

Application for the assessment of <proprietary name of pharmaceutical> for <indication>

Instructions for companies

This is the template for submission of evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new pharmaceutical or new indication for an existing pharmaceutical. The template is not exhaustive; companies must adhere to the current version of the guidelines alongside using this template when preparing their submission.

Appendices A-J, headings and subheadings are not to be removed. Additional subheadings can be added when appropriate. All sections in the template must be filled in. If a section or an appendix is not applicable, state “not applicable” and explain why. Examples of texts and tables are provided in the template. These can be edited or removed. The company can provide different table layouts to accommodate data, as long as the required information is provided.

The submission should be as brief and informative as possible. The main body of submission must not be longer than 100 pages, excluding the appendices. **Only material directly relevant for the application to the DMC should be included in the submission including appendices A-J. The application should not include information or descriptions about specific patients/medical history.** Submissions in Danish and English are accepted.

In addition to this template, the company must submit a health economic model in Excel, with full access to the programming code. All the information requested in this template and described in the guidelines must be presented in the application. The model can be accompanied by a technical document. The information in the technical document will, however, not be considered as part of the application. Hence, all relevant information for the application must also be described in the application (including appendices A-J) itself. This can be done by copying the relevant information from the technical document into the application, and by presenting it as described in this template and in the guidelines. Companies are encouraged to provide the European Public Assessment Report (EPAR) including the scientific discussion as an appendix to the submission (draft versions will be accepted).

When making an evidence submission, companies must ensure that all confidential information is highlighted in yellow and provide the expected date of publication. If confidential appendices are provided, these must be watermarked as “confidential”. Later in the appraisal process the application material must be assembled in one version consisting of the application, the appendices and any following or requested analysis – send to the DMS in one blinded version and one highlighted version.

Version 1.2

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Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[other]	[definition of color-code]

1. Basic information

Contact information	
Name	[name]
Title	
Phone number	[include country code]
E-mail	
Name	[name]
Title	
Phone number	[include country code]
E-mail	

Overview of the pharmaceutical
Proprietary name
Generic name
Marketing authorization holder in Denmark
ATC code
Pharmacotherapeutic group
Active substance(s)
Pharmaceutical form(s)
Mechanism of action
Dosage regimen
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)
Other approved therapeutic indications
Will dispensing be restricted to hospitals?

Overview of the pharmaceutical

Combination therapy and/or co-medication

Packaging – types, sizes/number of units, and concentrations

Orphan drug designation

2. Abbreviations

[Include a list of abbreviations used in this application.]

3. Tables and Figures

[Include a list of all tables and figures here with page references.]

4. Summary

[Provide a brief summary of the application (2-5 pages). Provide information about

- indication and population covered in the application (if the proposed position is narrower than the expected marketing authorization for this indication justify why)
- the pharmaceutical (the intervention)
- the comparator(s)
- most important efficacy endpoints in the comparative analysis. What proportion of the patient group is expected to benefit from the pharmaceutical?
- the safety of the pharmaceutical
- the structure and results of the health economic analysis
- included subgroup analysis (if relevant)]

5. The patient population, the intervention and choice of comparator(s)

[Complete the following sections according to sections 2.1, 2.2, 2.3, and 2.4 of the guideline.]

5.1 The medical condition and patient population

[Complete the following sections according to sections 2.1 and 2.3 of the guideline.

Describe the pathophysiology and clinical presentation/symptoms of the condition.

Describe as accurately and detailed as possible the patient population that is expected to use the pharmaceutical in Denmark and estimate the number of patients relevant for this assessment. If certain patient characteristics affect the prognosis or the effectiveness of the treatment, describe the distribution of these factors within the Danish patient

population. Describe which age groups are affected by the medical condition, and indicate the mean age (median age if relevant) for the patient group that is currently eligible for treatment in Denmark (not the age for potential study population(s)). This age should be supported by registry data, clinical experts or other relevant sources.

Are there any subgroups of patients for whom the pharmaceutical is likely to have a different level of efficacy and/or safety than anticipated for the entire population? Provide a rationale for the subgroup selection. Briefly describe any diagnostic tests and methods used for patient selection.

If dosing is based on bodyweight or body surface area, provide mean values for the eligible patient population, if available. Describe the prognosis. If any treatment options are currently available, provide the prognosis with the current treatment options.

Provide the incidence and prevalence for the past 5 years and the expected number of patients eligible for the new treatment during the next 5 years in the tables below.]

Example of table 1 Incidence and prevalence in the past 5 years

Year	[Year, e.g. 2016]	[Year, i.e. 2017]	[Year, i.e. 2018]	[Year, i.e. 2019]	[Year, i.e. 2020]
Incidence in Denmark					
Prevalence in Denmark					
Global prevalence *					

* For small patient groups, also describe the worldwide prevalence

Example of table 2 Estimated number of patients eligible for treatment

Year	[Year, i.e. 2021]	[Year, i.e. 2022]	[Year, i.e. 2023]	[Year, i.e. 2024]	[Year, i.e. 2025]
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years					

[Provide the source(s) for the information provided in the tables here.]

5.1.1 Patient populations relevant for this application

[State the patient populations that are included in this application, including any subgroups.]

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

[Describe the current treatment options in Danish clinical practice. Illustrate with a diagram if appropriate. Danish treatment guidelines should be referenced if available.]

