**Submission Template   
For Single Technology Assessment of Medicinal Products**

|  |  |  |
| --- | --- | --- |
| **Company** |  | |
| **Medicinal Product** | INN/Brand® | |
| **Relevant therapeutic indication** |  | |
| **IDXXXX\_XX (if the assessment is ordered from Bestillerforum RHF)** |  | |
| **Submission track:** | CUA: | Simplified: |
| **Submission checklist complete** |  | |
| **Company representative** | Name and email address | |
|  | Signature | |
| **Second company contact** | Name and email address | |
| **Date of submission** |  | |

**Version Control**

|  |  |  |
| --- | --- | --- |
| Version | Date | Description of key changes |
| 1.0 | 18/01/2021 | 1. First published version of a submission template by NoMA. |
| 2.0 | XX/XX/2023 | 1. Major revision and restructuring of the submission template together with updated submission guidelines. |

Background and introduction to the submission template

This submission template outlines the content and format of the written submission to the Norwegian Medicines Agency (NoMA)’s as part of single technology assessments (STA). The template and guidance are based on the NoMA’s Submission Guidelines. The template will be updated periodically. Please refer to [legemiddelverket](https://www.legemiddelverket.no/en/public-funding-and-pricing-of-medicines/single-technology-assessments/submission-of-documentation-for-single-technology-assessment-of-pharmaceuticals/unit-cost-database).no to obtain the most recent version of the guidelines and template prior to your submission.

The template is not exhaustive and should be used together with the most recent version of the Guidelines. NoMA generally encourage pre-submission meetings, to offer guidance in identifying and discussing any uncertainties regarding the decision-making process and preparation of the documentation for the STA.

The template must be followed for the compiling and submission of documentation for all STAs of medicinal products that are considered for reimbursement by public authorities. For Health Technology Developers applying for financing through the specialist health services documentation should be submitted in line with the wording of the order from Bestillerforum RHF (an ordering forum consisting of the four medical directors, one for each regional health authority, and two delegates from the Norwegian Directorate of Health). For Health Technology Developers applying for financing under the National Insurance Scheme (“Folketrygden”), documentation should be submitted in line with the order from NoMA.

NoMA is the single contact point for STA submissions.

Prior to final submission, make sure to complete the Submission checklist found on [legemiddelverket.no](https://www.legemiddelverket.no/en/public-funding-and-pricing-of-medicines/single-technology-assessments/submission-of-documentation-for-single-technology-assessment-of-pharmaceuticals/template-for-submission-of-documentation-for-the-single-technology-assessment-of-pharmaceuticals).

In case the predefined headings or subheadings are not relevant for your submission, please keep the main headings and simply state: "not applicable due to..". You may delete the subheadings and bullet points under each heading.

When inserting tables and figures, do not insert them as pictures (jpeg, etc) to the extent that it is possible. If needed, make sure the pictures have a high resolution. This is in order to make NoMA’s reports as accessible as possible to individuals with impaired vision.

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Glossary of terms

|  |  |
| --- | --- |
| Abbreviation | Definition |
|  |  |
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# Background

## Overview

### Intervention

Table 1. Summary table of the intervention

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Medicinal product | *INN, Brand®* | | | | |
| ATC-code |  | | | | |
| Pharmaceutical class |  | | | | |
| Mode of action | *Short description* | | | | |
|  | | For the indication relevant for the submission, state: | | | |
| Indication approved by EMA |  | | | | |
| Posology |  | | | | |
| Route of administration |  | | | | |
| Duration of treatment |  | | | | |
| Conditional approval | Yes: | | No: | If yes, specify: | |
| Does treatment require prior biomarker testing, companion diagnostics etc.? | Yes: | | No: | If yes, specify: | |
|  | Information on the clinical documentation: | | | | |
| Pivotal/main studies for the indication under review | e.g. *OVERVIEW-101*  *NCT10101010* | | | | Current data cut: dd.mm.yyyy  Next data cut: dd.mm.yyyy  Final analysis: dd.mm.yyyy |
| e.g. *OVERVIEW-101 OLE-study*  *NCT10101011* | | | | Current data cut: dd.mm.yyyy  Next data cut: dd.mm.yyyy  Final analysis: dd.mm.yyyy |
| e.g. *OVERVIEW-102*  *NCT10101010* | | | | Current data cut: dd.mm.yyyy  Next data cut: dd.mm.yyyy  Final analysis: dd.mm.yyyy |
| e.g. *OVERVIEW-102 OLE-study*  *NCT10101011* | | | | Current data cut: dd.mm.yyyy  Next data cut: dd.mm.yyyy  Final analysis: dd.mm.yyyy |

