THIS IS ONLY A SUMMARY OF THE CZECH VERSION.

IN THE EVENT A DISCREPANCY BETWEEN THE CZECH AND ENGLISH VERSIONS OCCURS THE CZECH VERSION SHALL PREVAIL AND SHALL BE AUTHORITATIVE.

PLEASE NOTE that the English summary of this procedure is intended to help marketing authorisation holders and other stakeholders when preparing cost-effectiveness analysis to be submitted to the State Institute for Drug Control. It is important to highlight that might be difficult to understand some expressions or terms as these are defined in the context of the Act on Public Health Insurance (AoPHI) which forms the basis of the national regulation of the Public Health Insurance in the Czech Republic.

1. OBJECTIVE

To determine the procedure for the appraisal of pharmacoeconomic evaluations submitted within administrative procedures.

2. USERS

This procedure applies to the assessors of the Price and Reimbursement Regulation Branch when reviewing pharmacoeconomic evaluations in administrative procedures regarding determination or change of the reimbursement price and reimbursement conditions of medicinal products/foods for special medical purposes.

3. DEFINITIONS OF BASIC TERMS AND ABBREVIATIONS

CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
CUA	cost-utility analysis
ICER	incremental cost-effectiveness ratio
LYG	life-year gained
RG	reference group, also “jumbo group”
QALY	quality-adjusted life-year
Institute	State Institute for Drug Control
RPC	reimbursement price and reimbursement conditions

Sensitivity analysis (SA) – Part of pharmacoeconomic evaluation, which evaluates the sensitivity of the result associated with the uncertainty of input parameters and the execution of the base case scenario. It validates the results in the base case scenario and the applied methodology of pharmacoeconomic evaluation.

Cost-effectiveness analysis (CEA) – An analysis which allows for the assessment of cost-effectiveness of the intervention under review against comparator intervention. Any relevant treatment-associated (direct) costs and benefits are assessed over a predefined period of time and outcome measure. The result is always the determination of the incremental cost-effectiveness ratio (ICER).

Cost-minimization analysis (CMA) – An analysis which allows for the assessment of cost-effectiveness of the intervention under review against comparator intervention, if the benefits (efficacy and safety) of these interventions are comparable. In such a case, only costs associated with these interventions are assessed.

Cost-utility analysis (CUA) – An analysis very similar to CEA analysis in terms of methodology. The outcome measure of this type of analysis is most often the QALY, which includes impact upon life expectancy and quality of life.

Dominant intervention – An intervention, which is less costly than the comparator intervention and, concurrently, generates greater benefit. The opposite situation is the scenario where the intervention under review is costlier and generates smaller benefit (*dominated*).

Pharmacoeconomic evaluation – An analysis which allows for the assessment of cost-effectiveness of the intervention under review against comparator intervention. The individual types of pharmacoeconomic evaluation, acceptable by the Act on Public Health Insurance, are CUA, CMA, and CEA.

Investigational intervention (II) – Medicinal product/food for special medical purposes, in respect of which the evaluation of cost-effectiveness as referred to under Section 15, paragraph 8 of the Act on Public Health Insurance is required.

Evaluation of cost-effectiveness – Activities resulting in the generation of a cost-effectiveness analysis: evidence search, data collection, data evaluation and synthesis, creation of a mathematical model, drafting of documentation, including a report, and updates of these steps in relation to the available knowledge.

Assessor (expert employee) – An employee of the Price and Reimbursement Regulation Branch responsible for expert processing and critical appraisal of source materials on the efficacy, safety, cost-effectiveness and budget impact.

Incremental cost-effectiveness ratio – A ratio of the total cost difference and total benefit difference of the reviewed and comparator intervention. It expresses the costs which have to be incurred to obtain one more unit of the benefit (in the outcome measure).

Clinical benefits of treatment – The properties of the reviewed and the comparator interventions which are assessed in clinical studies. These particularly include the parameters of clinical efficacy of the intervention in respect of the studied disease and safety parameters observed during the treatment with the studied intervention.

Quality of life (QoL) – A parameter to assess the impact of a disease on the physical, mental, and social condition of the patient.

Cost-effectiveness – Determination of the ratio between the costs and benefits associated with the use of the intervention under review compared to the use of the comparator intervention.

Cost-effective procedure – A procedure which, with comparable costs, provides the same or higher therapeutic effect resulting in extension of life expectancy, improved quality of life, or an improvement of a substantial measurable criterion of the respective disease. Or such a procedure which, with at least comparable therapeutic effect, means lower total costs for the health insurance system. Or such a procedure whose cost-benefit ratio is, with higher costs and higher therapeutic effect, comparable to other therapeutic procedures reimbursed from health insurance funds. This definition complies with the provision of Section 15, paragraph 8 of the Act on Public Health Insurance.

Cost – A financial amount expressed in Czech crowns (CZK), which is incurred in relation to a disease and its treatment, classified as direct or indirect costs. In pharmacoeconomic evaluation, direct costs associated with the use of the intervention under review and direct costs associated with the comparator intervention are to be included.

