Applicant's Evidence Assessment

Submission to the State Institute for Drug Control

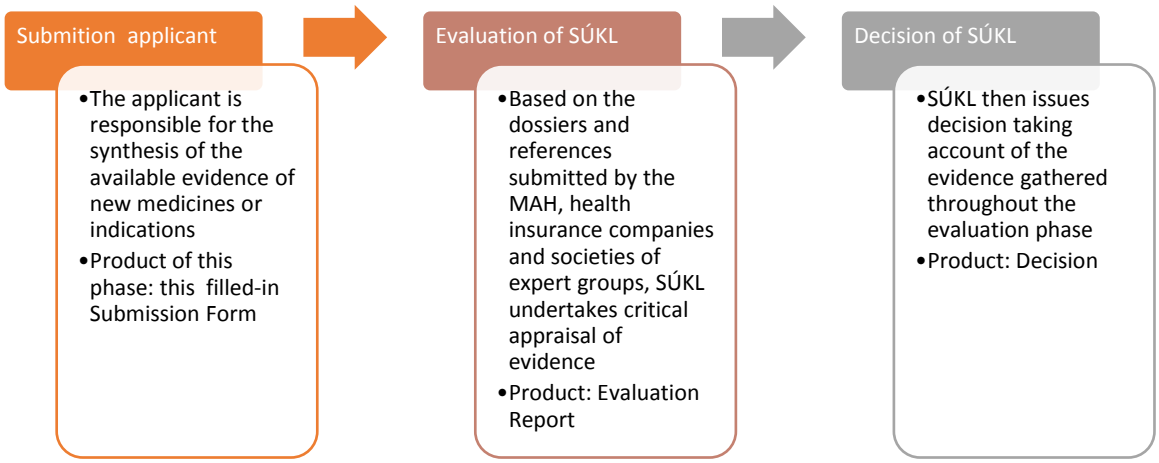
Applicant		
Medicinal product		
Therapeutic indication (short)		
Date		
Version		
This document contains any commercially confident information	NO	☐
	YES	☐
Highly innovative status is requested for the medicine	NO	☐
	YES	☐

Brief description of the HTA process of medicines in the Czech Republic

Administrative proceedings of new medicines or indications are initiated upon request/application that SÚKL receives from an applicant (marketing authorisation holder or health insurance company). Every application must be accompanied by documentation consisting of available evidence and full-text papers reporting results of clinical studies.

In order to give applicants sufficient notice and to facilitate applicant's works on evidence synthesis, this template summarises SÚKL's requirements on the minimum information. Concise information on the requirements can be found in the Guidelines on cost effectiveness and budget impact analyses no. SP-CAU-028 and SP-CAU-027, respectively, on www.sukl.cz.

Applicants may wish to consult the following flowchart to get a brief overview of the key milestones in the process.



Checklist for completion of Submission Form

Please ensure that you have completed all parts of the Submission Form and enclosed all the required attachments listed below before you make a submission to the Institute.

All parts of the Submission Form are completed	☐
Electronic version of the Submission Form is included in the submission (accepted formats are .doc, .docx, .pdf)	☐
Electronic full text versions of all references are included in the submission (including network meta-analysis or data on file)	☐
I am aware of the fact that failure to complete any of the abovementioned steps may delay the appraisal phase	☐

PART A Positioning

A-1 Therapeutic indications in SmPC

Present here the licensed indication(s) as per SmPC of the medicine under review.

A-2 Therapeutic indication(s) under review and sub-population

Clearly state the indication or subgroup of patients your submission is focused on.

A-3 Requested reimbursement conditions to be considered

Provide the exact wording of reimbursement conditions you have been suggesting.

A-4 Current conditions of reimbursement

If the medicine under review has been already reimbursed in the Czech Republic, state the conditions of reimbursement.

A-5 Published guidelines

Name published national and internationally recognised clinical guidelines relevant to the indication under review, enclose them in full-text versions, and provide a brief conclusion on the clinical pathway that is relevant to the submission.