5.2.2 Choice of comparator(s)

[The choice of comparator(s) must be done in accordance with section 2.4 of the guideline.]

Describe and explain which pharmaceutical(s) or treatment(s) would primarily be replaced by the introduction of this intervention. The submission should contain all relevant comparators. If any relevant treatments are omitted as comparators in the submission, provide a reason for this decision. State which comparators are included in the submission. Justify if the chosen comparator is not currently part of Danish clinical practice.

If the comparator has not been evaluated by the Medicines Council, include a supplementary analysis in the following sections, in accordance with section 2.4.2 of the guideline.]

5.2.3 Description of the comparator(s)

[Provide the following information for all the included comparators:

- Generic name(s) (ATC-code)
- Mode of action
- Pharmaceutical form
- Posology
- Method of administration
- Dosing
- Should the pharmaceutical be administered with other medicines?
- Treatment duration/criteria for end of treatment
- Necessary monitoring, both during administration and during the treatment period
- Need for diagnostics or other tests (i.e. companion diagnostics)
- Packaging

5.3 The intervention

[Describe how the intervention (the new pharmaceutical) is expected to be used in clinical practice, including

- Dosing
- Method of administration
- Treatment duration/criteria for treatment discontinuation
- Should the pharmaceutical be administered with other medicines?
- Necessary monitoring, during administration, during the treatment period, and after the end of treatment
- Need for diagnostics or other tests (i.e. companion diagnostics)

Describe how the introduction of the pharmaceutical can potentially change clinical practice. Where in the course of a treatment is the pharmaceutical expected to be used and how does this change the current treatment algorithm?]

6. Literature search and identification of efficacy and safety studies

[Overview of all included literature]

6.1 Identification and selection of relevant studies

[Describe the literature search here. Detailed information must be provided in appendix A in accordance with section 3 of the guideline.]

If a head-to-head study with a comparator relevant in Danish clinical practice already exists, the literature search can be omitted in some cases. If so justify why a literature search will not provide additional relevant documentation for efficacy and safety for both intervention and comparator.]

6.2 List of relevant studies

[For both intervention and comparator(s), provide a list or table of:

- **All included studies and references used in the assessment (title, author list, year, reference, reference number, NCT number). Study characteristics must be provided in detail in appendix B.**
- **Completed and ongoing studies not included in application]**

Example of table 3 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
				>intervention< vs. >comparator< for >population<

[*If only one comparison is included in the application, this column can be deleted]

For detailed information about included studies, refer to appendix B.

7. Efficacy and safety

[Complete this section according to sections 4 and 5 of the guideline for each comparison. If more than one comparison is included in the application, i.e. due to more than one comparator or more than one population, copy/paste the sections for each comparison.]

7.1 Efficacy and safety of [intervention] compared to [comparator] for [patient population]

7.1.1 Relevant studies

[Provide a brief description of each study used to demonstrate clinical efficacy and safety of the intervention and comparator in this comparison. Address any relevant differences between the studies (patient characteristics and study characteristics). Detailed information of study characteristics must be provided in appendix B, and baseline characteristics of included patients must be provided in appendix C.]

For detailed study characteristics refer to appendix B. For baseline characteristics of patients included in each study refer to appendix C.

7.1.2 Efficacy and safety – results per study

[Provide a summary of the key efficacy and safety findings for each study. Provide detailed information about included outcomes and results in appendix D. Additional safety information as described in the guideline section 4.2 must be provided in appendix E.

For each endpoint, describe the definition (operationalization), methods of data collection, and methods of analysis. If the endpoint uses a scale, state how it was validated; if it uses responder analyses, state and justify the responder definition. Clearly explain any inconsistencies between published data and EMA's scientific discussion. If the statistical analysis has been performed using methods that adjust for potential confounders and/or design features (e.g. by regression modeling or weighting techniques), the variables used for the adjustment must be clearly defined and specified. Methods for check of assumptions in the statistical analyses must be clearly stated and described.

For intermediate outcomes (or surrogate endpoints), describe how the outcome relates to the direct endpoints. Explain how the relationship was estimated, what sources of evidence were used, and how the sources of evidence were identified (e.g. systematic literature review).

If any outcomes, studies, or study arms are excluded from the summary of clinical outcomes, provide a justification for their exclusion.

Data should be presented according to the intention-to-treat principle, whenever possible. Additional, alternative presentations of the data should be justified. Whenever possible, data should be presented with confidence intervals.

In the case of survival analyses, Kaplan–Meier curves that include the number of patients at risk at various time points should be provided. In addition, the estimated median survival as well as the estimated hazard ratio (HR) and the estimated survival rates at relevant and appropriate time points should be presented. For hazard ratios a check of the proportional hazards assumption must be included.

Insert references for all data.

If only one head-to-head study comparing the intervention and comparator directly is included as evidence of efficacy and safety, the following section describing comparative analysis can be omitted. Justify here, why it is not necessary to include other studies from the literature or perform indirect comparisons (for example, there may be systematic reviews for the comparator, where results differ from those reported in the head-to-head study)].

For detailed efficacy and safety results, refer to appendices D and E.

7.1.3 Comparative analyses of efficacy and safety

Method of synthesis

[Clearly describe the method used for the comparative analysis, i.e. meta-analysis, indirect analysis or narrative synthesis. Choice of method should be justified and specific analytical decisions in relation to the method chosen should be clearly specified.