### Submitted analysis

Table 2. Summary of the submitted analysis

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Information about the submitted economic analysis: | | | | | | | | | |
| Type of health economic analysis: |
| CUA[[1]](#footnote-2) | | | CMA[[2]](#footnote-3) | | | BIA[[3]](#footnote-4) | | | |
| Type of economic model, if CUA | PSM/AUC: | | | | | | | |  | |
| Markov: | | | | | | | |  | |
| Decision tree: | | | | | | | |  | |
| Micro simulation/individual patient simulation: | | | | | | | |  | |
| Other: | | | | | | | |  | |
| Source of clinical evidence for relative efficacy | Head-to-head clinical study: | | | | | Evidence synthesis: | | | | |
| Brief description of PICO in the health economic analysis | Population:  Intervention:  Comparator:  Outcome: | | | | | | | | | |
|  | If CUA | | If CMA | | | | | | | |
| Result of the economic analysis (using AUP excl. VAT) | Cost pr. QALY: | |  | | | Total cost of intervention: | |  | | |
| Cost pr. LY: | |  | | | Total cost of comparator: | |  | | |
| Result of the economic analysis  (using relevant rebate excl. VAT for product under assessment) | Cost pr. QALY: | |  | | | Total cost of intervention: | |  | | |
| Cost pr. LY: | |  | | | Total cost of comparator: | |  | | |
| Absolute shortfall |  | | | | | | | | | |
|  | Information regarding budget impact analysis: | | | | | | | | | |
| Year 1 | Year 2 | | | Year 3 | | Year 4 | | | Year 5 |
| Total eligible patient population | *100* | *100* | | | *100* | | *100* | | | *100* |
| Patients expected to receive intervention | *20* | *50* | | | *100* | | *100* | | | *100* |
| Result on budget impact  (using AUP incl. VAT) | *200 000* | *500 000* | | | *1 000 000* | | *1 000 000* | | | *1 000 000* |

Table 3. Clinicians and/or key opinion leaders (KOL) contacted for preparation of the submission package.

|  |  |  |
| --- | --- | --- |
| **KOL:** | **Advisory board:** | **Other (specify):** |
| *Name, place of employment* | *Name, place of employment* | *Name, place of employment* |
| *Name, place of employment* | *Name, place of employment* | *Name, place of employment* |

## Description of the disease and patient population

* Provide a brief description of the disease/condition including an overview of natural history of the disease, diagnosis, symptoms, clinical outcomes, causes or risk factors, disease-specific mortality etc.
* Provide a short description of patient characteristics, including age, gender, risk-groups e.g. prognostic factors, in a Norwegian setting.
* Briefly describe any diagnostic tests and methods used for patient selection. Will the new intervention require additional/altered testing compared to today’s clinical practice? Describe.
* Specific characteristics that differentiate between (sub)populations reflected in the assessment scope are to be described here. Provide a rationale for the subgroup selection and indicate whether these groups were pre-defined (and how) in the clinical study(ies).
* Patient numbers are presented in detail and transparently in chapter 5 (Budget impact) in order to avoid repetition.

## Current clinical pathway

* Describe how the disease/condition is currently managed in Norway e.g., available treatments, current standard of care (routine care) and best practice. This should be supported by literature, guidelines and/or input from Norwegian clinical experts.
* Include both licensed and unlicensed therapies where applicable. A figure illustrating treatment/clinical pathway is preferred.
* Summarise Norwegian treatment/disease guidelines if available. Summarise other international guidelines which are followed in Norway and describe any variation in disease management.

## Description of the intervention, anticipated place in the clinical pathway, and subsequent displacement of current treatment

* Describe the intervention.
* Provide information of any current use of the intervention in Norway e.g., as part of a clinical study or early access program, or in an unlicensed capacity, which is relevant for the patient population under assessment.
* State the anticipated place in the clinical pathway of the intervention with respect to other available therapeutic options.
* Describe and explain which treatment(s) would primarily be replaced/displaced by the introduction of the intervention. This should be supported by literature, guidelines and/or input from Norwegian clinical experts. A description of subsequent displacement (e.g., displaced to a later/earlier treatment line, removal from the treatment pathway, etc.) of relevant comparator(s) must also be included.
* Based on the discussion above, justify the choice of comparator(s) for the assessment, in line with requirements outlined in Chapter 3 of the Guidelines.