A-6 Disease context and potential comparator(s)

Briefly describe current treatment pathway and the likely position of the medicine under review in it. Identify the potential comparators.

A-7 Relevant comparator(s)

Based on the current clinical practice and recommendations (especially those relevant for the Czech Republic and Europe), provide a list of all the treatments that are to be considered relevant comparators for the purpose of assessment, only comparators that are common and reimbursed from the public health insurance should be considered.

A-8 Comparators of similar effectiveness

Advise if there are any comparators of similar or comparable effectiveness and provide a brief justification for either statement (clinical study, reference).

Comparator	Similar effectiveness		Endpoint	Clinical evidence/study	Reference
Comparator 1	☐ Yes	☐ No			
Comparator 2	☐ Yes	☐ No			
	☐ Yes	☐ No			

A-9 Type of the clinical evidence supporting the clinical case

State whether the claimed benefits of the medicine under review are based on direct or indirect evidence. Specify what kind of clinical evidence the economic evaluation was based on.

Type of clinical evidence used for	Clinical case	Economic case
Direct comparative evidence		
Active-controlled study	☐	☐
Placebo-controlled study	☐	☐
Meta-analysis	☐	☐
Indirect comparative evidence		
Naïve or unadjusted indirect comparison	☐	☐
Adjusted indirect comparison (Bucher's comparison)	☐	☐
Network meta-analysis or mixed-treatment comparison (indirect)	☐	☐
Network meta-analysis or mixed-treatment comparison (both direct and indirect)	☐	☐
Matched-adjusted indirect comparison	☐	☐
Other		
…	☐	☐

Is there any other evidence on the effectiveness or safety that has not been included in this submission?	NO	☐
	YES	☐

If yes, provide the reasons why this has not been included:

PART B Overview

In **no more than three pages** describe the context within which the submission is being made. All supporting data should be fully referenced. Do not include any details – these will be provided in Parts C–G.

B-1 Summary of applicant's clinical case

B-1.1 Conclusions of clinical case

B-1.2 Strengths of clinical evidence

B-1.3 Weaknesses of clinical evidence

B-1.4 Key issues and uncertainties in the evidence with respect to the submitted clinical case

B-2 Summary of applicant's economic case

B-2.1 Conclusions of economic case

B-2.2 Strengths of economic evidence

B-2.3 Weaknesses of economic evidence

B-2.4 Key issues and uncertainties in the evidence with respect to the submitted economic case

B-3 Other HTA submissions or evidence

B-3.1 Previous submissions to the Institute relevant to the indication under review

Provide a summary of current and past submissions that have been made for the medicine under review or for any other medicine in the same or similar indication (taking account of the specifics, such as target population definition, line of treatment) in the Czech Republic.

No. of proceeding (the Institute´s)	Name of medicinal product	Indication	State and/or outcome*

* reimbursed – pending/in process – not reimbursed

B-3.2 Advice, recommendations or assessment reports of other healthcare or HTA agencies relevant to the indication under review

Provide a summary of current and past submissions that have been made to recognised foreign HTA agencies, e.g NICE (UK), SMC (UK), HAS (France), IQWIG (Germany), NCPE (Ireland), CADTH (Canada) and PBAC (Australia).

Agency (country)	Year	Indication	State and/or outcome

B-4 Highly innovative medicine

If you request the medicine to be considered highly innovative:

- state based on which provision of the Decree 376/2011 the status of high innovativeness is requested
- provide a brief justification of high innovativeness

This section should not exceed half a page. The justification should address only the aspects of high innovativeness. Clinical and other evidence is to be assessed in detail in subsequent parts.

