

16 March 2026
EMA/58860/2026

Overview of comments received on "Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCiG/IMiG)"

| 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) |
|---|-----------------------------|---|--|---|---|---|
| Françoise Rossi | General | | 0 | 0 IPFA welcomes the inclusion of CIDP as an established indication for human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCiG/IMiG) | | No Comment. |
| Françoise Rossi | General | | 0 | 0 We have no specific comments for change | | No Comment. |
| EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES | General | | 0 | 0 Shortcomings Regarding CIDP Although CIDP is included as an authorized immunomodulatory indication for SCiG, the guideline presents several major limitations for this pathology: 1. No requirement for dedicated clinical trials in CIDP: o The guideline allows extrapolation of efficacy from IViG data to SCiG use in CIDP, without requiring clinical trials specific to SCiG in CIDP, as long as justification is provided. o → This reduces clinical relevance and does not ensure direct evidence of effectiveness for SCiG in CIDP patients. 2. CIDP is the only neuroimmunological disorder considered: o Other conditions often treated with immunoglobulins in practice (e.g. myasthenia gravis, autoimmune encephalitis) are not addressed, indicating a narrow, limited view of neuroimmunological applications. 3. No CIDP-specific pharmacodynamic or disease-relevant measures: o While the guideline emphasizes pharmacokinetics for PID (e.g., trough levels), there are no equivalent CIDP-specific biomarkers or clinical endpoints proposed to assess treatment response. 4. Lack of tailored dosing guidance for CIDP: o The dosage recommendations for CIDP in SCiG are copied from IViG without proposing dose adjustments or schedules tailored to the subcutaneous route or to CIDP-specific needs. | | Not accepted; literature supports the use of IViG, SCiG and fSCiG in CIDP. In addition, the use of SCiG for CIDP has already been demonstrated for some immunoglobulins. Reference is also made by the European Academy of Neurology / peripheral nerve society guideline on diagnosis and treatment of CIDP: https://onlinelibrary.wiley.com/doi/10.1111/ene.14959 |
| EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES | General | | 0 | 0 CIDP Is Not Sufficiently Prioritized • PID-centered development approach: The entire clinical framework—including PK studies, efficacy criteria, and population selection—is built primarily around PID patients. CIDP is treated as an add-on indication rather than a disease deserving focused evaluation. • No CIDP-specific clinical outcome studies required: By relying on IViG extrapolation, the guideline overlooks potential route-specific differences in immunomodulation for CIDP, which may affect efficacy or patient outcomes. • No specific post-marketing surveillance focus on CIDP: The guideline does not propose CIDP-focused post-authorization data collection, even though long-term response and tolerability could differ from PID patients. | | See above |
| EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES | General | | 0 | 0 Recommendations to Improve CIDP Focus 1. Require at least one clinical trial specifically for SCiG in CIDP, with dedicated clinical endpoints (e.g., INCAT score, muscle strength testing, disability scales). 2. Include CIDP-specific immunological or neurophysiological markers to assess therapeutic impact beyond IgG levels. 3. Encourage comparative studies between IViG and SCiG for CIDP, focusing on efficacy, adherence, tolerability, and quality of life. 4. Set up a CIDP-specific post-marketing registry for real-world effectiveness and safety monitoring. | | See above |
| EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES | General | | 0 | 0 The document represents a limited but mixed step forward for access to treatment for patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). | | No comment. |
| EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES | General | | 0 | 0 1. Official recognition of CIDP for subcutaneous administration (SCiG) This is the first regulatory acknowledgment of CIDP as an indication for SCiG as maintenance therapy after stabilization with IViG. - It potentially broadens treatment access, particularly for patients who do not tolerate IViG well or prefer home-based subcutaneous administration. | | No comment. |
| EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES | General | | 0 | 0 2. Faster access through data extrapolation Allowing extrapolation from IViG clinical data could speed up the availability of SCiG products for CIDP, avoiding the time and cost of new large-scale trials. | | No comment. |
| EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES | General | | 0 | 0 - Key limitations – a missed opportunity 1. No requirement for CIDP-specific SCiG clinical trials This means that products can be approved for CIDP without direct clinical evidence of their effectiveness or tolerability in this population. - This weakens the scientific basis for the use of SCiG in CIDP and could reduce confidence among healthcare providers or payers. 2. Risk of unequal access between countries Without robust CIDP-specific data, some national health systems may refuse reimbursement or restrict use, leading to real-world access barriers for patients. 3. Lack of post-marketing surveillance tailored to CIDP The guideline includes no CIDP-specific real-world data collection or registry, which limits our ability to monitor long-term outcomes and ensure continued safety and efficacy. | | Not accepted, literature supports the use of IViG, SCiG and fSCiG in CIDP |
| EUROPEAN PATIENT ORGANISATION FOR DYSIMMUNE AND INFLAMMATORY NEUROPATHIES | General | | 0 | 0 Conclusion: A step forward—but not far enough It opens a regulatory path for SCiG in CIDP, potentially offering more flexible treatment options. But it's not sufficient, as the disease is not treated with the rigor or priority it deserves. Without dedicated studies or monitoring, patients may have access in theory but not in practice. | | Not agreed. See above |
| Plasma Protein Therapeutics Association (PPTA) | Specific | 228-230 | | PPTA supports the extrapolation of efficacy from primary immunodeficiency to secondary immunodeficiency in the revised draft guideline. Compared to the indications in the current guideline, the proposed revised language enables the use of subcutaneous immunoglobulins in a broader group of patients suffering from secondary immunodeficiencies with recurrent severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF) or serum IgG level of 4 g/L. | N/A | No comment |
| IPOPI | Specific | 122-124 | | We suggest rewording slightly the wording on the "ineffective antimicrobial treatment". In our opinion, it should be changed to "antimicrobial prophylactic treatment". | | Not agreed. The text is the same approved for Guideline for IViG. |
| Kedrion Spa | General | | 0 | 0 The Company supports the extrapolation of efficacy from primary immunodeficiency to secondary immunodeficiency in the revised draft guideline. Compared to the indications in the current guideline, the proposed revised language enables the use of subcutaneous immunoglobulins in a broader group of patients suffering from secondary immunodeficiencies with recurrent severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of 4 g/L. | | No comment. |

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| Kedrion Spa | General | | 0 | 0 | The Company supports EMA's position to include CIDP in the SC SmPC | | No comment. |
| Kedrion Spa | General | | 0 | 0 | The Company agrees with the industry recommendation to extrapolate to maintenance therapy for MMN if the efficacy in CIDP is established, without the need to perform separate clinical trial(s) in MMN. | | Not agreed. The extrapolation of therapeutic indication MMN is not agreed, due to the paucity of literature data available. Further clinical data are considered necessary to establish the correct posology. Further data will be monitored. |
| Kedrion Spa | General | | 0 | 0 | The company agrees with holding a possible EMA standalone workshop entirely dedicated to evaluating extrapolation from CIDP to its sister disorder, MMN. | | Not agreed. See comment above. |
| 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 comment is pertinent to guideline on CoreSmPC more than to Guideline on Clinical Investigation; the MoA working group has not been considered necessary. The text of Core SmPC on MoA (section 5.1) has been revised and implemented |
| 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 comment is pertinent to guideline on CoreSmPC more than to Guideline on Clinical Investigation; the physician chooses the better therapeutic option, on the basis of the characteristics 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 accepted, literature supports the use of IVig, SCg and fSCig in CIDP. |
| 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 [Koltan 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., Pastuszczyk M., Grywałska 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://jhp.or.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. | | Not agreed; further simplified clinical studies are not considered necessary due to the available literature that support the use of IVIG, SCIG and fSCIG in CIDP. |
