Proposal for assessment of new health technologies

Important information – read this first!

- Submitted proposals for national health technologies (HTAs) will be published in full. If the proposer thinks there is information necessary for filling out the form, that should not be made public, please contact the secretariat (Nye Metoder) before submission.

  The proposer is aware that the form will be published in its entirety (tick): ☒

- Proposer has filled out point 19 below «Interests and, if any, conflicts of interest» (tick): ☒
- This form serves the purpose to submit proposals for health technology assessment (HTA) at the national level in Nye Metoder - the national system for managed introduction of new health technologies within the specialist health service in Norway. The form does not apply to proposals for research projects. A health technology assessment is a type of evidence review, and for this to be possible, documentation is required, e.g. from completed clinical trials. Lack of documentation may be one of the reasons why the Commissioning Forum (Bestillerforum RHF) does not assign a health technology assessment.
- If the proposal concerns a medical device, the proposer is familiar with the document «Guidance criteria for management of medical devices in the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway» (link) (tick): ☐

Contact information:

Name of the proposer (organization / institution / company / manufacturer)**:**

Grifols Nordic AB

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Date and locality:

2022-10-10 – Stockholm, Sweden

1. Proposer's title on the proposal: *
   *This may be changed during the course of the process"

Human normal immunoglobulin (Xembify®) for replacement therapy in patients with primary immunodeficiency disorders or hypogammaglobulinemia.

2. Brief description of the health technology proposed to be considered:

Xembify® is a human normal immunoglobulin (Ig) in the form of a 200 mg/mL solution for subcutaneous injection. It is indicated for replacement therapy in adults, children, and adolescents (0-18 years) in:

- PID with impaired antibody production.
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL) in whom prophylactic antibiotics have failed or are contra-indicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients.
- Hypogammaglobulinaemia in patients pre- and post- allogeneic HSCT.

The dose may need to be individualized for each patient dependent on the pharmacokinetic and clinical response. The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/L and aim to be within the reference interval of serum IgG for age.

A loading dose of at least 0.2 to 0.5 g/kg (1 to 2.5 mL/kg) body weight may be required. This may need to be divided over several days, with a maximal daily dose of 0.1 to 0.15 g/kg body weight. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals, approximately once per week, to reach a cumulative monthly dose of the order of 0.4 - 0.8 g/kg body weight. Administration of Xembify® can be done with flexibility - weekly, biweekly or more frequently (2-7 times per week) – with the same total weekly dose.

Xembify® supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against bacterial, viral, parasitic, and mycoplasmal agents and their toxins.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Therefore, adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range.

The introduction of Xembify® may ensure that patients are not left untreated in case of decreased supply of Ig products in Norway. This is key as the emergence of potentially transmissible infections threatens donor availability and can interrupt the supply, which has been evidenced by the COVID-19 pandemic. Additionally, the use of Igs tripled between the years 2004 and 2018 and it is predicted to increase 5-7% annually until 2024, which will further increase the demand for plasma donations and could cause Ig shortages. Therefore, there is a need for additional Ig replacement therapies to enter the Norwegian market.

3. Brief description of current standard of care (SOC) (Which health technology (ies) are currently used. What is the status of the technology (ies)? Whether it provides curative treatment, life extension, etc.)
Will the proposed technology replace or be a supplement to today's SOC?

Immunodeficiency disorders are chronic and usually require lifelong treatment. There are currently no national professional guidelines for the treatment of primary immunodeficiency published by the Directorate of Health. However, the Norwegian Immunodeficiency Association has published guidelines for investigation, follow-up and treatment of primary immunodeficiency (published 01.10.2015).

Severe immunodeficiency, if diagnosed early, can be cured with a bone marrow transplant. Alternatively, or in addition to stem cell transplantation, symptomatic treatment is given with the objective of preventing and treating infections and progressive lung disease. This preventive treatment consists of intravenous or subcutaneous replacement therapy with IgG.

In patients with CLL or multiple myeloma with hypogammaglobulinemia and recurrent serious bacterial infections, replacement therapy with immunoglobulin is also recommended.

There are currently three subcutaneously administered products in the Norwegian market that are indicated for this replacement therapy and that are considered equivalent in terms of efficacy by Sykehusinnkjøp. These products are Gammanorm, Hizentra and HyQvia.

Xembify® could replace these three products.

4. This proposal concerns:

	Yes	No
A brand new and innovative health technology	☒	☐
A new application, or a new indication for an established method	☐	☒
A comparison between several methods	☐	☒
A technology that is already in use	☐	☒
If yes – technology used in clinical practice	☐	☐
If yes – technology used in research/clinical trials	☐	☐
A re-evaluation of technology used in clinical practice	☐	☒
The technology is relevant for disinvestment	☐	☒

There are currently at least three subcutaneously administered products indicated for replacement therapy in patients with abnormally low IgG in the Norwegian market: Gammanorm, Hizentra and HyQvia. Xembify® constitutes a new health technology for subcutaneous replacement therapy.