PART C Comparative efficacy and effectiveness

Provide detail information on comparative clinical efficacy and effectiveness. The efficacy section should include details of randomised controlled trials (RCTs), meta-analyses and other studies that provide evidence of the clinical benefits of the medicine in its licensed dose within the indication(s) under review relative to active comparator(s) used in clinical practice. Placebo-controlled and uncontrolled studies can also be included if they provide evidence of relevant clinical benefits not demonstrated in active-controlled studies.
If the submission is based on an indirect comparison(s) (Part A-9), provide its summary in Appendix (see Appendix XY) and also attach a full text to support the submission.

C-1 Overview of clinical evidence

No.	Methodology	Patient nos.	Treatment Allocations	Source of funding

*Key studies are highlighted in bold and will be appraised in detail

C-1.1 Study design

Describe conditions of randomization and stratification. Address any other relevant (potentionally confounding) factors, such as co-morbidities, concomitant treatment(s), previous treatment(s), etc. Characterize the sub-population if it is relevant in the context of this submission.

Trial ID	Study population	Inclusion criteria	Exclusion criteria
Trial 1			
Trial 2			

C-1.2 Outcomes used as endpoints

Summarise all the endpoints used in each clinical study (i.e. name all the observed outcomes, such as overall survival, occurrence of adverse events, health-related quality of life, etc.). Indicate, which outcomes were primary endpoints.

Trial ID	Clinical endpoints	Quality of life endpoints	Other endpoints (resource use, etc.)

C-1.3 Studies use in evidence synthesis

Indicate which clinical studies are used in evidence synthesis (meta-analysis, etc.) and in the economic case.

Trial ID	Included in meta-analysis	Included in indirect comparison	Used in economic case
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

C-1.4 Flow of participants

Trial ID	Intervention arm	No. randomised	Did not receive intervention	Lost to follow-up	Discontinued	Analysed	Source of information
Trial 1	Proposed medicine	*N*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	Reference
	Main comparator(s)	*N*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	Reference
Trial 2	Proposed medicine (high dose)	*N*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	Reference
	Proposed medicine (low dose)	*N*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	Reference
	Main comparator(s)	*N*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	Reference

Adapted from PBAC

C-1.5 Results

State the primary outcome(s), relevant secondary outcome(s). Provide outcomes separately for the sub–population if it is relevant.

C-1.5.1 Dichotomous data

Trial ID	Proposed medicine	Main comparator	Relative risk (95% CI)	Risk difference (95% CI)
Trial 1	*n/N* with event (%)	*n/N* with event (%)	[add]	[add]
Trial 2	*n/N* with event (%)	*n/N* with event (%)	[add]	[add]

Taken from PBAC

C-1.5.2 Continuous data

Trial ID	Proposed medicine (mean values)	Proposed medicine (mean values)	Proposed medicine (mean values)	Main comparator (mean values)	Main comparator (mean values)	Main comparator (mean values)	Mean difference (95% CI)	ANCOVA (95% CI)
Trial 1a	Baseline (SD)	End point (SD)	Change (SD)	Baseline (SD)	End point (SD)	Change (SD)	[add]	[add]
Trial 2a	[add]	[add]	[add]	[add]	[add]	[add]	[add]	[add]
[etc]	[etc]	[etc]	[etc]	[etc]	[etc]	[etc]	[etc]	[etc]

Taken from PBAC

C-1.5.3 Time-to-event data

Please, fill-in the table below and provide cumulative distribution function charts.

Trial ID	Proposed medicine	Proposed medicine	Main comparator	Main comparator	Difference in median	*P* value (log rank test)	Hazard ratio (95% CI)
Trial 1	*n/N* with event.* (%)	Median time to event (95% CI)	*n/N* with event (%)	Median time to event (95% CI)	[add]	[add]	[add]
Trial 2	[add]	[add]	[add]	[add]	[add]	[add]	[add]
[etc]	[etc]	[etc]	[etc]	[etc]	[etc]	[etc]	[etc]

Adapted from PBAC

**Provide the definition of the event*

C-1.6 Ongoing studies or updated analysis of study/studies described previously

Additional evidence to be published within the next 6 to 12 months regarding the medicine in the indication(s) under review

C-1.7 Strengths of clinical evidence

Discuss strengths of key clinical studies and provide a summary.

