG, but not to corticosteroids or plasma exchange. [Allen JA, Clarke AE, Harbo T. A Practical Guide to Identify Patients with Multifocal Motor Neuropathy, a Treatable Immune-Mediated Neuropathy. Mayo Clin Proc Innov Qual Outcomes. 2024 Jan 8;8(1):74-81] •MMN may worsen with corticosteroids or plasma exchange. •Accumulated evidence in the literature based on observational studies and an RCT consistently indicate that IG treatment offers substantial efficacy in MMN and is therefore considered to be the gold standard treatment for MMN. Rationale for dose recommendation: 1.Induction: IVIg (2 g/kg given over 2–5 days) should be the first line treatment (level A) 2.Maintenance: The frequency of IGF maintenance therapy should be guided by the response. Typical treatment regimens are 1 g/kg every 2–4 weeks or 2 g /kg every 1–2 months. [EFNS MMN guidelines Journal of the Peripheral Nervous System 15:295–301 (2010)]	<4.2 Posology and method of administration Immunomodulatory therapy in MMN: 1.Induction: IVIg (2 g/kg given over 2–5 days) should be the first line treatment (level A) 2.Maintenance: The frequency of IGF maintenance therapy should be guided by the response. Typical treatment regimens are 1 g/kg every 2–4 weeks or 2 g /kg every 1–2 months.>.	Extrapolation to MMN not agreed. See response to the comment above
Takeda	Specific	257-265		Please see Takeda Position, item #3, and Supporting Evidence section / topic on non-interchangeability of SCIg. Given the varying IgG concentrations in SCIg preparations (see line 168) – ranging from 10 mg/ml via 16.5 mg/ml to 20 mg/ml – it. is recommended to simplify the posology sections of the core SmPC by removing specific details about administrable volumes, which are only applicable to 16.5% SCIG products. It is advised to clarify that this posology is recommended for conventional SCIG (cSCIG) only, and not for enzyme facilitated SCIG using recombinant human hyaluronidase (fSCIG). fSCIG improves bulk fluid flow and bioavailability that allows for administration of higher volumes using fewer needle punctures and longer dosing intervals similar to IVIG [Ponsford M, et al. Clin Exp Immunol. 2015 Dec; 182 (3):302-13; Wassermann, RL, Immunol Allergy Clin N Am. 2019; 39(1)95–111]. Additional information, such as in green text boxes, should clarify that posology for facilitated SCIG and non-standard SCIG regimens must be supported by clinical data, as required by the "Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)" [EMA/CHMP/BPWP/496692/2023].	[Specific for conventional SCIG products only:] <A loading dose of at least 0.2 to 0.5 g/kg body weight may be required. (…) After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg. Each single dose may need to be injected at different anatomic sites.> [The posology specific for facilitated SCIG products and for products with a dose regimen different from the standard dosages for conventional SCIG should be supported by clinical data:]	Not agreed (please see comment above on interchangeability).
Takeda	Specific	259-261		The maximal daily dose of 0.1 to 0.15 g/kg does not appear to be grounded in clinical practice or evidence suggesting a safety threshold. Pooled clinical data on safety and tolerability of subcutaneous immunoglobulin 20% from two continents provide evidence that daily doses higher than 0.1 to 0.15 g/kg are well tolerated in a broad population of patients across a wide age range with PID: as reported by Suez et al., overall, 99.8% of infusions were administered without interruption or a reduction in the infusion rate and there was no apparent association between infusion volume or rate with the rate of a subcutaneous immunoglobulin 20%causally related local AEs. The median (range) number of sites per infusion was 2 (1–5) and of infusion volume per site was 30.3 (6.4–76.0) ml, administering mean doses of 222 mg/kg/week [Suez D, et al. Immunotherapy. 2019; 11(12):1057-1065). The dose for the weekly administrations was not divided over days. We therefore suggest adapting the wording in the core SmPC for SCIG accordingly.	A loading dose of at least 0.2 to 0.5 g/kg body weight may be required. This may need to be divided over several days, based on patient-specific considerations.	Not agreed. A maximum daily dose, on the basis of literature data, should be reported.
