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)**:**

AMRYT PHARMACEUTICALS DAC

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Date and locality:

Dublin, 12/10/2018

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

Lojuxta (lomitapide) for adult patients with homozygous familial hypercholesterolemia (HoFH)

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

An oral lipid lowering capsule that is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

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?

Current standard of care includes lifestyle management, lipid lowering agents including statins, ezetimibe, bile acid sequestrants, PCSK9 inhibitors and lipoprotein apheresis (LA), a procedure similar to dialysis. However even with these lipid lowering agents and weekly apheresis, few patients achieve the European Atherosclerosis Society (EAS) recommended target levels and as a result cardiovascular (CV) disease continues to progress. The life expectancy of a patient with HoFH is still significantly reduced versus the normal population with a mean age of survival of 45 - 48 years (calculated from an HoFH model), the survival deficit is a mean 33 - 36 years. Lojuxta is indicated as an adjunctive therapy in adult patients with HoFH. On achievement of EAS LDL-C targets with lomitapide, the treating physician may consider a reduction or removal of PCSK9 inhibitors and / or apheresis.

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	☐	☒

Not applicable (NA)

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

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

NA

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

NA

6. Application of the technology:

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

Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein apheresis (LA) in adult patients with homozygous familial hypercholesterolaemia (HoFH).

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?	☒	☐

There are 11 known HoFH patients in Norway. There are unlikely to be many more. One patient is currently on treatment with Lojuxta in Norway, financed according to an individual application to HELFO. Clinicians consider 3-4 more patients to be potential candidates for treatment with Lojuxta.

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

Yes	No
☐	☒

Oslo University Hospital (OUS) has guidelines: “Veileder for utredning og behandling av familiær hyperkolesterolemi (FH) i primærhelsetjenesten». These guidelines are primarily for heterozygous familial hypercholesterolaemia (HeFH).

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

Yes	No
☐	☒

NA

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)?)

Diagnosis of Homozygous FH is established at OUS Lipidklinikken. Treatment guidelines set by OUS and EAS are followed in regional lipiklinikken.

Physicians involved in homozygous FH management: lipidologists, endocrinologists, internal medicine, cardiologists, nephrologists, dieticians etc.

There are 11 homozygous FH patients diagnosed in Norway.

The technology does not affect other groups.

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.

Patients: 11 patients with homozygous familial hypercholesterolemia

Intervention: Lojuxta (lomitapide) Capsules

Comparison: Lojuxta was approved with a single open label study. Despite the lack of head to head data, lipoprotein apheresis is the most relevant economic comparator.

Outcome: Achievement of EAS recommended LDL-C targets, reduction in apheresis, prevention of Cardiovascular Events.

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

Due to the underlying genetic mutations in HoFH patients, current medications have lower levels of effectiveness in HoFH than in HeFH or a normal dyslipidaemic patient population. In about 50% of HoFH patients, these therapies will be ineffective in enabling HoFH patients achieve EAS recommended LDL-C target levels. As a result, these patients are at high risk of cardiovascular disease and premature death, as documented in the publication by Graesdal et al. In Norway there are a total of 3-4 patients who are not adequately treated despite current standard of care and treating physicians wish to prescribe lomitapide but are not able to because of the current reimbursement rules.

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

HoFH is a very rare, severe, inherited form of hypercholesterolaemia that begins in utero and causes premature atherosclerosis, progressive cardiovascular disease and premature death.

Expected effect

The aim of treatment is to lower LDL-C levels towards levels seen in normal individuals, to slow or prevent the progression of cardiovascular disease in this high-risk patient population and to reduce or eliminate the burden of apheresis on patients.

Safety

Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The long term consequences of hepatic steatosis associated with Lojuxta treatment are unknown. The most common adverse reactions are gastrointestinal effects such as diarrhoea, nausea, dyspepsia and vomiting.

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

5 eligible patients according to Lipidklinikken at OUS.

Consequences for resource use in the public health service

Use of lomitapide will likely reduce the resources needed for costly and time intensive lipoprotein apheresis with each procedure taking 3-4 hours per week. Up to 80% of patients stop apheresis or reduce the frequency of the procedure following treatment with lomitapide.