If head-to-head studies are combined in a meta-analysis, provide the details of the analysis in this section.

If the efficacy and safety documentation is based on an indirect comparison, provide a brief description of the methodology here and a detailed description of the methodology in appendix F. Tables and figures may be used for clarification.

If weighting techniques are used, e.g. matching adjusted indirect comparisons, summary statistics of the weights (or a histogram) should be provided and the effective sample size given. For inverse probability weighting describe the model for obtaining the probabilities and the choice of weights (e.g. average treatment effect).

If intermediate outcomes (or surrogate endpoints) are provided, describe how the outcome relates to the direct endpoints. Explain how the relationship was estimated, what sources of evidence were used, and how the sources of evidence were identified (e.g. systematic literature review).

For safety data, provide comparative analyses of summary data as defined in section 4.2 of the guideline, if possible.

If any studies or subpopulations are excluded from the comparative analyses, provide a justification for their exclusion.]

Results from the comparative analysis

[Provide a summary of the results from the comparative analyses. Detailed information of analysis and results must be provided in appendix F.

Extrapolation of data should be described in section 8.3]

7.2 Efficacy and safety of [intervention] compared to [comparator] for [patient population]

7.2.1 Relevant studies

7.2.2 Efficacy and safety – results per study

7.2.3 Comparative analyses

Method of synthesis

Results from the comparative analysis

8. Health economic analysis

[Complete this section according to section 6 of the guideline. Describe and justify the choice of health economic analysis (cost-utility analysis or cost-minimization analysis). If a complete cost-utility analysis was not conducted, not all of the following items will be relevant. All input data sources used in the health economic analysis must also be included in the submitted Excel model.]

8.1 Model

[Describe the model used in the health economic analysis (see section 6 of the guideline) and depict the structure of the model clearly showing the different stages and the main features of how it works. Explain the structure based on the clinical pathway of care (described in section 5), describe how the model structure and its health states capture the disease for the patient population (described in section 5) and, where appropriate, state the cycle length and whether half-cycle correction has been applied. If cost-effectiveness studies have been identified and used in the development of the model, list the studies and the method by which they were identified below. Finally, discuss the limitations of the model for analyzing the research question of the application.

Describe and justify the choice of time horizon (see section 6.8 of the guidelines).

Enter the discount rates used for costs and benefits (QALYs) (see section 6.9 of the guidelines).

Describe how the model has been validated. Refer to the relevant publication(s) if external validation has been performed (see section 6.4.3 of the guidelines).

Describe and justify key assumptions in the model.]

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

[The purpose of the next two chapters is to establish the context and possible deviations between the relative efficacy data used in the model, clinical data and Danish clinical practice.]

8.2.1 Presentation of input data used in the model and how they were obtained

[Present clearly in a table what estimates (clinical effect, adverse reactions and HSUV) have been used in the health economic model and how these have been obtained. Present results for relevant data/outcome measures used in the model. Primary outcomes must always be included in the table. Data from intention to treat (ITT) analyses should be presented if possible. When transition probabilities that were calculated from clinical data have been used, they must also be presented. Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix and describe the details of the transformation of clinical outcomes or any other relevant details here.

If there is evidence that transition probabilities may change over time for the treatment effect, condition or disease, confirm whether this has been included in the analysis. If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Describe the relevance of the selected estimates for Danish clinical practice.

Example of table 4 Input data used in the model [sources should be cited where available]:

Name of estimates*	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated**
Outcome A*			
Outcome B*			
Adverse reaction 1* (measured in costs)			
Adverse reaction 2* (measured as occurrence)			
Adverse reaction 3* (measured as utility loss)			
Health state A* (measured as utility)			
Health state B* (measured as utility)			
Transition probability 1			
Transition probability 2			
Etc.			

* Some of these estimates will be presented in other tables in the document. This table is a summary.

** Calculations: [If intermediate outcome measures were linked to final outcomes, describe them here (for example, if a change in a surrogate outcome was linked to a final clinical outcome). Explain how the relationship was estimated, what sources of evidence were used, how the sources of evidence were identified (e.g. systematic literature review) and what other evidence exists. Details must be provided in a separate appendix with reference here.]

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

[The purpose of the items below (PICO) is to identify any discrepancies between the clinical data, data used in the model, and Danish clinical practice (if known).

The term "clinical data" in this section has a wider definition than data from clinical studies, and should be interpreted as (in addition to data from clinical studies) also including estimates based on indirect comparisons, real world data, etc.]

8.2.2.1 Patient population

The Danish patient population: [Text]

Patient population in the clinical documentation submitted: [Text]

Patient population in the health economic analysis submitted: [Text]

[The text must be summarized in a table.]

Example of table 5 Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
BMI			
ECOG status			
Etc.			

[If the information in the columns in the table does not match, it must be discussed. This should be done with respect to transferability of results to the Danish setting.]

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 2.2):

Intervention in the clinical documentation submitted: [Text]

Intervention as in the health economic analysis submitted: [Text]

[The text must be summarized in a table.]

Example of table 6 Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology			
Length of treatment (time on treatment) (mean/median)			

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Criteria for discontinuation			
The pharmaceutical's position in Danish clinical practice			
Etc.			

