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)**:**

Takeda AS

Name of proposal contact:

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Date and locality:

Oslo, 06 March 2023

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

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

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

Human normal immunoglobulin (SCIG) Cuvitru as replacement therapy in adults, and 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 (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 haematopoietic stem cell transplantation (HSCT). <u>Posology:</u> The dose and dose regimen is dependent on the indication. In replacement therapy the dose may need to be individualised for each patient to 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. 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 0.3 to 1.0 g/kg . Each single dose may need to be injected at different anatomic sites. Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher trough levels.

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.

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 IG products in the Norwegian market that are indicated for this replacement therapy. Cuvitru, Hizentra and Hyqvia. Hizentra and HyQvia are listed in the LIS 2022 tender. Once approved, Cuvitru will be eligible for inclusion in the upcoming LIS tender and can be used instead of either of those two products. Another SCIG, Xembify, is undergoing a Nye Metoder evaluation for the same indication (ID2022_141).

4. This proposal concerns:

	Yes	No
A brand new and innovative health technology	☐	☒
Anew 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	☐	☒

"Please include further details about any use of the technology"

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	☐

"Please give a description here"

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?	☒	☐

"Please give a further description of responsibility for funding"

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

Yes	No
☐	☒

"Give more details about the relevant national guidelines or action programs."

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)?)

Cuvistru is indicated as replacement therapy in adults, and 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 (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 haematopoietic stem cell transplantation (HSCT).

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

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.

We suggested a price note prepared by LIS as SCIGs are subject to LIS national hospital tender. Please see Bestillerforum's decision on Xembify ID2022_141, which is another SCIG with the same indication.

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

A Nye Metoder evaluation is required to allow Cuvitru to participate in the LIS hospital tender for SCIGs. There is a global shortage of plasma-derived products and availability of Cuvitru will provide another option for Norwegian patients and physicians.

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

IG 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.

Expected effect

Efficacy, safety and PK of Novel Human Immune Globulin Subcutaneous 20 % were evaluated in two pivotal trials (Suez et al, 2016 and Borte et al, 2016). The primary efficacy assessment was the annualized rate of validated acute serious bacterial infections (VASBI). The rate of validated serious bacterial infections was 0.012 event/patient-year ($p < 0.0001$ compared with the historical control) and 0.022/patient-year ($P < 0.0001$), and the annualized rate of all infection was 2.41 events/patient and 4.38 events/patient, respectively.

Safety

The safety of Cuvitru administered subcutaneously was evaluated in two prospective, open-label, non-controlled, multi-centre studies in 122 subjects with primary immune deficiency and showed that show that the administration of Cuvitru was both safe and well tolerated with the majority (98.8%) of local adverse reactions were mild in intensity. One subject discontinued treatment due to a local AR (pain).

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 expected to be higher and Cuvitru will be instead of Hizentra, which is already an established treatment in these populations.

Consequences for resource use in the public health service

Cuvitru provides an additional effective and well tolerated option to Norwegian patients and clinicians. Cuvitru will participate in the LIS tender and will replace currently used SCIGs, Hizentra and Hyqvia.

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

N/A. IG replacement therapy is already established 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):

Borte M, et al. Clinical and Experimental Immunology (2016) 187: 146–159

Suez D, et al. J Clin Immunol (2016) 36:700–712

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

Baxalta Innovations GmbH Industriestrasse 67 1221 Vienna Østerrike

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

Norwegian marketing authorization was granted on 01.07.2016

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

"Click in the field and type"

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)

Takeda AS is responsible for the sales of Cuvitru in Norway.