| 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. | | The comment is pertinent to guideline on CoreSmPC more than to Guideline on Clinical Investigation; the MoA working group has not been considered necessary. The text of Core SmPC on MoA (section 5.1) has been revised and implemented |

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| Takeda | General | | 0 | 0 | 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. 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 in the text of CoreSmPC is referred only to classic SCIG is not agreed. Please see comment above on interchangeability. |
| 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 agreed, literature supports the use of IVIg, SCIG and fSCIG in CIDP. |
| 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] • 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. 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. | | Extrapolation to MMN not agreed. Please see response to comment above. |
| Takeda | Specific | 96-97 (156-158) (314-317) (331-332) (335-336) | | | cSCIGs are not considered interchangeable Please see Takeda Position, item #3, and Supporting Evidence section / topic on non-interchangeability of SCIG. • 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, 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 patients. Positions provided in the Guideline in section 5.2 "Pharmacokinetics", and section 6. "Change in the manufacturing process of authorised products" should further support that conventional SCIGs are not considered interchangeable. | Normal human immunoglobulin for subcutaneous and/or intramuscular administration are not considered interchangeable 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). Quality aspects, except relevant biological data, are outside the scope of this guideline, such as where a significant change in the manufacturing process has been made. | Not agreed. Please see response to comment above. |
| Takeda | Specific | 231-238 | | | Extrapolation from PID into maintenance therapy in CIDP Please see Takeda Position, item #4, and Supporting Evidence section / topic on extrapolation from PID into maintenance therapy for CIDP. Extrapolation from PID to CIDP could create concerns as there are fundamental differences between these two disorders in the pathophysiology, dosing, dose-response relationship, and inter- and intra-patient variability in treatment response to immunoglobulins. Takeda would suggest minimum clinical requirements to evaluate a "CIDP dosing regimen" to ensure patient safety. As suggested as a "general remark" above, options for simplified clinical pathway for SCIG development for CIDP could be considered. One such option could be an 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, not interchangeable cSCIG / fSCIG options, enabling more informed HTA evaluations, broader options for patients alongside timely patient access. | 5.3.3. CIDP as maintenance therapy If the efficacy in primary immunodeficiency syndromes is established, then an extrapolation to maintenance therapy for CIDP after stabilisation with IVIg might be possible without the need to perform separate clinical trials in this indication, if adequately justified. The dosage regimen should be supported by relevant clinical data. An open-label, single arm efficacy, safety, and tolerability study for label extension should be considered where success for efficacy is determined against a fixed threshold based on the published placebo rates in recent clinical trials. | Not agreed; literature supports the use of IVIg, SCIG and fSCIG in CIDP. Please see response to comment above. |
| Takeda | Specific | 238-239 | | | Further to text in lines 76-88 which states "The other immunomodulatory indications for IVIGs are not yet approvable for SCIGs as no clinical data are available" 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. | 5.3.4 MMN as maintenance therapy 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. | Not agreed. The extrapolation of therapeutic indication MMN is not agreed, due to the paucity of literature data available. Further clinical data are considered necessary to establish the correct posology. Please see response to comment above. |