Takeda	Specific	269-272		To accommodate the varying dose levels required for SID treatment and provide flexibility to patients in achieving a 'cumulative monthly dose' as per their preferences and fitting to their life-style, it is recommended to either remove 'approximately once per week' from the posology and dose regimen for SID, or specify a dosing frequency range from a minimum of daily to a maximum of every 2 weeks for conventional SCIG (comparable to line 254), and not for enzyme facilitated SCIG using recombinant human hyaluronidase (fSCIG). fSCIG improves bulk fluid flow and bioavailability that allows for administration of higher volumes using fewer needle punctures, and longer dosing intervals similar to IVIG [Ponsford M, et al. Clin Exp Immunol. 2015 Dec; 182(3):302-13; Wassermann, RL, Immunol Allergy Clin N Am. 2019; 39 (1)95–111]. Additional information, such as in green text boxes, should clarify that posology for facilitated SCIG and non-standard SCIG regimens must be supported by clinical data.	[Specific for conventional SCIG products only:] <The recommended dose administered at a regular level is to reach a cumulative monthly dose of the order of 0.2-0.4 g/kg. Each single dose may need to be injected at different anatomic sites.> Option 1: we suggest removing "approximately once per week" from the posology and dose regimen for SID. Option 2: we suggest indicating a time span, for example:<for conventional SCIG> <"approximately once per week; minimum: daily; to maximum: every 2 weeks".> [The posology specific for facilitated SCIG products and for products with a dose regimen different from the standard dosages for conventional SCIG should be supported by clinical data:]	Not agreed (please see comment above on interchangeability)
Takeda	Specific	292-298		Inclusion of the immunomodulatory therapy in CIDP should remain a selectable component of the core SmPC, not a default text. For comparison see selectable information "Hepatitis A prophylaxis" in line 278. It is advised to clarify that this posology is recommended for conventional SCIG (cSCIG) only, and not for enzyme facilitated SCIG using recombinant human hyaluronidase (fSCIG). fSCIG improves bulk fluid flow and bioavailability that allows for administration of higher volumes using fewer needle punctures and longer dosing intervals similar to IVIG [Ponsford M, et al. Clin Exp Immunol. 2015; 182(3):302-13; Wassermann, RL, Immunol Allergy Clin N Am. 2019; 39(1)95–111]. Additional information, such as in green text boxes, should clarify that the posology for facilitated SCIG and non-standard SCIG regimens must be supported by clinical data, as required by the "Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)" [EMA/CHMP/BPWP/496692/2023]	<Immunomodulatory therapy in CIDP> [Specific for conventional SCIG products only:] <(…) The recommended subcutaneous dose for conventional SCIg is 0.2 to 0.4/g/kg body weight per week (…). For every two weeks, the weekly dose should be doubled.> [The posology specific for facilitated SCIG products and for products with a dose regimen different from the standard dosages for conventional SCIG should be supported by clinical data:]	Not agreed (please see comment above on interchangeability)
Takeda	Specific	315		We suggest clarifying this applies to conventional SCIG, as it differs from facilitated SCIG.	For subcutaneous use <only> using <conventional><facilitated> SCIg	Not agreed since not necessary in the CoreSmPC
Takeda	Specific	242, 242, 317-320		To align with the evolution in healthcare roles and to ensure greater flexibility and accessibility in patient care, the SCIg core SmPC should explicitly allow therapy and home treatment to be initiated and monitored by a 'qualified healthcare professional'. In the EU, the role of nurses has significantly expanded over the last decade, reflected by new laws granting prescribing rights in 12 countries, including Denmark, Finland, France, Ireland, Netherlands, Poland, and Sweden. These laws are supported by robust regulatory and educational requirements to ensure patient safety, often involving physician oversight (Maier, C.B., Hum Resour Health 17, 95 (2019)). To align with other approved SmPCs, referencing home treatment with biological therapies for injection as well as for SCIG, it is recommended that the SCIg core SmPC explicitly states that subsequent treatment should be administered by a healthcare professional or may be administered at home by a patient, a qualified healthcare provider or caregiver after adequate training in the subcutaneous injection technique.	Replacement therapy should be initiated and monitored under the supervision of a qualified healthcare provider experienced in the treatment of immune system disorders. Subcutaneous infusion for home treatment should be initiated and monitored by a qualified healthcare professional experienced in the guidance of patients for home treatment. Subsequent treatment should be administered by a healthcare professional or may be administered at home by a patient, a qualified healthcare professional or caregiver after adequate training in the subcutaneous injection technique. The patient must be instructed in the use of a syringe driver, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.	The Comment has been partially accepted; the text has been modified as follows: Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. The patient, healthcare professional or caregiver must be instructed in the use of a infusion device, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.