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

No

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):

Blom D J, Averna M R, Meagher E A, et al. (2017) Long-Term Efficacy and Safety of the Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide in Patients With Homozygous Familial Hypercholesterolaemia. Circulation 136, 332-335

Blom et al. (2018) Target achievement and cardiovascular event rates with Lomitapide in homozygous Familial Hypercholesterolaemia. Orphanet Journal of Rare Diseases (2018) 13:96. https://doi.org/10.1186/s13023-018-0841-3.

Bruckert E, Kalmykova O, Bittar R et al. (2017) Long-term outcome in 53 patients with homozygous familial hypercholesterolaemia in a single centre in France. Atherosclerosis 257, 130-137

Cuchel M, Blom DJ, Averna MR et al (2013) Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 381, 40-6

Cuchel et al. (2014) Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society Eur Heart Journal 2014; doi:10.1093/eurheartj/ehu274

D'Erasmo L, Cefalu A B, Noto D, et al. (2017) Efficacy of Lomitapide in the Treatment of Familial Homozygous Hypercholesterolaemia: Results of a Real-World Clinical Experience in Italy. Advances in Therapy 34, 1200-1210

Graesdal A, Bogsrud MP, Holven KB, et al. (2012) Apheresis in homozygous familial hypercholesterolemia: the results of a follow-up of all Norwegian patients with homozygous familial hypercholesterolemia. Journal of clinical lipidology. Jul-Aug 2012;6(4):331-339.

Leipold R, Raal F, Ishak J, Hovingh K, Phillips H (2017) The effect of lomitapide on cardiovascular outcome measures in homozygous familial hypercholesterolemia; a modelling analysis. European Journal of Preventative Cardiology.

Stefanutti et al. (2016) Management of homozygous familial hypercholesterolaemia in real-world clinical practice: a report of seven Italian patients treated in Rome with lomitapide and lipoprotein apheresis, J Clin Lipidol 2016, doi: 0.1016/j.jacl.2016.02.009.

Thompson GR., Dirk J et al. (2018) Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol. European Heart Journal, 2018 Apr 7;39(14):1162-1168.

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

AMRYT PHARMACEUTICALS DAC

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

Lojuxta is EMA approved since 07/2013

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

HoFH has an estimated prevalence of 3 per million population when genetically diagnosed or 1-1.5 per million when clinically and genetically diagnosed. The underlying genetic mutations in HoFH mean that the LDL receptor (LDL-R) pathway is either non-functional (negative, <2% activity) or is defective (2-30% activity). Statins and PCSK9 inhibitors work through up-regulating the LDL-R and hence these therapies have lower levels of effectiveness in HoFH than in other patient populations. Lomitapide (Lojuxta) inhibits the Microsomal Triglyceride Transfer Protein, resulting in a reduction in LDL-C production in the liver and absorption from the intestine and thereby in circulating LDL-C plasma levels. Unlike other lipid lowering therapies this activity is independent of the LDL receptor. Despite current standard of care, many patients fail to achieve the EAS recommended target levels and as a result, cardiovascular disease continues to progress (Graesdal et al). Lojuxta is therefore considered a suitable therapy for: • Patients with receptor negative mutations • Patients who do not respond sufficiently to standard of care, to achieve the EAS recommended LDL-C target levels. Based on the available data ~30% patients diagnosed with HoFH will have receptor negative mutations and about 50% of remaining HoFH patients may require additional therapy on top of standard of care including PCSK9 inhibitors. It is well established in the scientific literature that the aim of therapy in HoFH patients is to achieve EAS recommended LDL-C targets. With newer therapies, such as lomitapide, LDL-C target levels are achievable in HoFH patients with up to 70% patients achieving a target < 2.5 mmol/L. Modelling data shows that additional LDL-C lowering by lomitapide of 38% may increase life expectancy by median 11.2 years and delay the time to first major adverse cardiovascular event by median 5.7 years (formal outcomes studies are not possible due to the rarity of HoFH).

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)

NA