[If the information in the columns in the table does not match, it must be discussed. This should be done with respect to transferability of results to Denmark.]

8.2.2.3 Comparators

The current Danish clinical practice (as described in 5: [Text]

Comparator(s) in the clinical documentation submitted: [Text]

Comparator(s) in the health economic analysis submitted: [Text]

[The text must be summarized in a table.]

Example of table 7 Comparator

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology			
Length of treatment			
The comparator's position in the Danish clinical practice			
Etc.			

[If the information in the columns in the table does not match, it must be discussed. This should be done with respect to transferability of results to Denmark.]

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: [Text]

Relevance of the documentation for Danish clinical practice: [Text]

The relative efficacy outcomes in the submitted health economic analysis: [Text]

[Present here the value of parameterization from observed data if the value (outcome measure) is generated by parameterization. The text must be summarized in a table. It is suggested to distinguish between the actual numerical values of the outcome measures, the measurement method and the relevance of outcomes.]

Example of table 8 Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study (endpoint's name)		
Overall survival (OS)		
Progression-free survival (PFS)		
<hr/>		
Secondary endpoint (endpoint's name)		

[If the information in the columns in the table does not match, it must be discussed. This should be done with respect to transferability of results to Denmark.]

Example of table 9 Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study (endpoint's name)			
<hr/>			
Secondary endpoint (endpoint's name)			

[If the information in the columns in the table does not match, it must be discussed. This should be done with respect to transferability of results to Denmark.]

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: [Which outcomes, text]

Adverse reaction outcomes in the health economic analysis submitted: [Text]

[The text must be summarized in a table.]

Example of table 10 Adverse reaction outcomes

Adverse reaction outcome	Clinical documentation	Used in the model (numerical value)
<hr/>		

Adverse reaction outcome	Clinical documentation	Used in the model (numerical value)
--------------------------	------------------------	-------------------------------------

[If the columns in the table are not interrelated, it must be discussed. This should be done with respect to transferability of results to Denmark.]

8.3 Extrapolation of relative efficacy

[Follow section 6.4.2 of the guidelines and the online appendix "Anvendelse af forløbsdata i sundhedsøkonomiske analyser"¹. If the extrapolation is not based on the time-to-event data (i.e. survival data), please explain and justify any assumptions made on how the effect differs beyond the study period. Does the effect remain the same, decrease, increase?]

8.3.1 Time to event data – summarized:

[If extrapolations from time-to-event data have been made, please present the main results and the method used here. The full method description and results should be presented in Appendix G. Specify which parametric function was selected for both intervention and comparator. All standard parametric models (exponential, Weibull, Gompertz, gamma, log normal, log logistic and generalized gamma) and other considered extrapolations should be available in the Excel model.

Graphical representation of the time-to-event data curves where both the Kaplan-Meier (KM) estimate and the parametric distributions are shown in the same figure must also be presented in this section (for both intervention and comparator). A tabular presentation of the proportion of patients in each state at relevant time points must be presented for both intervention and comparator (e.g. for proportion of patients alive and patients on treatment). Specify whether adjustment have been made for treatment switching/cross-over (intervention and/or comparator). If adjustment have been made, specify and document the methods in an appendix.

Describe and explain how the extrapolations have been validated, and present the results. When relevant, present graphical representation of the validation.]

8.4 Documentation of health-related quality of life (HRQoL)

[Section 7 of the guidelines must be followed. The literature search must be presented in appendix H].

8.4.1 Overview of health state utility values (HSUV)

[Present in a table the different sources for the HSUV that have been considered in the assessment. This may be from the literature search (1), from the clinical studies (2) that underlie the relative efficacy in this assessment and/or from mapping (3). If the quality of life data was derived from the studies on which the relative efficacy's documentation is based, table (12) below must be completed. Below are also examples of three different tables. These are only meant as examples of possible table structures.

Describe the method used for mapping according to section 7 (and 7.1.1) of the guidelines. Always include details of the methodology used, how the method was validated and whether it has been published. Present the results.]

¹ https://medicinraadet.dk/media/tdandcfg/anvendelse-af-forloebdata-i-sundhedsoekonomiske-analyser-vers-11_adlegacy.pdf

Example of table 11 Overview of HSUV derived from the literature search (presented in appendix H)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
<i>Health state A</i>				
Study 1	0.761 [0.700-0.810]	EQ-5D-5L	DK	For example: EQ-5D-5L data was collected in X trial. Estimate is based on mean of both trial arms.
Study 2				
Study 3				
<i>Health state B</i>				
...				
<i>Adverse reaction A</i>				

Example of table 12 Overview of the HSUV measured during clinical trials forming the basis for the relative efficacy (see section 7) [This table must always be completed if the quality of life data came from clinical trials forming the basis for the relative efficacy]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Health state A				
Study 1	0.767 [0.712-0.835]	EQ-5D-5L	DK	For example: mean estimate is based on mean of both trial arms.
Study 1				
Study 2				
Health state B				
...				
Adverse reaction				

Example of table 13 Overview of HSUV based on mapping (presented in appendix I)

	Results [95% CI]	From Instrument	To instrument	Comments
Health state A				
Study 1	0.740 [0.701-0.800]	EQ-5D-3L	EQ-5D-5L	<i>Describe the method for mapping briefly here. Describe in detail in appendix I.</i>

8.4.2 Health state utility values used in the health economic model

[The selection of HSUV used in the model must be justified. If EQ-5D-5L and Danish preference weights have not been used this must be justified according to sections 7.1.3 and 7.2 of the guideline.]