# Clinical evidence

## Information retrieval

* Identify all studies relevant for the STA in question.
* Published and unpublished pivotal marketing authorisation studies and all other relevant studies, data, analyses, “data on file”, grey literature and other evidence and documents, must be included.
* All clinical efficacy and safety evidence included in the submission must be selected following an information retrieval process including a systematic literature search. The search date of the systematic literature review (SLR) must be no older than six months prior to the date of submission of the STA. See Chapter 5 of the Guidelines for further details and requirements.
* A complete report of the SLR may be submitted as a separate document or as an appendix, but a summary must be provided here and include the following points (minimum):
  + Describe the rationale and objective of the literature search.
  + Describe the methods use, including eligibility criteria (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.), development of a search strategy and search string, databases or registers searched.
  + Describe the results of the SLR, including a PRISMA-chart, list of included studies/publications, number of participants, relevant characteristics of the studies, main outcomes, and summary estimates if relevant.
  + Discuss the limitations of the SLR (e.g., potential bias, narrow search strings or eligibility criteria).
  + Quality assessment using validated tools are required when performing evidence synthesis (presented in 2.3) and encouraged when clinical evidence is from a single study (presented here).
  + List supplementary manual searches if relevant.
* The complete SLR report should follow the PRISMA 2020 Checklist ([ref 1](https://www.bmj.com/content/bmj/372/bmj.n71.full.pdf), [ref 2](https://www.bmj.com/content/bmj/372/bmj.n160.full.pdf)) in docx-format including all tables.

## Clinical efficacy evidence

### Summary of identified studies relevant for establishing relative efficacy

* Summarise the relevant efficacy studies in Table 4. Add or remove sections to/from the table as necessary.
* Relevant studies in this context are studies used to estimate relative efficacy and included in the health economic analysis and include published and unpublished pivotal marketing authorisation studies and all other relevant studies, data, analyses, “data on file”, grey literature and other evidence and documents used in the health economic analyses

Table 4. Summary of clinical studies relevant for establishing relative efficacy

|  |  |  |
| --- | --- | --- |
| <Name of clinical study 1> | | |
| Study ID (NCT number) |  | |
| Study design |  | |
| Study location(s) |  | |
| Population  *important inclusion and exclusion criteria, stratification factors, n* |  | |
| Intervention |  | |
| Comparator |  | |
| Primary endpoint |  | |
| Important secondary endpoint(s) |  | |
| Observation time |  | |
| Data cuts  *primary analysis and later planned analyses* |  | |
| Was the study part of the EMA MA approval process relevant for this STA? | | check if yes |
| **<Name of clinical study 2>** | | |
| Study ID (NCT number) |  | |
| Study design |  | |
| Study location(s) |  | |
| Population  *important inclusion and exclusion criteria, stratification factors, n* |  | |
| Intervention |  | |
| Comparator |  | |
| Primary endpoint |  | |
| Important secondary endpoint(s) |  | |
| Observation time |  | |
| Data cuts  *primary analysis and later planned analyses* |  | |
| Was the study part of the EMA MA approval process relevant for this STA? | | check if yes |

### Summary of relevant supportive studies

* Provide summary of supporting studies of relevance to the decision problem including randomised/non-randomised observational studies, phase IV post-marketing studies etc. in the following table. Add sections to the table if needed (i.e. more than one supportive study).

Table 5. Summary of relevant supportive studies.

|  |  |
| --- | --- |
| <Name of supportive study 1> | |
| Study ID (NCT number) |  |
| Study design |  |
| Study location(s) |  |
| Population  *important inclusion and exclusion criteria, stratification factors, n* |  |
| Intervention |  |
| Comparator |  |
| Primary endpoint |  |
| Key secondary endpoints |  |
| Observation time |  |
| Data cuts  *primary analysis and later planned analyses* |  |
| Was the study part of the EMA MA approval prosses relevant for this STA? |  |

### Clinical study design and analysis

* Describe the relevant study(ies) in further detail, including a detailed description of the study design and methodology, inclusion and exclusion criteria, treatments and concomitant medications, and study endpoints.
* Results of the study(ies) must be presented later in section 3.6.

### Summary of relevant ongoing studies

* Add sections to the table if needed (i.e. more than one relevant ongoing study).

Table 6. Summary of relevant ongoing studies

|  |  |
| --- | --- |
| <Name of relevant ongoing study 1> | |
| Study ID (NCT number) |  |
| Study design |  |
| Study location(s) |  |
| Population  *important inclusion and exclusion criteria, stratification factors, n* |  |
| Intervention |  |
| Comparator |  |
| Primary endpoint |  |
| Key secondary endpoints |  |
| Primary data cut |  |
| Estimated completion date |  |
| Relevance of this study for the decision problem |  |

## Clinical evidence synthesis

* Complete this section if evidence synthesis methods were used to combine multiple sources of evidence to estimate comparative effectiveness and/or safety, e.g. a pairwise meta-analysis, indirect comparison or network meta-analysis.
* Requirements and methods for the documentation of evidence synthesis are described in detail in the Chapter 7 in the Guidelines. The documentation requested below will be based on the literature search presented in chapter 2.1.

