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)**:**

Pierre Fabre Pharma Norden AB

Name of proposal contact:

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Date and locality:

2019.05.15, Reading, England

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

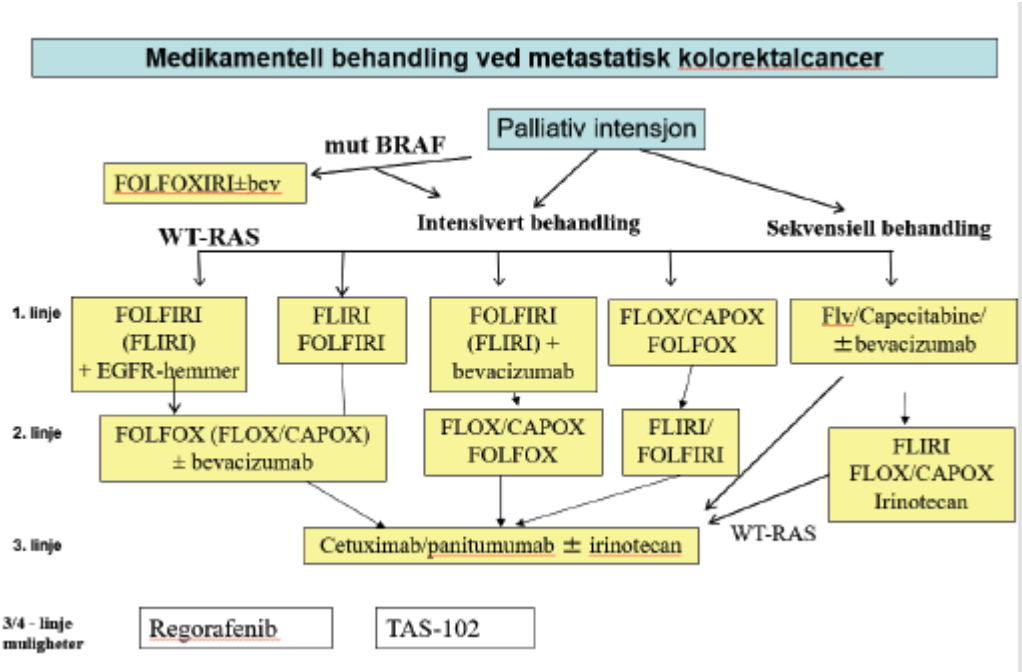
Encorafenib and binimetinib in combination with cetuximab (triple therapy) for the treatment of adult patients with BRAF V600E mCRC

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

The technology is a triplet combination of encorafenib, a BRAF inhibitor, binimetinib, a MEK inhibitor and cetuximab, an anti-EGFR antibody. Pierre Fabre expect to submit for EMA approval in Q3/Q4 2019 for the treatment in patients with BRAF V600E-mutant metastatic colorectal cancer (CRC) whose disease has progressed after one or two prior regimens. Dosing: Oral encorafenib 300 mg daily + oral binimetinib 45 mg twice daily, plus standard weekly cetuximab.

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?

According to "Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft i tykktarm og endetarm" the SOC in BRAF-mutant metastatic colorectal cancer whose disease has progressed after one or two prior regimens depends on the regimes given in earlier lines as presented in this flow-chart:



If approved, the technology is expected to replace the current SOC (one of: FOLFIRI; FLOX/CAPOX; FOLFOX+/-bevacizumab; Cetuximab/Panitumumab+/-irinotecan) in patients with BRAF-mutant metastatic colorectal cancer whose disease has progressed after one or two prior regimens. However, it will be a supplement to cetuximab which is currently used.

Current treatment options for BRAF V600E-mutant metastatic CRC patients are limited. Encorafenib in combination with binimetinib (and cetuximab) is one of the first treatment regimens to target these patients who have a mortality risk more than double than of metastatic patients without the mutation. It is also one of the first combinations to target the BRAF and MEK pathway and also has the advantage that both encorafenib and binimetinib are taken orally rather than intravenously.

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	☐	☒

N/A

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

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

N/A

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

N/A

6. Application of the technology:

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

Encorafenib abd binimetinib can be self-administated orally at home. Cetuximab may be given through intravenous infusion.

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?	☒	☐

We assume that the specialized health service will have the responsibility for funding binimetinib and encorafenib in line with other drugs for treatment of metastatic colorectal cancer.

Cetuximab is already used and financed by the specialized health service.

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

Yes	No
☐	☒

IS-2790: Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft i tykktarm og endetarm

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

Yes	No
☐	☒

N/A

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)?)

Treatment area: Oncology. Patients with BRAF-mutant metastatic colorectal cancer whose disease has progressed after one or two prior regimens.

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.

Decision problem: Is the triplet combination of encorafenib, binimetinib and cetuximab a cost-effective treatment option that should be funded by the specialized health service?

