Medicinrådet

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

Contents

General information

This application form should be submitted to the Danish Medicines Council (*Medicinrådet*) for the assessment of new medicines and new indications. The purpose of the form is to provide an overview of the basic information, literature search, study, and analysis results that will serve as the basis for the assessment. It indicates the minimum required information needed for the assessment.

The assessment of the pharmaceutical will be based on the outcomes defined in the protocol. Results for all critical and important outcomes (*kritiske og vigtige effektmål*) must be addressed in the application. The results of less important outcomes (*mindre vigtige effektmål*) do not need to be addressed. For all the data provided, a reference is mandatory.

During the completion of this form, elements should not be removed from the document. All sections should be filled in (if a section is not applicable, state "not applicable" and explain why). Table examples are provided in the form. Layout may deviate from the template to accommodate data; however, all requested information must be stated. We accept submission of appendices. Audits of literature searches and data analyses will occur.

In order to minimize translation errors between the application and the assessment report, submission in Danish is preferred.

If confidential data are submitted, highlight the data in yellow and write the expected publication date in a comment. If confidential data are submitted in an appendix, the document must in addition be watermarked as "confidential."

The application will be published simultaneously with the final assessment and recommendation report on the Danish Medicines Council's web page (www.medicinraadet.dk). Any data that will be considered in the assessment report will be published with the final application.

Checklist before submitting the application form:

- Are all relevant fields in the application form filled in?
- Are references indicated for all data?
- Is the application explicit and self-explanatory?
- Does the application meet the general requirements defined in the *Process and Methods Guide (version 2.0)* of the Danish Medicines Council for new medicines and new indications?
- Does the application meet the specific requirements in the protocol?
- Are deviation(s) from the protocol (if any) described?
- Are deviation(s) from the protocol (if any) justified?

1 Basic information

Table 1 Contact information

Name	e.g., Anders Andersen
Title	e.g., medical director
Area of responsibility	e.g., clinical/medical, economic, or negotiation
Phone	include country code
E-mail	
Name	e.g., Anders Andersen
Title	e.g., medical director
Area of responsibility	e.g., clinical/medical, economic, or negotiation
Phone	include country code
E-mail	

Table 2 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?	
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 Summary

Provide a structured one-page (maximum) summary of the content of this application.

4 Literature search

The protocol will guide you in relation to the relevance of performing a literature search.

If a literature search is requested, the search strategy must be carried out as defined in the protocol. The identified literature must be screened and assessed to be relevant for answering the clinical questions (PICOs) described in the protocol. The applicant must provide a PRISMA flow diagram showing the number of references identified and the number of included and excluded references. A list of references excluded after full-text screening must be provided, as an appendix including the reasons for exclusion of each reference.

In addition, the applicant is required to consult EMA's relevant scientific discussion, both with regards to the new medicine and the comparator(s).

If EMA's European public assessment report (EPAR) is not available online at the time of submission, the applicant is encouraged to send the preliminary EPAR together with the application.

Databases and search strategy

- Include the complete search strategy used to search each database.
- The search strategy must include (as a minimum):
    - which database(s) were searched (and, when relevant, the platforms used)
    - applied search strings (if relevant, including filters and limits)
    - time period covered
    - date of the search
    - number of references in the search result.
- The study selection must be depicted in a flow diagram, PRISMA, (either inserted below the search strategy or attached as a separate file). See example:

4.1 Relevant studies

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)	Relevant for clinical question <x>*
*when multiple clinical questions are defined in the protocol				

4.2 Main characteristics of included studies

Present the main characteristics of all studies included in the assessment of the clinical questions defined in the protocol. Include as a minimum the study type and the study design, the method of randomization and blinding, patient inclusion and exclusion criteria, the method of analyses, the follow-up time, and the baseline characteristics. Table A2 can be used as a template. One table per each study should be filled in.

5 Clinical questions

Complete the following information for each clinical question.

5.1 <Clinical question 1>

5.1.1 Presentation of relevant studies

Briefly summarize the studies that are used in the assessment of this clinical question.

Address any differences between the studies (patient characteristics and study characteristics).

5.1.2 Results per study

Provide a summary of the results for each outcome relevant for this clinical question. The study results presented should reflect the outcomes defined in the protocol.

Table A3 can be used as a template.

Describe the relevant endpoints, including the definition (operationalization) of the endpoint, 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, the variables used for the adjustment must be clearly defined and specified.

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 always 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 time points prespecified in the protocol should be presented.

Insert references for all data.

5.1.3 Comparative analyses

Provide a summary of the results from the comparative analyses for each outcome relevant for this clinical question. For dichotomous outcomes, both the estimated relative difference as well as the estimated absolute difference should be presented.