### Background

* Context and rationale

### Objective

* Describe the objective of the analysis by defining each of the PICO components (Population, Intervention, Comparator, Outcome) and study design.
* These should correspond to the decision problem in terms of population, intervention, and comparator.

### Methods

* Systematic search methods – SLR (see chapter 2.1 Information retrieval)
* Describe the basic assumption of exchangeability (Guidelines chapter 7.3) with the listed requirements.
* A table outlining the following must be submitted along with an evidence synthesis and the differences between studies discussed:
  + definition of endpoints
  + statistical analysis (including estimand, how intercurrent events and missing data were addressed)
  + dates of the study
  + duration of follow-up
  + reasons for and proportion of censored observations
  + countries covered by the studies, the posology of the comparator
  + types and distributions of a subsequent treatment received in the study, and
  + any other factors that might be different between the studies
* Quality assessment using a validated tool (e.g. ROB2 (ROBINS-I for nonrandomized evidence))
* Describe data synthesis methodology, see specific requirements according to methodology in the Guidelines chapter 7.4.

### Results

* Present results of the evidence synthesis. If multiple methods are used, make sure to highlight results used in later cost-effectiveness analysis.
* Identify and discuss any between-study differences, particularly those which relate to potential prognostic variables and treatment-effect modifying variables.

### Discussion

* Provide discussion on results, internal validity, external validity, assumption of exchangeability, and limitations.

# Health economic analysis – methods and PICO

## Decision problem

* Describe the decision problem the STA is intended to address.

## Model structure and applicability

### Model Structure

* Give a detailed description and justification of the model used to answer the decision problem. This includes, but is not limited to, a model diagram, description of disease states, use of surrogate/intermediate outcomes, etc.
* State the source of clinical data included in the model; data-cut, follow-up time, population (ITT or subgroup etc).
* In general terms, describe and justify how the clinical data was implemented in the model, including how transitions between health states are modelled, sources of transition probabilities, any assumptions made on transitions, treatment effect, discontinuation, etc. For time-to-event data describe here the general approach for fitting parametric curves and extrapolation.
  + Specific model inputs and choices related to each outcome should not be described here, but in the specific sections for the outcome in question.

### Perspective and formalities

Table 7. Perspective and formalities applied in the health economic analysis.

|  |  |  |
| --- | --- | --- |
| Topic | Description | |
| Model type | <brief description, e.g. partitioned survival model> |
| Cycle length | <timeframe, e.g. 2 weeks> |
| Half cycle correction | <performed, yes/no> |
| Discount rates | <refer to guidelines, e.g. 4% for costs and utilities> |
| Utility age adjustment | <e.g. yes, utility adjusted according to guidelines> |
| Perspective | <e.g. health care perspective, limited societal perspective> |
| Time horizon | <e.g. life time, 20 year> |

### Applicability of the model to the decision problem

* Discuss whether the model is appropriate to answer the decision problem.

### Model requirements

* State that NoMA’s model requirements, listed in guidelines 12.2, have been met.

## Population

### Norwegian clinical practice

* Describe the characteristics of the population eligible for treatment with the intervention in a Norwegian setting.
* Consider differences in the prevalent patient population and the incident patient population.

### Clinical documentation

* Describe the baseline characteristics of the population(s) who were recruited in the pivotal study(ies) for the intervention.
* If relative effect estimates are from an indirect comparison, describe the characteristics of the populations who participated in the compared studies for the comparator, and discuss whether there is sufficient overlap in population characteristics, prognostic factors, etc. for a comparison to be valid.
* Describe in text or table form the most important patient characteristics (e.g. effect modifiers (EM) and prognostic factors (PF)) that exert an influence on clinical response.

### Health economic model

* If the modelled population(s) differs from the population described in section 3.3.1 and 3.3.2, provide a complete description of baseline characteristics for the modelled population(s).
* Describe the characteristics of the population(s) implemented in the submitted cost-effectiveness model.
* Describe the characteristics of all submitted subgroups.

### Summary

* Provide a table summarising and comparing the populations from the clinical study(ies), the relevant Norwegian population, and the modelled population, see example below.
* Provide sources/references for each parameter.
* If there is misalignment between populations, deviations must be discussed and justified with respect to transferability of results from the clinical study to the Norwegian setting.