| Grifols | General | | 0 | 0 | Grifols endorses EMA's position of including SID and CIDP indications in the EMA core SmPC without necessitating a clinical trial as specified in the current draft Guideline on clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIG/IMIG) (EMA/CHMP/BPWP/496692 /2023 rev 2). It is scientifically sound and enhances patients care. The extrapolation to CIDP for SCIG is similar to that used for the core SmPC and clinical investigation guidelines for IVIg (EMA/CHMP/BPWP/94038/2007 Rev. 6 and EMA/CHMP/BPWP/94033/2007 rev. 4, respectively). The sentinel studies in CIDP: the ICE study of Gamunex-C (Hughes et al., 2008), the PATH study of Hizentra (van Schaik et al., 2018), and the ADVANCE study of HIQVIA (Bril et al., 2023), have demonstrated efficacy in CIDP across administration routes. Therefore, there is a substantial clinical precedent for the benefits of immune globulin administered via subcutaneous or intravenous routes in CIDP. Regarding efficacy, Grifols proposes to expand the immunomodulatory indications for SCIG to include multifocal motor neuropathy (MMN). This recommendation is based on the substantial body of evidence available confirming that SCIG is feasible, safe, and equally effective as IVIg in treating MMN. Additional details are provided below for section 4 and 5.3.3. | | No comment on the extrapolation to CIDP. The extrapolation to MMN is not agreed. Please see response to comment above. |
| Grifols | Specific | 127-129 | | | Grifols proposes to expand the immunomodulatory indications for SCIG to include the multifocal motor neuropathy (MMN). This recommendation considers: - 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). - The number of MMN patients available for clinical trials is limited, and there are ethical, economic, and practical considerations in conducting further studies for regulatory approval in MMN—an orphan indication where the benefit-risk profile of IgG is well documented. | <*<Proposed text added*> Immunomodulation in: - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), as maintenance therapy after stabilisation with IVIg. <*- Multifocal motor neuropathy (MMN), as maintenance therapy after stabilisation with IVIg.*> | Not agreed. The extrapolation of therapeutic indication MMN is not agreed, due to the paucity of literature data available. Further clinical data are considered necessary to establish the correct posology. |

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| Grifols | Specific | 231-238 | | Grifols proposes to expand the immunomodulatory indications for SCiG to include the multifocal motor neuropathy (MMN). | <*Proposed text added*> 5.3.3. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) <*>and multifocal motor neuropathy (MMN)*> as maintenance therapy (CIDP) If the efficacy in primary immunodeficiency syndromes is established, then an extrapolation to maintenance therapy for CIDP <*>and MMN*> after stabilisation with IViG might be possible without the need to perform separate clinical trials in this indication, if adequately justified. The dosage regimen should, however, be justified. If other dosage regimens than the ones provided in the guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCiG/IMiG) are requested, they should be supported by relevant clinical data. | Not agreed. Please see comment above. |
| Grifols | Specific | 348 | | Inclusion 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. <i>European Journal of Neurology</i> , 26 (10), 1289-1295. 2. Braine, M. E., & Woodall, A. (2012). A comparison between intravenous and subcutaneous immunoglobulin. <i>British Journal of Nursing</i> , 21(8), S21-S27. 3. Brill, V., et al. (2023). Hyaluronidase-facilitated subcutaneous immunoglobulin 10% as maintenance therapy for chronic inflammatory demyelinating polyradiculoneuropathy: The ADVANCE-CIDP 1 randomized controlled trial. <i>Journal of the Peripheral Nervous System</i> , 28(1), 35-46. https://doi.org/10.1111/jns.12573 4. Cocito, D., Merola, A., Pei, E., Mazzeo, A., Fazio, R., Francia, A., ... & Lopiano, L. (2014). Subcutaneous immunoglobulin in CIDP and MMN: a short-term nationwide study. <i>Journal of Neurology</i> , 261(11), 2159-2164. 5. 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. <i>Journal of the Peripheral Nervous System</i> , 14(2), 93-100. 6. 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. <i>Scientific Reports</i> , 11(1), 9216. 7. Hadden, R. D. M., & Marreno, F. (2015). Switch from intravenous to subcutaneous immunoglobulin in CIDP and MMN: improved tolerability and patient satisfaction. <i>Therapeutic Advances in Neurological Disorders</i> , 8(1), 14-19. 8. 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. <i>European Journal of Neurology</i> , 16(5), 631-638. 9. 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. <i>Journal of Neurology</i> , 266(11), 2734-2742. 10. Hughes, R. A. C., et al. (2008). Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): A randomized placebo-controlled trial. <i>The Lancet Neurology</i> , 7(2), 136-144. https://doi.org/10.1016/S1474-4422(07)70329-0 11. Katzberg, H. D., Rasutis, V., & Brill, V. (2016). Subcutaneous immunoglobulin for treatment of multifocal motor neuropathy. <i>Muscle & Nerve</i> , 54(5), 856-863. 12. 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. <i>Journal of the Peripheral Nervous System</i> , 16(2), 92-97. 13. Racosta, J. M., Sposato, L. A., & Kimpinski, K. (2017). Subcutaneous versus intravenous immunoglobulin for chronic autoimmune neuropathies: A meta-analysis. <i>Muscle & Nerve</i> , 55(6), 802-809. 14. van Schaik, I. N., et al. (2018). Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): A randomized, double-blind, placebo-controlled, phase 3 trial. <i>The Lancet Neurology</i> , 17(1), 35-46. https://doi.org/10.1016/S1474-4422(17)30378-2 | 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. |