Takeda	Specific	322-327		We suggest clarifying administration speed per infusion site.	[Specific for conventional SCIG products:] <{{Invented) name} may be injected into sites such as abdomen, thigh, upper arm, and lateral hip. It is recommended to use an initial administration speed of {XX} mL/hour/infusion site. If well tolerated (see section 4.4), the infusion speed can be enhanced by {YY} mL/hour/infusion site every subsequent infusion. The recommended maximum speed is {ZZ} mL/hour/infusion site. More than one pump can be used simultaneously.>	The administration speed is already reported in the text. The specification that the text is specific for conventional SCIG products is not agreed.
Takeda	Specific	327-328		It is suggested to clarify that this statement only applies to conventional SCIG (cSCIG), whereas facilitated SCIG allows for administration of volumes up to 600 ml per injection site in adults.	[Specific for conventional SCIG products:] <In adults, doses over 30 ml may be divided according to patient preference. >	Not agreed. The sentence doesn't limit the maximum volume to be administered in a single site but suggests simply the possibility to divide the cumulative dose in more infusion sites
Takeda	Specific	388		Cerebral vascular accident" is an old terminology and is recommended to be replaced by terminology currently in use, such as "ischemic stroke".	[Product specific for products with immunomodulatory indications:] <The mechanism of action in indications other than replacement therapy is not fully elucidated, but could include immunomodulatory effects, involving reduction of pathogenic antibodies through increased saturation and functional blockade of Fc receptors on macrophages, neutralization of pathogenic autoantibodies, suppression of inflammatory cytokine production, attenuation of complement-mediated tissue damage, and reduction of proinflammatory subsets of peripheral blood monocytes. Inhibition of inflammation owing to immunomodulatory properties is considered to be the mechanism of action of IgG treatment in neuroimmune disorders and other autoimmune inflammatory conditions.>	Agreed.The text has been amended.
Takeda	Specific	541-543		Please see Takeda Position, item #2, Supporting Evidence section / topic on mechanisms of immunomodulatory actions. With the proposed introduction of CIDP as a therapeutic indication for SCIg, the roles and mechanisms of action also in "immunomodulation" should be adequately specified. The term "immunomodulatory effects" lacks clarity and should be further explained within the constraints of scientific evidence. Although the role and the mechanism of action of human plasma-derived human normal immunoglobulin has not been fully elucidated, immune globulins exhibit immunomodulatory properties that include reduction of pathogenic antibodies through increased saturation and functional blockade of Fc receptors on macrophages, neutralization of pathogenic autoantibodies, suppression of inflammatory cytokine production, attenuation of complement-mediated tissue damage, and reduction of proinflammatory subsets of peripheral blood monocytes. Inhibition of inflammation owing to immunomodulatory properties is considered to be the mechanism of action of IgG treatment in neuroimmune disorders and other autoimmune inflammatory conditions [Gelfand EW. N Engl J Med. 2012; 367(21):2015-25; Ballow M. J Allergy Clin Immunol. 2011; 127(2):315-23; Norris PAA, Kaur G, Lazarus AH. Curr Opin Hematol. 2020; 27(6):392-398; Samuelsson A, Towers TL, Ravetch JV. Science. 2001; 291(5503):484-6]	[Product specific for products with immunomodulatory indications:] <The mechanism of action in indications other than replacement therapy is not fully elucidated, but could include immunomodulatory effects, involving reduction of pathogenic antibodies through increased saturation and functional blockade of Fc receptors on macrophages, neutralization of pathogenic autoantibodies, suppression of inflammatory cytokine production, attenuation of complement-mediated tissue damage, and reduction of proinflammatory subsets of peripheral blood monocytes. Inhibition of inflammation owing to immunomodulatory properties is considered to be the mechanism of action of IgG treatment in neuroimmune disorders and other autoimmune inflammatory conditions.>	The comment has been accepted. The text on MoA has been updated. See response to comment above.
Plasma Protein Therapeutics Association	Specific	541-543		Proposed revised language does not specify any putative mechanisms of action in context of immunomodulatory use of the immunoglobulins. Although the exact mechanism of immunomodulatory action have not been identified, several publications have pointed towards the involvement of certain immune pathways (Schwab, I., Nimmerjahn, F. Nat Rev Immunol 13, 176–189 (2013), Anthony, R. et al. Nature 475, 110–113 (2011). Gelfand EW. N Engl J Med.367, 2015-2025 (2012). PPTA recommends the development and inclusion of a statement on putative mechanisms of immunomodulatory actions which supports the immunomodulatory use of these medicines in autoimmune diseases.		The comment has been accepted. The text on MoA has been updated. See response to comment above.