Justifications:

HSUV for health state

[Text]

HSUV for health state B

[Text]

HSUV for adverse reaction A

[Text]

[If the clinical studies on which the relative efficacy's documentation is based (see table (12) above) include quality of life data, or data that can be transformed into quality of life data, and this data has not been used in the analysis, please explain why.]

Justification for not using the quality of life data from the studies: [Text]

[Describe how the HSUV have been adjusted for age. See section 7.3 of the guideline.]

Example of table 14 Summary of the HSUV used in the model

	HSUV	95% CI	Source (literature search, study, ITC, etc.)
Health state			
A			
B			
Adverse reaction			
A			
B			
...			

[Describe the strengths and weaknesses of the quality of life data used. If sensitivity analyses with different HSUV have been conducted, these must also be described and justified].

8.5 Resource use and costs

[Follow section 8 of the guidelines and refer to the online Appendix “Værdisætning af enhedsomkostninger”². In this section, present all costs used in the health economic analysis. For continuous variables, mean values should be presented and used in the analysis. For all variables, measures of precision should be detailed.

Describe each cost in its own section below, including resource use, unit costs (consult, if applicable, the Appendix “Værdisætning af enhedsomkostninger”) and how it was included in the model. Describe the use of resources in clinical practice for each cost. Show all the relevant calculations in detail and cite the sources.]

Cost A (e.g. pharmaceutical costs)

Resource use for cost A: [Text] [Clinical practice, what monitoring is required, resource use, etc.]

Unit cost(s) for cost A: [Text]

Value used in the model for cost A: [Text] [Must be given as cost per unit, e.g. per admission, per cycle, for any projection, see section 8.1 in the guidelines.]

Cost B (e.g. hospitalization)

Resource use for cost B: [Text]

[Clinical practice, what monitoring is required, resource use, etc.]

Unit cost(s) for cost B: [Text]

Value used in the model for cost B: [Text] [Must be given as cost per unit, e.g. per admission, per cycle, for any projection, see section 8.1 in the guidelines.]

Summarize and tabulate the costs included in the health economic analysis. A suggested format for tables is provided below.

Example of table 15a Pharmaceutical costs used in the model

Costs	Number of units		DKK (per unit of measurement used in the model)
	Intervention	Comparator	
e.g. pharmaceutical cost (A)			DKK (per time period /patient)

² https://medicinraadet.dk/media/weslftgk/vaerdisaetning-af-enhedsomkostninger-vers-13_adlegacy.pdf

Example of table 15b Hospital costs used in the model

Costs	Number of units		DKK (per unit of measurement used in the model)
	Intervention	Comparator	
e.g. hospitalization (B)			DKK (per admission)
e.g. blood glucose strips			DKK (per year)
e.g. health state A cost			DKK (per cycle)
e.g. monitoring			

Example of table 15c Patient costs used in the model

Costs	Number of units		DKK (per unit of measurement used in the model)
	Intervention	Comparator	
e.g. patient time spent in treatment			DKK (per time period /patient)
e.g. patient time spent on adverse reaction X			
e.g. patient transport cost			

Example of table 15d Municipality costs used in the model

Costs	Number of units		DKK (per unit of measurement used in the model)
	Intervention	Comparator	
e.g. home care service cost			DKK (per time period /patient)

8.6 Results

8.6.1 Base case overview

[Provide an overview of the base case including the central aspects]

Example of table 16 Base case overview

Comparator	Standard care
Type of model	Markov model
Time horizon	30 years (life time)
Treatment line	1 st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study x (reference). Danish population weights were used to estimate health-state utility values
Included costs	Pharmaceutical costs Hospital costs Costs of adverse events Patient costs
Dosage of pharmaceutical	Based on weight
Average time on treatment	Intervention: X Comparator: Y
Parametric function for PFS	Intervention: X Comparator: Y
Parametric function for OS	Intervention: X Comparator: Y
Other important assumptions...	

8.6.2 Base case results

[Complete the table. The text in column 1 should be customized for each individual assessment. The results for the intervention and comparator as well as the difference must always be presented.]

Example of table 17 Base case results

Per patient	Intervention	Comparator	Difference
Life years gained			
Total life years gained			
Life years gained (health state A)			

Per patient	Intervention	Comparator	Difference
Life years gained (health state B)			
QALYs			
Total QALYs			
QALYs (state A)			
QALYs (state B)			
QALYs (adverse reactions)			
Costs			
Total costs			
Drug costs			
Administrative costs			
Hospital admissions			
Adverse reactions costs			
Patient time and transport costs			
Municipality costs			
Incremental results		Intervention vs. Comparator	
ICER (per QALY)			

8.7 Sensitivity analyses

[Section 9 of the guideline must be followed.]