| EuropaBio | Specific | Lines 231-238 5.3.3. Chronic inflammatory demyelinating polyradiculoneuropathy as maintenance therapy (CIDP) If the efficacy in primary immunodeficiency syndromes is established, then an extrapolation to maintenance therapy for CIDP after stabilisation with IViG might be possible without the need to perform separate clinical trials in this indication, if adequately justified. The dosage regimen should, however, be justified. If other dosage regimens than the ones provided in the guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCiG/IMiG) are requested, they should be supported by relevant clinical data. | | Efficacy in CIDP should not be extrapolated from PID (Ig replacement) to CIDP (immunomodulation) due to the different Mechanism of Action (MoA) in replacement and immunomodulation therapies. Furthermore, it cannot be assumed that all SCiG products have the same potency. Each dosing and administration schedule claimed for the indication CIDP should be justified by product specific clinical data. A trial in PID will provide no dosing information for the indication CIDP (common dosing in PID is 100 mg/kg /week, common dosing in CIDP is 0.2-0.4 g/kg/week). The requirement for product specific clinical data in an immuno-modulatory indication has been implemented in Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IViG), EMA/CHMP/BPWP/94033/2007 rev. 4. We suggest that the guideline for the clinical investigation of SCiG should follow the same principles. The guideline should provide guidance for a trial in CIDP. e.g. a placebo-controlled withdrawal trial, switching patients on stable therapy with IViG, an approved SCiG or facilitated SCiG product to the product under investigation or placebo. The endpoint can be deterioration assessed with a suitable instrument, such as INCAT or I-RDSS. Showing superiority over placebo is necessary, as many patients may not deteriorate on placebo. A placebo-controlled design is ethically justifiable as patients deteriorating are rapidly rescued with IViG. (example: A Study of HyQvia and Gammagard Liquid (Kiovig) in Adults With Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) ClinicalTrials.gov ID NCT02549170). A study in CIDP should establish efficacy of at least one dose and administration schedule. Pharmacokinetic modelling and simulation might support alternative dosing schedules. | Lines 231-238 and text below should be deleted: "5.3.3. Chronic inflammatory demyelinating polyradiculoneuropathy as maintenance therapy (CIDP) If the efficacy in primary immunodeficiency syndromes is established, then an extrapolation to maintenance therapy for CIDP after stabilisation with IViG might be possible without the need to perform separate clinical trials in this indication, if adequately justified. The dosage regimen should, however, be justified. If other dosage regimens than the ones provided in the guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCiG/IMiG) are requested, they should be supported by relevant clinical data." | Not agreed; literature supports the use of IViG, SCiG and FSCiG in CIDP. Please see response to comment above. |
| EuropaBio | Specific | Line 303-306 5.4.5. Other safety issues The effect of passive transmission of haemagglutinins (anti-A/anti-B), and anti-D should be evaluated in patients receiving high doses of SCiG by searching for haemolysis and performing a Direct Antiglobulin Test (DAT - Direct Coombs Test) in the patient. | | The guideline should be more specific. Does this require a trial at the highest dose claimed?; e.g. 0.4 g /kg/week is this dose is claimed for CIDP. Experience with IViG clearly shows that isoagglutinin mediated hemolysis is dose dependent (Wallenhorst, C. et al. AntiA/B isoagglutinin reduction in an intravenous immunoglobulin product and risk of hemolytic anemia: a hospital-based cohort study. <i>Transfusion</i> 60, 1381-1390 (2020).) Also, other potential safety issues should be investigated at the highest dose that will be claimed. | | Not agreed. The literature data confirm the safe use of SCiG at the doses indicated. |