Trial ID	Strengths

C-1.8 Limitations of clinical evidence

Discuss limitations and potential bias of key clinical studies and provide a summary.

Trial ID	Limitations	Potential for bias

PART D Comparative safety

D-1 Overview of safety evidence

No.	Methodology	Patient nos.	Treatment Allocations	Source of funding

*Key studies are highlighted in bold and will be appraised in detail

D-2 Description of adverse events

Overall adverse event profile

D-3 Description of comparability of adverse events (AEs)

Provide a comparison with the comparator(s) listing serious AEs and severe (grade≥3) AEs

PART E Health economic evaluation

E-1 Type of economic evaluation

Select what type of economic evaluation was used and provide brief justification.

Type of economic evaluation	Yes
Simple cost comparison	☐
Cost minimisation analysis	☐
Cost utility analysis	☐
Cost effectiveness analysis	☐

E-2 Design of the economic study

E-2.1 Patients

E-2.1.1 Target patient population

Describe the target population. If it does not reflect the wording of the licensed indication provide some clarification.

E-2.1.2 Subgroups of patients

Provide relevant information whether any chosen subgroups of patients were considered or intentionally omitted.

E-2.2 Comparator

State all the comparators included in the analysis (you may want to refer to section A-7). If various sequences of treatments are used in the comparator arm, provide a detailed description.

E-2.3 Study parameters

E-2.3.1 Perspective of the analysis

Describe the selected perspective.

E-2.3.2 Time horizon

Present the exact length and justification for the time horizon used.

E-2.3.3 Discounting

E-2.4 Model

E-2.5 Type of the model

Name of the medicine, short indication, date

E-2.5.1 Model structure

Present a diagram of the model structure.

E-2.5.2 Model description

Provide a description of the model and justify the choice of its structure, cycle length, half-cycle correction, etc.

E-3 Clinical evidence

E-3.1 Source of clinical evidence

If any indirect comparison is used as a basis for the economic case, provide full details in Appendix H-1.

E-3.2 Key strengths of the clinical evidence in the context of the submitted economic evaluation

E-3.3 Key weaknesses of the clinical evidence in the context of the submitted economic evaluation

E-3.4 Extrapolation

If it is necessary to extrapolate clinical data, please, describe and justify the methods used. Justify the selection of the most appropriate model for the base case. Relevant alternative scenarios should be included in sensitivity analysis or scenario analysis.

E-3.4.1 Akaike´s information criterion, Bayesian information criterion

E-3.4.2 Extrapolation of the survival curves

Fit a range of alternative survival models to the observed data (eg. exponential, Weibull, log-normal, log-logistic, gamma, Gompertz).

E-3.4.3 Log-log cumulative hazard plots

E-3.5 Transition probabilities

State the transition probabilities if it is used in the economic model.

E-3.6 Expert panel

Provide details on the expert panel that was held.

Meeting date:		Meeting place:	
Composition of the panel	Name of the expert 1, workplace 1		

	Name of the expert 2, workplace 2 [Add more rows, as needed]		
Question	mean/ median	the lowest value	the highest value
Number of visiting per month	3,3 / 4,0	2,0	4,0
[Add more rows as needed]			

E-4 Health benefits

E-4.1 Clinical health outcomes

Describe the clinical outcomes that were used to inform the model. State if the analysis was based on surrogate clinical parameters which were transformed into patient-relevant outcomes or whether these were taken directly from a relevant source.

E-4.2 Patient-oriented outcomes

E-4.3 Health-related quality of life

E-4.3.1 Methods to estimate utility weights

Describe the method of elicitation of impact the medicine under review has on patients' quality of life.

E-4.3.2 Mapping

If mapping was used, describe the details of the methodology, incl. from which tool to which one the mapping was performed (for example SF–36 to EQ–5D). State details of validation of the mapping technique. Are the mapping techniques published? If yes, reference the publication and briefly describe it.