5. This health technology involves (Multiple ticks are possible)

Pharmaceutical	☒
Medical device/IVD medical device that is CE-marked*	☐

"*If the technology is CE-marked: What is it CE- marked as and for which indication? Please describe"

Medical device/IVD medical device that is not CE-marked	☐
Procedure	☐
Screening	☐
Highly specialized services / national offers	☐
Organization of the health services	☐
Other (describe)	☐

"If relevant, please include who should be responsible for developing the technology."

6. Application of the technology:

Prevention	☐
Assessment and diagnostics	☐
Treatment	☒
Rehabilitation	☐
Specialist health care	☒
Primary health care	☐

Xembify® supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against bacterial, viral, parasitic, and mycoplasmal agents and their toxins. The aim of subcutaneous replacement therapy with Xembify® is to normalize low levels of IgG in patients with PID or hypogammaglobulinemia and to prevent and treat infections.

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

7. Responsibility for funding

	Yes	No
Is the specialized health service responsible for financing the technology today?	☐	☒
May the specialized health service become responsible for funding the health technology?	☒	☐

If the Decision Forum (Beslutningsforum) decides that Xembify® should be introduced for replacement therapy in patients with primary immunodeficiency disorders or hypogammaglobulinemia, the specialized health service would be responsible for funding.

8. Is the technology mentioned in the national guidelines or action programs prepared by the Norwegian Directorate of Health?

Yes	No
☐	☒

There are currently no national professional guidelines for the treatment of primary immunodeficiency published by the Directorate of Health. However, the Norwegian Immunodeficiency Association has published guidelines for investigation, follow-up and treatment of primary immunodeficiency (published 01.10.2015).

9. Does the technology involve the use of radiation (ionizing/ non- ionizing)?

Yes	No
☐	☒

"Give a short description of type of radiation source, device and degree of radiation exposure"

10. Which discipline(s) does the health technology apply to, and which patients are affected? (Could the health technology also affect other groups (e.g. health personnel or relatives)?)

Xembify® is indicated for Immunoglobluin replacement therapy in adults, children, and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia in whom prophylactic antibiotics have failed or are contra-indicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma patients.
- Hypogammaglobulinaemia in patients pre- and post- allogeneic haematopoietic stem cell transplantation.

11. Which aspects are relevant to the assessment? (Multiple ticks are possible)

Clinical efficacy	☒
Safety/adverse effects	☒
Costs/resource use	☒
Cost-effectiveness	☐
Organizational consequences	☐
Ethical	☐
Legal	☐

12. Please suggest the main scope/objective for the health technology assessment, as well as secondary scopes/objectives (in compliance with question 10). For those familiar with "PICO" (Patient, Intervention, Comparator, Outcome) – please include tentative suggestions for PICO.

P: adults, children, and adolescents (0-18 years) with primary immunodeficiency syndrome (PID) or with hypogammaglobulinemia in need of replacement therapy.

I: Xembify® human normal immunoglobulin 200 mg/mL solution for subcutaneous injection.

C: Human normal immunoglobulins HyQvia 100 mg/ml, Gammanorm 165 mg/ml, Hizentra 200 mg/ml.

O: Decrease and reduction in mean annualised serious bacterial infection (SBI) rate, infections of any kind, hospitalizations, days on antibiotics, days of abscence from work/school missed in a year due to infection or treatment. Xembify® will represent a vaiable alternative to the availabe Immonuglobulin replacement therapies in Norway.

13. Please give a brief explanation of why it is important that the health technology assessment proposed should be conducted.

Immunoglobulin replacement therapy represents an essential, lifesaving and usually lifelong treatment for patients with primary immunodeficiency syndrome. Moreover, treatment with Immunoglobulin is associated with a significant reduction of infection risk in patients with haematological malignancies and hematopoietic stem cell transplants recipients who develop secondary immunodeficiency. Therefore, the consequences of not initiating or discontinuing treatment may be severe. Moreover, as the production of Immunoglobulin products relies on donated plasma, these treatments are susceptible to shortages, which increases the risk of patients left untreated.

14. Please comment on the technology that is proposed to be assessed with regard to the following points:

The severity of the disease/condition the health technology targets

Primary immunodeficiency syndrome (congenital immunodeficiency) is a collective term for several rare diseases with failures in various parts of the immune system. Many of the immunodeficiency diseases are hereditary, and the clinical spectrum of the diseases ranges from very serious congenital disease to mild forms that can appear in adulthood. Patients with immunodeficiency often get frequent bacterial infections that can be serious or life-threatening, or infections with microbes that normally do not cause illness, highly impacting the quality of life of the patients.