Table 8. Summary and comparison of patient population relevant for the decision problem (including example text).

|  |  |  |  |
| --- | --- | --- | --- |
| Patient characteristics | Expected in Norwegian clinical practice (including reference) | Clinical documentation (including reference) | Health economic model (including reference) |
| BMI | 29 (estimated by Dr. Ola Nordmann) | 32 (clinical study 1) | 32 (clinical study 1) |
| ECOG status | 0-2 (clinical guidelines) | 0-1 (clinical study 1) | 1 (assumed based on xxx) |
| Etc. |  |  |  |

## Intervention

### Norwegian clinical practice

* Describe the intervention and its expected use in a Norwegian setting with reference to the SmPC.

### Clinical documentation

* Describe the intervention as prescribed in the pivotal clinical study(ies).

### Health economic model

* Describe the intervention as used in the model with regards to dosing, relative does intensity (RDI), frequency, etc. and the transferability/generalisability to a Norwegian setting.
* Time-to-treatment discontinuation (TTD) must be described here. State which population is used to calculate TTD.
* Describe and justify parametrisation and extrapolation if this is applied and which criteria guided the choice of model.
* Describe and justify assumptions regarding response/discontinuation rates, waning treatment effects, stopping rules, subsequent treatments, and other relevant factors, that impact results.

### Summary

* Describe / discuss the relevance of any deviations between how the intervention is prescribed in a Norwegian setting and how it was used in the clinical study(ies), e.g., differences in dosing, frequency, route of administration, etc.

Table 9. Summary and comparison of use of the intervention relevant for the decision problem.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics of the intervention | Expected in Norwegian clinical practice (including reference) | Clinical documentation (including reference) | Health economic model (including reference) |
| Posology | 20 mg/day (SPC) | 20 mg/day (study 1) | 20 mg/day (study 1) |
| Duration of treatment |  |  |  |
| Premedication/co-medication |  |  |  |
| Subsequent treatment |  |  |  |
| Other relevant aspects; specify |  |  |  |

## Comparator(s)

### Norwegian clinical practice

* Describe the comparator(s) as used in a Norwegian setting with reference to SmPC.

### Clinical documentation

* Describe the comparator(s) as prescribed in the pivotal clinical study(ies).
* If relative effect estimates are derived from an indirect comparison, describe the comparator(s) in the compared studies, and discuss whether the results are valid when transferred to a Norwegian setting.

### Health economic model

* Describe the comparator(s) as used in the model with regards to dosing, frequency, etc., and the transferability/generalisability to a Norwegian setting.
* Time-to-treatment discontinuation (TTD) must be described here. Describe and justify parametrisation and extrapolation if this is applied and which criteria guided the choice of model.
* Describe and justify assumptions regarding response/discontinuation rates, waning treatment effects, stopping rules, subsequent treatments, and other relevant factors, that impact results.

### Summary

* Describe / discuss the relevance of any deviations between how the comparator(s) is prescribed in a Norwegian setting and in the clinical study(ies)s, e.g. study medication, differences in dosing, frequency, form of administration, etc.

Table 10. Summary and comparison of use of the comparator(s) relevant for the decision problem.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics of the comparator(s) | Expected Norwegian clinical practice (including reference) | Clinical documentation (including reference) | Used in the model (including reference) |
| Posology | 20 mg/day (SPC) | 20 mg/day (study 1) | 20 mg/day (study 1) |
| Duration of treatment |  |  |  |
| Concomitant treatment/ pre-treatment |  |  |  |
| Subsequent treatment |  |  |  |
| Other relevant aspects; specify |  |  |  |

## Clinical outcomes and model inputs

* Describe the clinical outcomes and relative efficacy estimates from relevant clinical studies (refer to 2.2.1 for definition of relevant studies).
* Describe the clinical parameters and variables included in the cost-effectiveness analysis.
* Ideally, the result for each endpoint of the clinical study(ies) should be presented individually, followed by a complete and transparent description of how the outcomes are included in the health economic model. The following chapters must always allow the reviewers an accessible overview of results from clinical study(ies) and subsequent inclusion in the health economic model.