8.7.1 Deterministic sensitivity analyses

[Present in a table the results obtained from deterministic one-way sensitivity analyses]

Example of table 18 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	-		
<hr/>					
Efficacy outcome A intervention					
<hr/>					
Efficacy outcome B intervention					
<hr/>					
Hazard Ratio (HR) Overall Survival (OS)	0.7	Lower CI from study X			
	1.8	Upper CI from study X			
<hr/>					
Risk of hospitalization					
<hr/>					
Adverse reaction A					
<hr/>					
Drug costs of comparator	30% down				
	50% down				
<hr/>					
Discounting	0 %				
	6 %				
<hr/>					
Administrative costs	500	50 % down			
	1500	50 % up			
<hr/>					
QALY-weight (state A)	0.50	Alt. source 1			
	0.65	Alt. source 2			
<hr/>					
Etc.					
<hr/>					
<hr/>					

[If there is a need for longer justifications/descriptions, provide them in text form.

Present tornado diagram.

Present in a table and/or in a graph all ICERs estimated with different values for the drug price of the intervention.

Varying from 100% (max PRP) to as low as to where the curve crosses the x axis (where the ICER becomes negative).

[Table and/or price/ICER curve.]

[If conducted, describe two-way, multi-way and/or scenario analyses and present their results when appropriate in a table.]

8.7.2 Probabilistic sensitivity analyses

[In appendix J, show in a table which data/assumptions (expected value and standard error) form the basis for the selected probability distributions used in the probabilistic analysis. Present the PSA analyses according to section 9.2.2 of the guideline (Scatter plot and CEAC).]

9. Budget impact analysis

[Section 10 of the guideline must be followed. The calculations must be delivered in spreadsheets and the assumptions and sources for patient number estimates and market developments in the budget calculations must be described. If the number of patients does not match with section 5, it must be discussed. The tables below demonstrate how the calculation of additional expenses for the regional hospital budgets can be done.]

Number of patients

Example of table 19 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration					
Competitive pharmaceutical 1					
Competitive pharmaceutical 2 (etc.)					
Total number of patients					

Example of table 20 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration					
Competitive pharmaceutical 1					
Competitive pharmaceutical 2 (etc.)					
Total number of patients					

Expenditure per patient

Example of table 21 Costs per patient per year - if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient					
For competitive pharmaceutical 1					
For competitive pharmaceutical 2 (etc.)					

Example of table 22 Costs per patient per year - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient					
For competitive pharmaceutical 1					
For competitive pharmaceutical 2 (etc.)					

Budget impact
Example of table 23 Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	X1	X2	X3	X4	X5
Of which: Drug costs					
Of which: Administrative costs					
Of which: Hospital costs					
Of which: Adverse reaction costs					
Minus:	Y1	Y2	Y3	Y4	Y5
The pharmaceutical under consideration is NOT recommended					
Of which: Drug costs					
Of which: Administrative costs					
Of which: Hospital costs					
Of which: Adverse reaction costs					

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact of the recommendation	X1 - Y1	X2 – Y2	X3 -Y3	X4 – Y4	X5 –Y5

10. Discussion on the submitted documentation

[Describe the strengths and weaknesses of the documentation submitted (max 2 pages). Focus must be on the uncertainty related to the clinical documentation used and other key input data, the health economic model structure, and the relevance for the Danish context.]

11. List of experts

[Provide names of any experts consulted during this application submission.]

12. References

[Insert the reference list]

[All published articles used in the clinical analyses and the health economic model(s) must be enclosed as separate pdf-files. If "data on file" is used as documentation in the technology assessment, the relevant part of the documentation must also be submitted in a separate e-mail labeled with "data on file".]

Version log		
Version	Date	Change
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.
1.1	9 February 2022	<p>Appendix K and onwards have been deleted (company specific appendices)</p> <p>Color scheme for text highlighting table added after table of contents</p> <p>Section 6: Specified requirements for literature search</p> <p>Section 7: Stated it explicitly that statistical methods used need to be described</p> <p>Section 8.3.1: Listed the standard parametric models</p> <p>Section 8.4.1: Added the need for description of quality of life mapping</p> <p>Appendix A: Specified that the literature search needs to be specific for the Danish context and the application</p> <p>Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices</p>

Version log

1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
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Appendix A Literature search for efficacy and safety of intervention and comparator(s)

[Follow section 3 of the guidelines. Describe how the literature search was performed. Explain the selection of the search criteria and terms used, search filters, the inclusion and exclusion criteria.]

In case of (re)using an existing/global systematic literature review (SLR), Appendix A must be filled out with data/information from such SLR specific to the current application, i.e. in- and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs are not accepted as Appendix A.

Objective of the literature search: [What questions is the literature search expected to answer?]

Databases: [Describe briefly which databases, registers and any conference material used in the literature search.]

Example of table: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline	Ovid		dd.mm. yyyy
PsychInfo			dd.mm. yyyy
			dd.mm. yyyy

Abbreviations:

Example of table: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov		dd.mm.yyyy
WHO ICTRP registry	https://apps.who.int/trialsearch/		dd.mm. yyyy
EU Clinical Trials Register	EU Clinical Trials Register		dd.mm. yyyy

Abbreviations:

Example of table: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
Conference name	state website	Manual search	

Conference	Source of abstracts	Search strategy	Words/terms searched
------------	---------------------	-----------------	----------------------

Search by individual words in the congress material

List: Supplementary manual searches

[Enter which other sources have been manually searched (e.g. web pages, EPAR/HTA agencies, etc.), incl. date of search/access.]

Search strategy

[Describe the development of a search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line, incl. results, for each database.]