P: Patients with BRAF-mutant metastatic colorectal cancer whose disease has progressed after one or two prior regimens

I: Triplet combination of encorafenib, binimetinib and cetuximab

C: We currently expect, depending on the line of treatment and the previous treatment: FOLFOX+/-bevacizumab; Cetuximab/Panitumumab+/-irinotecan (see question 3)

O: Cost and resource usage, QALYs gained, Cost per QALY gained, Overall survival, Objective response rate, Progression free survival and Quality of life.

A cost-effectiveness model is expected to be a relevant method to investigate the decision problem.

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

The OS and PFS are substantially improved over historical data for current standard-of-care options when the technology is used:

After first-line therapy, standard second-line therapies provide limited benefit, with objective response rates (ORRs) < 10%, and median overall survival (OS) of 4.6 months (median OS for all 2L mCRC patients is about 10 months according to IS2790).

BRAF V600E mutation occurs in 10%-15% of patients with mCRC and confers a poor prognosis. These patients may have a mortality risk more than double than of metastatic patients without the mutation.

BEACON CRC (NCT02928224) is a 3-arm phase 3 trial of triplet therapy with encorafenib + binimetinib + cetuximab vs encorafenib + cetuximab vs a control arm (irinotecan/FOLFIRI + cetuximab) in patients with BRAFV600E mCRC in the second or third-line setting. A safety lead-in study of the triplet therapy was conducted in 29 patients prior to initiation of the randomized part of the trial. This showed that the median OS was 15.3 months and an objective response rate of 48%. Primary completion of BEACON CRC is estimated to be in July 2019 and EMA approval is expected Q2/Q3 2020.

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

The expected remaining QALYs for 59-year-olds (median age in BEACON-CRC lead in) is 20.0. (SLV) The 10 months (IS2790) expected from standard second-line therapies imply an absolute shortfall of at least 19.1 QALYs. In practice this shortfall is likely to be greater given the presence of the BRAF V600E mutation.

Expected effect

Median overall survival was 15.3 months in the BEACON safety lead-in study, which can be compared to the ~4-5 months months of expected survival for all CRC patients treated with second line (IS2790).

Analysis of efficacy in the full BEACON-CRC trial is event-driven and results are not yet available.

Safety

In the BEACON CRC safety lead in study, the triple-combination was well-tolerated. Only 1 patient discontinued because of a treatment-related AE (grade 2 fatigue). Common AEs were those associated with BRAF, MEK, and EGFR inhibitors and included gastrointestinal and skin toxicities. Severe skin AEs were observed less frequently in the combination than reported rates for cetuximab monotherapy.

Full details of the safety results in the lead in study are presented here.

Additional safety results will be available for all treatment arms when the results from the BEACON CRC study are published.

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

Assuming CRC incidence of 4887 patients per year, 25-37% metastatic setting and 8-10% BRAFv600 mutation.

It is estimated based on Pierre Fabre research that 50% of this population would be eligible for a first line treatment and of this upto 85% could be eligible for second line treatment with encorafenib, binimetinib and cetuximab. Pierre Fabre estimates the maximum number of eligible patients to be ~100 per annum.

Consequences for resource use in the public health service

Colorectal cancer patients are treated within the specialized health service and introduction of binimetinib and encorafenib is not expected to a have a major impact on the hospital resources. However, as binimetinib and encorafenib are oral treatments, a reduction in the administration costs may be expected. The effect on the pharmaceutical budget will depend on the price of the product and the reduction in comparator treatments.

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

The national guidelines should be updated to include the technology if it is approved by Beslutningsforum.

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):

Van Cutsem E, Huijberts S, Grothey A. et al. Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E–Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study. J Clin Oncol 37. 2019.

Kopetz S, Grothey A, Yaeger R, et al. Updated results of the BEACON CRC safety lead-in: Encorafenib (ENCO) + binimetinib (BINI) + cetuximab (CETUX) for BRAFV600E-mutant metastatic colorectal cancer (mCRC). Presented at: 2019 Gastrointestinal Cancers Symposium; January 17-19; San Francisco, CA. Abstract 688. https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.4_suppl.688

Van Cutsem, E, Cuyle P-J, Huijberts S, et al. BEACON CRC study safety lead-in in patients with BRAF V600E metastatic colorectal cancer. Presented at: 2018 Gastrointestinal Symposium; January 18-20; San Francisco, CA. Abstract 627. https://www.primeoncology.org/app/uploads/prime_activities/50258/2018-gastrointestinal-poster-san-francisco-van-cutsem-prime-oncology1.pdf

https://clinicaltrials.gov/ct2/show/NCT02928224

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

Pierre Fabre Pharma Norden AB

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

EMA submission is expected Q3/Q4 2019. EMA approval expected Q2/Q3 2020. If approved, the regimen is expected to be on the market in this indication in the second half of 2020.

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

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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)

The proposer is Pierre Fabre Pharma Norden AB. Proposer will be the marketing authorization holder of the binimetinib and encorafenib.