### Relative efficacy

* Follow requirements presented in relevant chapters of the guidelines.
* For each outcome used in the health economic model:
  + Clearly define what data have been used to inform treatment effectiveness outcomes. Specify date of data-cut and population (ITT, mITT, subgroups, etc) for each endpoint. Make sure the population(s) used to estimate treatment effectiveness have been described in chapter 3.3.
  + The effect estimate for the primary study outcome or hard outcomes should be applied in the model.
  + If surrogate outcomes are used, describe how these are linked to final outcomes.
  + If transition probabilities are used, describe the estimation and application of probabilities.
  + Describe the selection and applications of survival analysis techniques (when relevant) and validation of the clinical parameters. Describe and justify parametrisation and extrapolation and which criteria guided the choice of parametric model (such as AIC/BIC, visual fit, hazard plots, clinical plausibility, etc), guidelines chapter 8.
  + If adjustment for treatment switching is applied, see guidelines chapter 9.
  + Discuss uncertainty regarding the estimation and modelling of treatment effects.
  + Validate that the modelled outcomes reflect the study outcomes. Validation of study outcomes should be done prior to any local adaption that may alter outcomes. Discuss the impact and validity of local adaption.
* When external data sources are used:
  + Describe how external data sources have been used to model disease progression. This applies when surrogate outcomes are being used, and when external data is used to inform transition probabilities, background mortality, etc.
  + Selection of external data used to model natural disease progression must be a result of an unbiased systematic literature review.
  + Sources for parameters must be listed and their applicability in Norwegian clinical practice must be discussed and justified.

#### < Outcome one >

##### Study outcome

* Present the efficacy results from the clinical study(ies) for the ITT population.
* In addition, present the results from the clinical study(ies) for any/all populations submitted in the health economic model.

##### Modelling of study outcome (intervention and comparator)

* In 3.2 a general description for the specific analysis in question should be included, therefore the description here should be aligned with 3.2. Describe and justify specific choices related to how this outcome is modelled. Including, but not limited to, parameterisation and extrapolation, assumptions made on transitions, treatment effect, discontinuation, external validation, clinical opinion, etc.

#### < Outcome two, etc. >

##### Study outcome

##### Modelling of study outcome (intervention and comparator)

#### Relevant supportive outcomes not used in the health economic model

* Study outcomes that are not modelled in the cost-effectiveness analysis, but that supports assumptions or claims of clinical benefit may be presented in this section. This could for example be a primary composite outcome where the individual outcomes are modelled separately.

### Safety

* Describe the reported adverse events (AE) included in the health economic model.
* Tabulate the observed incidence rates of AEs in the relevant clinical study(ies), as well as the corresponding values used in the model. Justify the inclusion/exclusion of modelled adverse events.

#### Clinical documentation

* Describe the reported adverse events (AEs) in the clinical evidence for the intervention and comparator.
* Describe how AEs affect treatment discontinuation, interruptions, and dose modification for the intervention and comparator.

#### Health economic model

* Describe the reported AEs included in the health economic model.
* Describe how AEs have been implemented in the health economic model.

### Health-related quality of life (HRQoL)

* Follow requirements presented in guidelines 11.

#### Clinical documentation

* Describe the HRQoL outcomes measured during the clinical development program, describe the methods and results of the analysis. Provide details of all analyses conducted to estimate utility values, including:
  + Number of subjects who responded to the PRO questionnaire (compliance rates by visit and by treatment), including reasons for missing questionnaires, and differences, if any, between non-responders and responders.
  + The choice of statistical model for HRQoL analyses (e.g. regression model), including the full model equation, with a justification of variable selection, and description and justification of the correlation structure.
  + Handling of missing data, including description of patterns, assumptions (missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR)) supported, where possible, with graphical approaches or formal tests for association and methods of imputation.
* If HRQoL was not measured during the clinical development program, provide a description of the systematic literature review that have been carried out to identify relevant studies.

#### Health economic model

* Describe the outcomes captured by the model in terms of the expected health-related outcomes represented by model health states and/or events.
* Tabulate the mean parameter values and ranges used in the model, as well as alternative values gathered. Justify the choice of base case values, including strengths and weaknesses of the possible alternative choices.
* All outcomes that impact patients’ HRQoL should be included. Justify the inclusion or exclusion of selected outcomes in the model.
* Detail and justify all assumptions regarding the application of utility values in the model.
* Describe and justify any adjustments made to utility values, e.g. baseline HRQoL value or age adjustments.
* Discuss the applicability of HRQoL values gathered from literature with respect to modelling of specific health states.
* Detail any adjustments made to utility or disutility values (e.g., due to differences in baseline utility).

## Resource use, costs and model inputs

* Medicine acquisition costs must be reported as the maximum pharmacy retail price (AUP) excluding value added tax (VAT).
* Other costs must include VAT if payable.
* Information should primarily be presented in tables.

### Medicine acquisition costs of intervention and comparator(s)

* Describe/tabulate medicine acquisition costs for the intervention and comparator(s). Include product numbers if available. As a minimum, include the information outlined in the following table:

Table 11. Medicine acquisition costs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Product number | Strength | Pack size | Maximum AUP excluding VAT, pr. pack |
| Non-proprietary name (proprietary name) | e.g., 595728 | e.g., 500 mg | e.g., 60 tablets | e.g., NOK 199 |
| Non-proprietary name (proprietary name) |  |  |  |  |
| Non-proprietary name (proprietary name) |  |  |  |  |

AUP, Pharmacy retail price; VAT, value added tax

* If multiple strength, dosages, and pack sizes are available, be explicit about assumptions regarding how costs are applied in the model.
* Be explicit about assumptions related to wastage.