Example of search strategy table:

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

Systematic selection of studies

[Insert the PRISMA flow diagrams here ([see example here](#)).

Provide a list of excluded references/full text papers with a short reason.]

Example of table: Overview of study design for studies included in the technology assessment/analysis:

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

Quality assessment

[Describe strengths and weaknesses of the performed literature search.]

Unpublished data

[The quality of any unpublished data must be specifically addressed. Submission of a publication plan for unpublished data is encouraged].

Appendix B Main characteristics of included studies

[Complete the table for each included study. Comply with section 3 of the guideline.]

Trial name:	NCT number:
Objective	<i>Briefly state the overall objective of the study</i>
Publications – title, author, journal, year	<i>State all publications related to the trial.</i>
Study type and design	<p><i>State the phase of the trial and describe the method of randomization, degree of blinding, extent of crossover, status (ongoing or completed), etc.</i></p> <p><i>E.g.: Double-blinded randomized placebo-controlled phase 3 study. Enrolled patients were randomly assigned 1:1 using a stratified permuted block randomization scheme via an interactive response system. No crossover was allowed. The investigators, patients, and sponsor were masked during treatment assignment.</i></p>
Sample size (n)	
Main inclusion and exclusion criteria	<i>Insert the inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov</i>
Intervention	<i>State the intervention including dose, dosing schedule, and number of patients receiving the intervention</i>
Comparator(s)	<i>State the comparator(s) including dose, dosing schedule, and number of patients receiving the comparator</i>
Follow-up time	<i>E.g.: median follow-up of 7.3 months (range 0.5–16.5)</i>
Is the study used in the health economic model?	<p><i>Yes/No</i></p> <p><i>[For studies not included in the economic model but considered relevant to the submission, please provide the rationale]</i></p>
Primary, secondary and exploratory endpoints	<p><i>State <u>all</u> primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results must be provided in appendix D.</i></p> <p>Endpoints included in this application:</p> <p><i>E.g.: The primary endpoint was progression-free survival as assessed by the investigator, according to RECIST version 1.1. Secondary endpoints were overall survival, confirmed objective response according to RECIST version 1.1, response duration, progression-free survival assessed by an independent review facility, health-related quality of life (HRQoL) as assessed by QLQ-C30, and safety.</i></p> <p>Other endpoints:</p> <p><i>E.g.: Time-to-next-treatment and objective response rate were included as secondary end points in the study, but results are not included in this application.</i></p>

Trial name:**NCT number:****Method of analysis**

State the method of analysis, i.e. intention-to-treat or per-protocol.

E.g.: All efficacy analyses were intention-to-treat analyses. We used the Kaplan–Meier method to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons. Hazard ratios adjusted for XX and YY were estimated with Cox proportional hazards regression. The proportional hazards assumption was assessed by looking for trends in the scaled Schoenfeld residuals.

Subgroup analyses

For each analysis, provide the following information:

- characteristics of included population
- method of analysis
- was it pre-specified or post hoc?
- assessment of validity, including statistical power of the analysis.

Other relevant information

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

[Provide a table of baseline characteristics of patients included the studies used in the comparative analysis. One table for each comparison in the application should be provided. An example table is shown below. Adjust the table to match the relevant information. Turn the page horizontal to include more studies. The table should make it possible to compare baseline characteristics across included studies for each comparison. Information about all relevant prognostic factors and effect modification factors should be included. Below the table, provide a description of the comparability of the baseline characteristics across the studies and how well the study populations align with patients treated in Danish clinical practice.]

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety						
[Study name]	[Study name]		[Study name]		[Study name]	
[int./comp.]	[int./comp.]	[int./comp.]	[int./comp.]	[int./comp.]	[int./comp.]	[int./comp.]
<i>Age</i>						
<i>Gender</i>						
<i>Time since diagnosis</i>						
<i>Performance status</i>						
<i>Disease stage</i>						
<i>Previous treatments</i>						

Comparability of patients across studies

[Describe any relevant differences across studies, and how they affect the comparability of study results.]

Comparability of the study populations with Danish patients eligible for treatment

[Describe any relevant differences between the study populations and the Danish patient population, and how this affects transferability of results to Danish clinical practice.]

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

[The definition of each included outcome measure should be provided in the table below. If different definitions are used across the included studies, please provide a description of these differences in the table. Describe how the validity and clinical relevance of the outcomes has been investigated. Include references.]

Outcome measure	Definition	Validity	Clinical relevance
[outcome measure 1]	[Provide definition used in the studies]	[State whether the validity of the outcome measure has been investigated and how. Provide references.]	[State how the clinical relevance of the outcome measure has been investigated, including information about the minimal important difference if available. Provide references.]
[outcome measure 2]			

Results per study

[Complete the table for all included studies, regardless of whether they have been used in the health economic model. Explain how all estimates, CIs and p-values have been estimated. State any corrections used, e.g. in cases with 0 counts. Specify how assumptions were checked. Survival rates: State at which time-point these are reported for]

Table A3a Results of [trial name (NCT number)]

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
<i>Example: median overall survival</i>	XXX	247	22.3 (20.3–24.3) months	4.9	1.79–8.01	0.002	HR: 0.70	0.55–0.90	0.005	<i>The median survival is based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.</i>	
	ZZZ	248	17.4 (15.0–19.8) months								
<i>Example: 1-year survival</i>	XXX	247	74.5% (68.9–80.2)	10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	<i>The survival rates are based on the Kaplan–Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for stratification, and study arm.</i>	
	ZZZ	248	63.8% (57.6–70.0)								
<i>Example: HRQoL</i>	XXX	211	–1.5 (–3.1 to 0.1)	4.5	–8.97 to –0.03	0.04	NA	NA	NA	<i>The absolute difference in effect is estimated using a two-sided t-test.</i>	
	ZZZ	209	–6.0 (–10.2 to –1.8)								
<i>Insert outcome 4</i>	Intervention										
	Comparator										

Appendix E Safety data for intervention and comparator(s)

[Provide safety data for the intervention and comparator(s) in accordance with section 4.2 of the guideline.]