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

Clearly describe any inconsistencies between the methods defined in the protocol and the methods used for the comparative analyses. Any inconsistencies should be justified. The choice of method for synthesis (meta-analysis or narrative synthesis) should be justified, and specific analytical decisions in relation to the method chosen should be clearly specified.

5.2 <Clinical question 2>

5.2.1 Presentation of relevant studies

5.2.2 Results per study

5.2.3 Comparative analyses

5.3 <Clinical question 3 ….>

5.3.1 Presentation of relevant studies

5.3.2 Results per study

5.3.3 Comparative analyses

6 References

References should be formatted using the *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References* by the *International Committee of Medical Journal Editors (ICMJE)* (www.nlm.nih.gov/bsd/uniform_requirements.html). Further details of the requirements can be found in *Citing Medicine* (www.nlm.nih.gov/citingmedicine). In-text citations should follow the Vancouver style and use square brackets ([x]).

7 Appendices

Literature search

Table A1 Inclusion and exclusion criteria

Inclusion criteria	Population: Intervention(s): Comparator(s): Outcomes: Settings (if applicable): Study design: Language restrictions: Other search limits or restrictions applied:
Exclusion criteria	Population: Intervention(s): Comparator(s): Outcomes: Settings (if applicable): Study design: Language restrictions: Other search limits or restrictions applied:

Main characteristics of included studies

Study characteristics

Table A2 Main study characteristics
(Complete this table for each included study.)

Trial name	*Insert trial name*
NCT number	*Insert NCT number*
Objective	*Briefly state the overall objective of the study*
Publications – title, author, journal, year	*State all publications related to the trial.* *E.g.: Comparing XXX vs ZZZ in refractory patients, Andersen et al., NEJM, 2016*
Study type and design	*State the phase of the trial and describe the extent of crossover, method of randomization, degree of blinding, status (ongoing or completed), etc.* *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 to treatment assignment.*
Follow-up time	*E.g.: median follow-up of 7.3 months (range 0.5–16.5)*
Population (inclusion and exclusion criteria)	*Insert the inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov*
Intervention	*State the intervention including dose, dosing schedule, and number of patients receiving the intervention*
Baseline characteristics	*Describe the relevant baseline characteristics of the patient population, i.e.,* *- age (median, range…)* *- gender distribution (n, %...)* *- performance status* *- previous treatments* *- average weight / body surface area* *- organ function.*
Primary and secondary endpoints	*State the primary and secondary outcomes of the study.* *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.*
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.*
Subgroup analyses	*For each analysis, provide the following information:* *- characteristics of included population* *- method of analysis* *- prespecified or post hoc* *- assessment of validity, including statistical power of the analysis.*

Results per study

Table A3a Results of study <x>

Trial name:	*Insert trial name*										
NCT number:	*Insert NCT number*										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/ Risk ratio	95% CI	*P* value		
Example: median overall survival	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	*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.*	
	ZZZ	248	17.4 (15.0–19.8) months								
Example: 1-year survival	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	*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.*	
	ZZZ	248	63.8% (57.6–70.0)								
Example: HRQoL	XXX	211	−1.5 (0.1–3.1)	4.5	−8.97 to −0.03	0.05	NA	NA	NA	*The absolute difference in effect is estimated using a two-sided t-test.*	
	ZZZ	209	−6.0 (−1.8 to −10.2)								
Insert outcome 4	Intervention										
	Comparator										
Insert outcome 5	Intervention										
	Comparator										

Table A3b Results of study <y>

Trial name:	*Insert trial name*								
NCT number:	*Insert NCT number*								
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Hazard/Odds/Risk ratio	95% CI	*P* value	
Example: median overall survival	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	*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.*
	ZZZ	248	17.4 (15.0–19.8) months							
Example: 1-year survival	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	*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.*
	ZZZ	248	63.8% (57.6–70.0)							
Example: HRQoL	XXX	211	−1.5 (0.1–3.1)	4.5	−8.97 to −0.03	0.05	NA	NA	NA	*The absolute difference in effect is estimated using a two-sided t-test.*
	ZZZ	209	−6.0 (−1.8 to −10.2)							
Insert outcome 4	Intervention									
	Comparator									
Insert outcome 5	Intervention									
	Comparator									

Results per PICO (clinical question)

Table A4 Results referring to <clinical question x>

Results per outcome	*Attach forest plots and statistical results as a separate file.* *Results from the comparative analysis should be given in the table below, if possible.*							
		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Hazard/Odds/Risk ratio	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).*
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.*
Example: HRQoL		***−4.5***	*−8.97 to −0.03*	*0.05*	*NA*	*NA*	*NA*	*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.* **Fill in the name of an appropriate, measure of HRQoL.*
Insert outcome 4								
Insert outcome 5								
Insert outcome 6								
Insert outcome 7								