### Other relevant medicine acquisitions costs

* Describe/tabulate medicine acquisition costs including costs for subsequent and/or accompanying treatments if relevant. Include product numbers if available. Use a similar table as in section 3.7.1.
* If multiple strengths, dosages, and pack sizes are available, be explicit about assumptions regarding how costs are applied in the model.

### Medicine administration costs

* Describe any relevant medicine administration costs associated with the treatments included in the analysis.

### Health state and event costs

* Describe/tabulate costs associated with each health state and/or events, including costs and costs components associated with each state/event.
  + E.g. 59,866 NOK per hospitalisation = average 3.2 inpatient days \* 18,708 NOK/inpatient day.
* If costs incur across health states, this must be clearly stated.
* Include sources for each state and event.

### Adverse events costs

* Describe/tabulate the costs and cost components for the adverse events included in the model.

### Miscellaneous costs

* Describe/tabulate the costs and cost components for monitoring and/or other costs included in the model.

# Health economic analysis - Results

## Incremental analysis of costs and outcomes

### Base case results

* Complete the following table for the main analysis. Copy Table 12 for any potential subgroup analysis. Results from any subgroup analysis requires a description of the analysis in the context of relevance and applicability to Norwegian clinical practice.
* Base case results must be presented with maximum pharmacy retail price (AUP) excluding VAT for all medicinal products included in the analysis. Use anticipated AUP if no public price exists at the time of submission.

Table 12. Summary of results of the incremental cost-effectiveness analysis.

|  |  |  |  |
| --- | --- | --- | --- |
| Per patient | <Intervention> | <Comparator> | Difference |
| **Life years gained** | | | |
| Total life years gained |  |  |  |
| Life years gained <health state A> |  |  |  |
| Life years gained <health state B> |  |  |  |
|  | | | |
| **QALYs** | | | |
| Total QALYs |  |  |  |
| QALYs <state A> |  |  |  |
| QALYs <state B> |  |  |  |
| QALYs, adverse reactions |  |  |  |
|  | | | |
| **Costs** | | | |
| Total costs |  |  |  |
| Medicine costs |  |  |  |
| Administrative costs |  |  |  |
| Hospital admissions |  |  |  |
| End of life costs |  |  |  |
| Adverse reactions |  |  |  |
| Other costs |  |  |  |
|  | | | |
| Incremental results | **Intervention vs. Comparator** | | |
| ICER (per QALY) |  | | |
| ICER (per life year gained) |  | | |

### Sensitivity and scenario analysis

#### Deterministic sensitivity analysis

* Present relevant sensitivity/scenario analysis, either in tables (e.g. Table 13) or using corresponding/relevant figures, e.g. tornado diagram. Arbitrary intervals around the mean (e.g. +/- 20%) should be avoided.
* Provide justifications/descriptions in text form, including details on relevant scenarios and why they may be plausible in this context.

Table 13. Deterministic one-way sensitivity analysis example.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Change | Reason / Rational / Source | Incremental cost (NOK) | Incremental benefit (QALYs) | ICER (NOK/QALY) |
| Base case | | | | |  |
| Efficacy outcome A intervention |  |  |  |  |  |
| Efficacy outcome B intervention |  |  |  |  |  |
| Hazard Ratio (HR)  Overall Survival (OS) | 0.71 | Lower C.I. |  |  |  |
| 1.83 | Upper C.I |  |  |  |
| Risk of hospitalisation |  |  |  |  |  |
| Adverse reaction A |  |  |  |  |  |
| Medicine costs of comparator | 30 % down |  |  |  |  |
| 50 % down |  |  |  |  |
| Time horizon |  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| Discounting | 0 % |  |  |  |  |
| 6 % |  |  |  |  |
| Administrative costs | 500 | 50 % down |  |  |  |
| 1500 | 50 % up |  |  |  |
| QALY-weight (state A) | 0.52 | Alt. source 1 |  |  |  |
| 0.67 | Alt. source 2 |  |  |  |
| Etc. |  |  |  |  |  |
|  |  |  |  |  |  |

#### Probabilistic sensitivity analysis

* Probabilistic sensitivity analysis may be presented.
* It must be stated where in the model the assumptions for the probabilistic analysis can be found. These assumptions can either be referred to in the table or described in text. Arbitrary intervals around the mean (e.g., +/-20%) should be avoided.
* Provide justifications/descriptions in text form.
* Adhere to Chapter 14 of the Guidelines

## Quantification of severity

* Severity must be quantified according to Guidelines Chapter 13 and Appendix.
* Provide a detailed description of how severity was calculated.
* Uncertainty in the severity calculation must also be presented.
* Describe sources of uncertainty in the assumptions.
* Present the consequences of the uncertainty, for example in table and/or diagram where the calculation of severity (absolute shortfall) as a function of age and/or prognosis is presented.
* Complete the table below. An excel tool is available that can be used in most cases.

