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)**:**

CSL Behring AB

Name of proposal contact:

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Erik.ahlzen@cslbehring.com

Date and locality:

2022-09-05, Stockholm

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

Respreeza for maintenance treatment to slow the progression of emphysema in patients with alpha1-proteinase inhibitor deficiency (AATD).

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

Respreeza is approved by EMA since 20 Aug 2015 with the indication maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha1-proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second 3 (FEV1) predicted, impaired walking capacity or increased number of exacerbations).

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?

Respreeza supplements best supportive care; bronchodilators and corticosteroids and oxygen therapy in late stage disease. This SoC is only symptomatic and limited to short-term benefits and do not address the underlying cause of disease. Lung transplantation may be considered as an end-stage therapy, although it is not a viable option for many patients and suitable lung donors may be difficult to find. Still, international registry data suggest AATD patients currently comprise 5% of the lung transplant population. Respreeza is the only AATD therapy with proven disease-modifying activity, delaying the progression of emphysema due to severe AATD by slowing breakdown of lung tissue.

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	☐	☐

Alpha-1 antitrypsin therapy (Respreeza) is not yet introduced in Norwegian clinical practice.

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	☐

Respreeza is the only AATD therapy with proven disease-modifying activity, delaying the progression of emphysema due to severe AATD by slowing breakdown of lung tissue.

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?	☐	☐

Respreeza is contracted by Sykehusinnkjøp as "basislegemiddel" following the LIS tender *LIS2201a-c:* https://sykehusinnkjop.no/avtaler-legemidler/basislegemidler.

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

Yes	No
☐	☒

There are no Norwegian, national treatment guidelines published on the management of AATD. AATD may be included in a subsection of COPD treatment guidelines in the future.

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)?)

Pulmonology. The treatment is intended for patients diagnosed with severe AATD that show evidence of progressive lung disease.

AATD is a rare, genetic condition characterised by low serum levels of alpha-1 proteinase inhibitor. Patients with severe AATD have less protection against the effects of neutrophil elastase, leading to progressive loss of lung tissue

Emphysema due to severe AATD is associated with a high disease burden due to loss of lung tissue, progressive disability and increased mortality.

Progressive disability and work incapacity associated with emphysema due to severe AATD has a significant impact not only on patients but also on their carers and family members.

Respreeza is the only AATD therapy with proven disease-modifying activity, delaying the progression of emphysema. Early treatment is important in order to delay irreversible loss of lung tissue and disease progression to terminal respiratory failure and/or the need for lung transplantation. Delaying disease progression may decrease the number of AATD patients in need for care at lung transplant units.

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.

Patient: Patients with severe AATD deficiency showing evidence of progressive lung disease.
Intervention: Respreeza, 60 mg/kg body weight, once weekly, in addition to best supportive care as maintenance therapy.
Comparator: Established clinical management.
Outcome: Delayed disease progression (breakdown of lung tissue).

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

Treatment available in Norway today for patients with severe AATD is only symptomatic and does not address the underlying cause of disease.

By delaying disease progression through irreversible loss of lung tissue, treatment with Respreeza may improve organ availability in other patient groups in need of lung transplantation (eg. COPD, interstitial lung disease and cystic fibrosis).

In January 2020 the Danish Medicines Council recommended Respreeza as standard treatment in Denmark. Since then approximately 80-100 Danish ATTD patients have stated treatment. It is of importance to assess how Norwegian patients could have equal access to Respreeza as a proven disease-modifying therapy.

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

Severe AATD is associated with a high disease burden due to loss of lung tissue, progressive disability and increased mortality.

Expected effect

Respreeza is the only AATD therapy with statistically significant efficacy (delaying the progression of emphysema due to severe AATD by slowing breakdown of lung tissue) demonstrated in the largest randomised clinical trial to date.

Safety

Respreeza has demonstrated long-term tolerability similar to placebo over a four-year study period (RAPID RCT/ RAPID OLE trials).

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

An estimated number of 50-100 patients may be treated in Norway based on prevalence numbers, based on relevant clinical experience from neighboring Nordic countries.

Consequences for resource use in the public health service

By delaying disease progression through irreversible loss of lung tissue, treatment with Respreeza may improve organ availability in other patient groups in need of lung transplantation (eg. COPD, Interstitial lung disease and cystic fibrosis).

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

There are no national treatment guidelines on AATD published in Norway to date. A subsection for AATD may be suitable within the National COPD treatment guidelines.

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. Respreeza SmPC, Dec 2021, EMA
2. Chapman, K. R., Burdon, J. G. W., Piitulainen, E., Sandhaus, R. a, Seersholm, N., Stocks, J. M., … McElvaney, N. G. (2015). Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. The Lancet, 386(9991), 360–368. https://doi.org/10.1016/S0140-6736(15)60860-1
3. McElvaney, N. G., Burdon, J., Holmes, M., Glanville, A., Wark, P. A. B., Thompson, P. J., … Chapman, K. R. (2017). Long-term efficacy and safety of α1 proteinase inhibitor treatment for emphysema caused by severe α1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE). The Lancet Respiratory Medicine, 5(1), 51–60. https://doi.org/10.1016/S2213-2600(16)30430-1
4. Miravitlles, M., Dirksen, A., Ferrarotti, I., Koblizek, V., Lange, P., Mahadeva, R., … Stockley, R. A. (2017). European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α 1 -antitrypsin deficiency. European Respiratory Journal, 50(5), 1700610. https://doi.org/10.1183/13993003.00610-2017
5. Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Lung And Heart-Lung Transplantation Report-2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant. 2017 Oct;36(10):1047-1059. https://doi.org/10.1016/j.healun.2017.07.016

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

CSL Behring GmbH

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

Date of first authorisation: 20 August 2015 (EMA).

Respreeza is marketed in Norway.

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

The RAPID study investigated the effect of Respreeza on the progression of emphysema, assessed by lung density decline measured by computer tomography (CT). This endpoint was suggested by clinical experts and regulatory agencies as the most appropriate measure of progression in AATD. The RAPID trial was not powered to detect differences in the secondary endpoints including forced expiratory volume (FEV_1) and quality of life (QoL), outcomes previously used in cost-utility analyses (CUA) with large interindividual variations. Powering estimates for FEV_1 would require >1000 subjects whereas only 180 AATD subjects were identified and recruited to RAPID.

CSL have explored the feasibility of performing a CUA in order to facilitate the assessment process in Norway and while the RAPID study provides AATD-specific and disease relevant outcomes, they are not suitable for health economic modelling due to the limited clinical data available because of the rarity of the disease. Since AATD is a rare and under-diagnosed condition, CSL expects few patients in Norway to be eligible for treatment. However, the positive impact on the healthcare system can be significant as Respreeza is a disease modifying treatment that effectively slows the irreversible loss of lung tissue potentially leading to improved long-term survival and therefore reductions in lung transplantations.

Respreeza is licensed for patient self-administration, which is expected to reduce the burden in the hospital sector, leading to budget savings, and contributing to increased patient autonomy over their own disease management and a reduction in workplace absence.

In conclusion, the RAPID trial demonstrates the effectiveness of Respreeza for patients with AATD. There is additional unquantifiable value for the individual patient, the healthcare system, and Norwegian society as a whole following the introduction of Respreeza that are not translatable to health economic specific outcomes. CSL therefore requests that the SLV consider evaluating Respreeza under track D.

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)

CSL Behring is market authorization holder of Respreeza in Norway.