Appendix F Comparative analysis of efficacy and safety

[For meta-analyses, the table below can be used. For any type of comparative analysis (i.e. paired indirect comparison, network meta-analysis or MAIC analysis), describe the methodology and the results here in an appropriate format (text, tables and/or figures).]

Table A4 Meta-analysis of studies comparing [intervention] to [comparator] for patients with [indication]									
Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
Example: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the included studies were synthesized using random effects meta-analysis (DerSimonian–Laird).	Yes/No
Example: 1-year survival		10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The HRs for the included studies were synthesized using random effects meta-analysis (DerSimonian–Laird). The absolute difference was estimated by applying the resulting HR to an assumed 1-year survival rate of 64.33% in the comparator group.	

Table A4 Meta-analysis of studies comparing [intervention] to [comparator] for patients with [indication]

<i>Example: HRQoL</i>	<p style="text-align: center;">-4.5</p>	<p style="text-align: center;">-8.97 to -0.03</p>	<p style="text-align: center;">0.04</p>	<p style="text-align: center;">NA</p>	<p style="text-align: center;">NA</p>	<p style="text-align: center;">NA</p>	<p><i>HRQoL results for the included studies were synthesized using the standardized mean difference (SMD). The estimated meta-analytical SMD of -0.3 (95% CI -2.99 to -0.01) was transformed to the scale of ZZZ* assuming a population standard deviation of 15 on the ZZZ* scale.</i></p> <p><i>*Fill in the name of an appropriate, measure of HRQoL.</i></p>
<i>Insert outcome 4</i>							

Appendix G Extrapolation

[Describe how extrapolation and parameterization is performed in accordance with sections 6.4.2 and 6.4.3 of the guideline and the online appendix "Anvendelse af forløbsdata i sundhedsøkonomiske analyser³".]

³ https://medicinraadet.dk/media/tdandcfg/anvendelse-af-forloebdata-i-sundhedsoekonomiske-analyser-vers-11_adlegacy.pdf

Appendix H – Literature search for HRQoL data

[Follow sections 3 and 7.1.2 of the guideline.]

Describe how the literature search for the health-related quality of life data was performed.

Explain the selection of search criteria and terms, inclusion and exclusion criteria.

Objective of literature search: [What questions is the literature search expected to answer?]

Databases: [Describe briefly which databases, registers and any conference material used in the literature search, either in text or table.]

Example of table: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm. yyyy
Specific health economics databases ⁴			dd.mm. yyyy
			dd.mm. yyyy

Abbreviations:

Table: [Registers included in the search]

Table: [Conference material included in the search]

List: [Supplementary manual searches]

[Enter which other sources have been manually searched (e.g. web pages, EPAR/HTA institutes, journal issues, reference lists, etc.).]

Search strategy

[Describe the development of the search strategy and search string. Enter the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time frame, etc.)

The search must be documented for each database or resource incl. terms and syntax used, number of results retrieved, and date searched/accessed, either in text or table.

Describe which criteria have been used to reject irrelevant studies (for example of a table to record exclusions, see table 5 in NICE DSU Technical Support Document 9) and how the final selection has been made. Use PRISMA charts if appropriate ([see example here](#)).]

Literature search results included in the model/analysis:

[Insert results in a table]

Quality assessment and generalizability of estimates

[Provide a complete quality assessment for each relevant study identified. When non-Danish estimates are used, generalizability must be addressed.]

⁴ Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Unpublished data

[The quality of any unpublished data must be specifically addressed. Submission of a publication plan for unpublished data is encouraged.]

Appendix I Mapping of HRQoL data

[Describe the method used for mapping according to section 7 (and 7.1.1) of the guidelines. Always include details of the methodology used, how the method was validated and whether it has been published. Present the results.]

Appendix J Probabilistic sensitivity analyses

[Show in a table which data/assumptions (expected value and standard error) form the basis for the selected probability distributions used in the probabilistic analysis.

The table below may be copied directly from the model (such as the spreadsheet). It must be stated where in the model the assumptions for the probabilistic analysis are found. These assumptions can either be referred to in the table or described in text.]

Example of structure and content of table:

	Expected value	Standard error	Reason / Rationale / Source	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Probabilities							
Efficacy Outcome A	0.72	0.06		Beta	α : 165	β : 78	Prob_dists!C43
HSUV							
State A	0.79	0.01		Beta	α : 1112	β : 301	Prob_dists!C133
Costs							
Hospitalization	20000			Gamma	α : 4	β : 5613	Prob_dists!C248

[If there is a need for longer justifications/descriptions, provide them in text.]