Table 14. Severity calculations

|  |  |  |
| --- | --- | --- |
| Average age at treatment initiation | A | XX |
| Expected remaining QALYs (undiscounted) for the general population without the disease | QALYsA | XX |
| Expected remaining QALYs (undiscounted) for those with the disease and without the new treatment (that is, prognosis of patients treated with current standard treatment) | PA | XX |
| *If adjustments are made:* Expected remaining QALYs (undiscounted) for those with the disease without the new treatment (prognosis) - adjusted.  *If adjustments are not made, this row in the table can be deleted* | P\*A | XX |
| Number of QALYs lost due to disease (absolute shortfall) | AS | XX |

# Budget impact analysis

## Epidemiology of the disease in Norway

* Describe the epidemiology of the disease under review in Norway (globally if relevant), including development of prevalence and incidence numbers/rates over the last 5 years.
* Describe how the prevalence and incidence is expected to develop over the next 5 years.

## Eligible patient population and market share

* Describe the eligible patient population. Use funnel charts (or equivalent) describing how the final eligible patient population has been calculated. There are multiple ways of estimating patient numbers and considerations that could be included (such as demographic development, age dependent prevalence, diagnostic developments, etc.). Adapt as necessary. Example chart below.

Eksempel på graf

* The calculations must also be submitted in a spreadsheet, preferably within the same workbook as the budget impact calculation, clearly illustrating how the size of the eligible patient population has been estimated, including references for each parameter applied. The calculations should be made in a manner that allows assessors to make step-wise alterations to parameter values and thereby change the estimated patient numbers.

## Budgetary consequences

* The numbers in the following chapters must be derived from the submitted budget impact model, based on the template published on [legemiddelverket.no](https://www.legemiddelverket.no/en/public-funding-and-pricing-of-medicines/single-technology-assessments/submission-of-documentation-for-single-technology-assessment-of-pharmaceuticals/template-for-submission-of-documentation-for-the-single-technology-assessment-of-pharmaceuticals).
* Assumptions regarding uptake/market share must be clearly stated and justified. Use graphs to illustrate and justify the assumptions.
* The budget impact analysis must cover the following 5-year period after a potential approval for public financing.
* Base case results must be presented with maximum pharmacy retail price (AUP) including VAT for all medicinal products included in the analysis. Use anticipated AUP if no public price exists at the time of submission.
* Present the present-day scenario without the intervention, and the scenario where the intervention under assessment is granted public financing.
* The budget impact analysis must clearly illustrate the expected number of patients, the costs per patient, and the total costs.
* See Guidelines 15 for further details about requirements for budget impact analysis.

### Consequences for the medicinal budget

* For interventions covered by the Regional Health Authorities, describe the consequences for the Regional Health Authorities medicinal budget. Describe and justify any assumptions made.
* For interventions relevant for coverage by the National Insurance Scheme (*Folketrygden*), describe the budgetary consequences for the National Insurance Scheme medicinal budget (see *Legemiddelforskriften* § 14-7). Describe and justify any assumptions made.

### Budgetary consequences for the Regional Health Authorities overall

* Describe the budgetary consequences incurring within the Regional Health Authorities overall (e.g. including costs related to administration). Describe and justify any assumptions made.
* For STA submissions relevant for coverage by the National Insurance Scheme, this heading may be deleted.

### Budgetary consequences for the health care sector overall

* Present the budgetary consequences for the health care sector overall. This applies to medicinal products covered by both the Regional Health Authorities and the National Insurance Scheme.
* Copy and paste the mandatory summary tables from the spreadsheet template that is relevant for the submission. The BIA template must be submitted in its entirety.

### Discussion of budget impact uncertainty

* Discuss relevant factors that may contribute to higher or lower budgetary consequences than estimated.

# Conclusion

* Provide an overview of the main findings of the submission.

References

* Provide a list of references.

Appendices

1. Cost-utility analysis [↑](#footnote-ref-2)
2. Cost-minimization analysis [↑](#footnote-ref-3)
3. Budget impact analysis [↑](#footnote-ref-4)