E-4.3.3 Population characteristics

Compare patient characteristics of the HRQoL data source study and of the population under review, identify any important differences and justify the use of the data. Provide a discussion on how the base case result can be influenced by those differences.

E-4.3.4 Utility weights used

State the key utility values which were used.

Health state	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Health state 1	HS1			
Health state 2	HS2			
[Add more rows as needed]				

Adverse reaction 1	AR1			
Adverse reaction 2	AR2			
Abbreviations: HS, health state; AR, adverse reaction.				

Taken from NICE

E-4.4 Previously published utility weights

List any other previously published studies which focus on quality of health in the context of this submission. Justify the differences.

E-4.5 Summary

State the key strengths and weaknesses in the context of clinical evidence and health benefits. Could the weaknesses influence the results of the economic evaluation?

E-5 Resource use and costs

E-5.1 Medicine costs

List the used medicine costs. If relevant, include also administration costs, adverse events cost, subsequent treatment costs etc.

E-5.1.1 Dose and duration of treatment used in the economic analysis

If the dose and duration of treatment was not same as in the clinical evidence justify the assumptions.

E-5.1.2 List the sources of medicine costs

If another approach than the methodology of the Institute SP–CAU–28 is used, justify the assumptions.

E-5.2 Other costs and savings

E-5.3 Summary

State the key strengths and weaknesses in the context of resource use and costs. Could the weaknesses influence the results of the economic evaluation?

E-6 Key assumptions

Briefly describe all of the key assumptions made and indicate whether their impact on results was explored in the sensitivity or scenario analyses.

Base case assumption	**Page/section of justification**	**Mark if included in sensitivity analysis**
Description of base case assumption 1		☐

Description of base case assumption 2		☐
Description of base case assumption 3		☐

E-7 Analysis of Results

E-7.1 Base-case result (without any confidential discounted costs)

Present the base case results in a form recommended in the table X, including disaggregated costs and outcomes.

E-7.1.1 Cost breakdown

Table X. Disaggregated summary of costs

Costs by category	Costs for intervention under review	Costs for comparator	Incremental costs	% of total incremental costs
Technology cost				
Mean total treatment cost				
Administration cost				
Monitoring cost				
Examinations cost				
Hospitalization cost				
Adverse events cost				
Treatment cost after progression				
(Add more rows as needed)				
Total costs				

Costs by health state	Costs for intervention under review	Costs for comparator	Incremental costs	% of total incremental costs
Health state 1				
Health state 2				
(Add more rows as needed)				

E-7.1.2 Outcomes breakdown

Table X. Disaggregated summary of health outcomes (QALYs)

QALYs by health state	QALYs for intervention under review	QALYs for comparator	Incremental QALYs	% of total incremental QALYs
Health state 1				
Health state 2				
(Add more rows as needed)				
Total QALY				

Table X. Disaggregated summary of health outcomes (LYGs)

LYGs by health state	LYGs for intervention under review	LYGs for comparator	Incremental LYGs	% of total incremental LYGs
Health state 1				
Health state 2				
(Add more rows as needed)				
Total QALY				

E-7.1.3 Economic results for sub-groups considered

E-7.1.4 External and internal model validation

Outcome	Clinical trial result	Model result
Progression-free survival	C1	R1
Post-progression survival	C2	R2
Overall survival	C1+2	R1+2
Adverse reaction 1	C3	R3

E-7.2 Base-case result (with confidential cost of assessed medicine)

Present the base case results in a form recommended in the table X, including disaggregated costs and outcomes.

E-7.2.1 Cost breakdown

Table X. Disaggregated summary of costs

Costs by category	Costs for intervention under review	Costs for comparator	Incremental costs	% of total incremental costs
Technology cost				
Mean total treatment cost				
Administration cost				
Monitoring cost				
Examinations cost				
Hospitalization cost				
Adverse events cost				
Treatment cost after progression				
Total costs				

Costs by health state	Costs for intervention under review	Costs for comparator	Incremental costs	% of total incremental costs
Health state 1				

Health state 2				

E-7.3 Base-case result (with confidential costs of assessed medicine and key comparators)

Present the base case results in a form recommended in the table X. For the medicine under review, present two scenarios – with and without the offered patient access scheme; and for key comparators, consider a potential discount ranged 0–100% of the publicly available costs using a 5% decrement.