Expected effect

The primary effifcacy endpoints evaluted in the pivotal clinical trial GTI1503 show a mean annualised SBI rate of 0.016 overall during the subcutaneous phase. The rate of SBI per person per year was 0.017 (2-sided 98% CI: 0.006-0.036). The rate of SBIs per person per year in the overall SCIg20% Treatment phase was 0.017 (1-sided 99% upper CL of 0.036).

Across age categories, in the ≤16 years age group, the rate of SBI per person per year was 0.037 (2-sided 98% CI: 0.009-0.096). In the >16 years age group, the rate of SBI per person per year was 0. The primary efficacy endpoint was thus met.

Additionally, only 1 paediatric subject, who had one event of pneumoniae treated in the outpatient setting with oral antibiotics, was diagnosed as an SBI in stage 2 of the study. This SBI was not considered by the investigator, to be related to the study drug.

Moreover, human normal immunoglobulin contains the IgG antibodies present in the normal population and it has a distribution of IgG subclasses closely proportional to that in native human plasma. Therefore, adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range.

Safety

The safety results from the studies used to assess the safety and effifcacy profile of Xembify®, GTI1503 and GTI1502, show that the administration of SCIg 20% was both safe and well-tolerated in the populations included in both studies. The majority (97%) of the adverse events observed were mild to moderate in severity, and only 7 unrelated, treatment-emergent serious adverse events in 7 subjects were reported in Study GTI1503.

Total number of patients in Norway the health technology is applicable to

It is estimated that around 600 people in Norway have primary immunodeficiency diseases. Number of patients with hypogammaglobulinemia in need of replacement therapy is more difficult to determine since the condition can have many different causes. According to the Norwegian Prescription Database, 850 and 943 patients were prescribed subcutaneous human normal immunoglobulin in 2019 and 2020 respectively.

Consequences for resource use in the public health service

By increasing the response of the immune system in patients affected by PID or SID syndromes, they are less likely to end up in hospital or suffer from disease that will require treatment. Therefore, it is reasonable to not expect an increase in resource use for the public health service.

Need for revision of existing national guidelines or preparation of new guidelines

No need for review of the current guidelines, Ig replacement therapy is already in use in Norway

15. Please provide references to documentation of the health technology's effect and safety (i.e. previous technology assessments). (Up to 10 key references can be provided, please do not send attachments in this step of the process):

1. Santamaria, M., et al., A Multi-Center, Open-Label, Single-Arm Trial to Evaluate the Efficacy, Pharmacokinetics, and Safety and Tolerability of IGSC 20% in Subjects with Primary Immunodeficiency. J Clin Immunol, 2022.

2. Sleasman, J.W., et al., *Immune globulin subcutaneous, human–klhw 20% for primary humoral immunodeficiency: an open-label, Phase III study.* Immunotherapy, 2019. 11(16): p. 1371-1386.

16. Please provide the name of the marketing authorization holder/manufacturer/supplier of the health technology (if applicable/available):

Grifols Nordic AB is responsible for the sales of Grifols products in the Nordic countries. In this case Xembify®, with the market authorization holder Instituto Grifols S.A.

17. Marketing Authorization Status (MA) or CE-marking: When is MA or CE- marking expected? If possible, provide the time of planned marketing:

Approval process ongoing.

18. Additional relevant information (up to 300 words.)

The clinical development program for Xembify® included two Phase 3 studies, Study GTI1503 and Study GTI1502. Overall, data from the pivotal study GTI1503 established the efficacy of Xembify® in preventing serious bacterial infection (SBI) in subjects with PIDs. The primary endpoint was the rate of SBIs per person per year. The primary endpoint of Study GTI1502 was pharmacokinetics and the efficacy in terms of serious infections per year was a secondary endpoint. The results for prevention of SBIs in GTI1502 were comparable to those observed in GTI1503.

Patients eligible for treatment with Xembify® are expected to correspond to the patient population that is currently receiving subcutaneous (SC) immunoglobulin (SCIg) - replacement therapy (SCIgRT) in Norway. In line with previous NoMA assessment for SCIgRTs (Cutaquig), the most cost-effective treatment alternatives in comparable doses and packaging sizes are Cuvitru or Hizentra as they contain the same active substance in the same strength (the same concentration of immunoglobulin, 200mg/ml).

Based on a naïve treatment comparison of efficacy and safety, Xembify® is clinically equivalent to other Ig replacement therapies (IgRTs), therefore it could represent a more suitable and sustainable alternative in the cost profile.

In conclusion, Xembify® is a new, valuable addition for the treatment of PIDs and some forms of SID (hypogammaglobulinemia in CLL, MM and HSCT) that is clinically equivalent in terms of efficacy and safety and cost neutral to other SCIgs and should therefore be included in the Norwegian reimbursement scheme.

19. Interests and potential conflicts of interests

Please describe the proposer's relationships or activities that may affect, be influenced by, or be perceived by others to be important for further management of the health technology that is proposed assessed. (E.g. proposer has financial interests in the matter. Proposer has or has had assignments in connection with the technology or to other actors with interest in the technology)

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