Comparator 1 discount	Comparator 1 corresponding cost	Results at public price	Results using confidential costs at the discount level
100%			
95%			
90%			
85%			
80%			
75%			
70%			
65%			
60%			
55%			
50%			
45%			
40%			
35%			
30%			
25%			
20%			
15%			
10%			
5%			
0%			

E-7.4 Sensitivity analysis

E-7.4.1 One–way sensitivity analysis

Summarize the ranges individual variables were studied in and provide corresponding results to lower/upper bound of the interval and Tornado diagram.

Variable	Lower bound (LB)	Upper bound (UB)	ICER (LB)	ICER (UB)
Variable 1				
Variable 2				

E-7.4.2 Scenario sensitivity analysis

In this section, the effect of key assumption should be studied. Note that this section will be compared with section E-6 Key assumptions.

Base case assumption	Alternative scenario	Results
Description of base case assumption 1	Description of alternative assumption 1	Alternative assumption 1
Description of base case assumption 2	Description of alternative assumption 2	Alternative assumption 2

E-7.4.3 Probabilistic sensitivity analysis

Describe the methods and tabulate the results, provide a cost-effectiveness acceptability curve and cost-effectiveness scatter plot including the deterministic and probabilistic results.

E-8 Interpretation and conclusions of this part

PART F Budget impact evaluation

F-1 Patients

F-1.1 Size of eligible patient population

Provide the number of eligible patients and describe the algorithm used to define the size of eligible patient population and list numbers of patients.

F-1.2 Market share

Provide market shares of all treatments that are considered, i.e. all comparators and medicine under review in scenarios with the medicine (as if it is present on market) and without the medicine (as if is not present on market).

F-1.3 Size of treated patient population

F-2 Costs

F-2.1 Pharmaceutical costs

F-2.2 Other costs

F-3 Results

F-3.1 Results without any confidential costs

F-3.1.1 Scenario with the medicine under review

F-3.1.2 Scenario without the medicine under review

F-3.1.3 Net budget impact

F-3.1.4 Sensitivity analysis

F-3.2 Base-case result (with confidential costs of assessed medicine and key comparators)

Present the base case results in a form recommended in the table X. For the medicine under review, present two scenarios – with and without the offered patient access scheme; and for key comparators, consider a potential discount ranged 0–100% of the publicly available costs using a 5% decrement.

Comparator 1 discount	Comparator 1 corresponding cost	Net budget impact year 1	Net budget impact year 2	Net budget impact year 3	Net budget impact year 4	Net budget impact year 5

100%						
95%						
90%						
85%						
80%						
75%						
70%						
65%						
60%						
55%						
50%						
45%						
40%						
35%						
30%						
25%						
20%						
15%						
10%						
5%						
0%						

F-4 Strengths and weaknesses of the analysis

F-5 Interpretation and conclusions of this part

PART G References

List here all references using one of the recognised referencing styles.

PART H Appendices

H-1 Summary of meta-analysis or indirect comparison

H-1.1 Overview

Fill in case that the economic analysis was based on the data (clinical benefits and adverse events) from meta-analysis or indirect or mixed treatment comparisons. Provide an overview and details of them, if it is not done in Section D.

H-1.1.1 Methodology

Provide search strategy, the inclusion and exclusion criteria, patient populations etc.

H-1.1.2 Diagram of the network of the data sources

H-1.1.3 Results of meta-analysis, indirect or mixed treatment comparison

State the hazard ratios and 95% confidence or credible intervals

H-1.1.4 Limitation of meta-analysis, indirect or mixed treatment comparison