Underlying study – A study (e.g.: systematic review with a meta-analysis, a randomised clinical study, observational study, data from a register, etc.) which is the source of data about the benefits of treatment with the reviewed or comparator intervention for the purposes of pharmacoeconomic evaluation.

Cost-effectiveness analysis critical appraisal – Activities which result in the review of individual steps of the submitted evaluation with emphasis upon their justification, correctness, and completeness.

Head-to-head study – A clinical study monitoring groups of patients treated with the investigational and comparator intervention.

Comparator intervention (CI, comparator) – A therapeutic procedure reimbursed from health insurance funds (medicinal product/food for special medical purposes or other therapeutic procedure), which is generally accepted for the indication under review as common pursuant to Section 15, paragraph 8 of the Act on Public Health Insurance (see below).

Utility – A parameter which quantifies the quality of life. It usually assumes a value from 0 (quality of life associated with a condition with zero value of health – death) to 1 (quality of life associated with

the maximum value of health). Some utility resources generate also conditions with negative values – i.e. conditions worse than death.

Outcome measure – For the purposes of this procedure the term outcome measure is defined as a treatment benefit parameter generated by the use of the investigational and comparator interventions, it is common to both and it is relevant for the result of the pharmacoeconomic evaluation.

Base-case – The basic setup of pharmacoeconomic evaluation which reflects the current clinical practice and available evidence to the maximum degree practicable. It is a scenario based on the best justified key assumptions, such as the input data averages (efficacy, safety, costs, transition probabilities between model statuses, etc.).

4. ASSOCIATED INTERNAL REGULATIONS

This version does not contain references to internal regulations and forms.

5. ASSOCIATED GENERALLY EFFECTIVE REGULATIONS, STANDARDS AND REGULATIONS OF THE EUROPEAN UNION

Act No 48/1997 Coll., on Public Health Insurance and on Amendment to Some Related Acts, as amended ("Act on Public Health Insurance", also abbreviated as "AoPHI").

Decree No 376/2011 Coll., implementing some provisions of the Act on Public Health Insurance ("Decree No 376/2011 Sb.").

Decree No 134/1998 Coll., on the list of medical services (LMS) and their point values. Decree on the determination of point value, amounts of reimbursement of reimbursed services, and regulatory restrictions for the year in question, including annexes thereto.

Decree No 384/2007 Coll., on the list of reference groups, as amended ("Decree No 384/2007 Coll.").

Act No 500/2004 Coll., the Code of Administrative Procedure, as amended (the "Administrative Code").

6. PROCEDURE

This procedure focuses on the assessment of completeness and quality of the pharmacoeconomic evaluation submitted for the purposes of administrative procedure regarding the determination or change of the reimbursement price and reimbursement conditions of a medicinal product/food for special medical purposes in the public health insurance system of the Czech Republic.

The procedure stipulates the methodology of cost-effectiveness analysis critical appraisal and specification of the basic requirements for its presentation and quality. It is not possible to predict all the situations that may arise, particularly due to the rapid development in the sphere of pharmacoeconomics and related disciplines; for this reason, when applying this procedure, it is necessary to take into account also the current international standards in the respective area. It should hence be borne in mind that it is possible to admit the existence of another shortcoming not directly implied by this procedure which, however, may arise from other recommendations or available evidence and may have a direct impact upon the correctness of the conducted pharmacoeconomic evaluation (particularly with a view to the specific individual properties of the assessed interventions). The evaluation of cost-effectiveness should be conducted *lege artis*, i.e. in accordance with the current knowledge in the given field and requirements and recommendations of recognised authorities and professional societies, a non-exhaustive list of which is provided under section 6.3.

Should the author of the analysis deviate from the recommendations or requirements set forth herein or from any other relevant guidelines, he/she should properly discuss the facts leading to the course of action opted for, including the provision of any relevant evidence, as well as the potential impact of such course of action upon the result.

In cases where it is necessary to emphasise the local requirements governing inputs or analysis setup, such requirement is specified in the relevant chapter of this Procedure.

6.1.When is evaluation of cost-effectiveness required?

Cases where evaluation of cost-effectiveness is required are listed under the provision of Section 15, paragraph 8 of the Act on Public Health Insurance. Specifically, the evaluation is required for:

1. Medicinal products/foods for special medical purposes not included in any group of essentially therapeutically replaceable medicinal products/foods for special medical purposes (reference/jumbo group) as referred to under the provision of Section 39c, paragraph 1 of the Act on Public Health Insurance, and determination or change of reimbursement price and conditions has been requested;
2. Medicinal products/foods for special medical purposes for which a prescription or indication restriction is proposed on a different basis than that for medicinal products/foods for special medical purposes classified in a relevant group of essentially therapeutically replaceable medicinal products/foods for special medical purposes;
3. Medicinal products/foods for special medical purposes for which determination or change of an additional increased amount reimbursement and conditions of such reimbursement is requested as per the provision of Section 39b, paragraph 11 of the Act on Public Health Insurance;
4. Medicinal products/foods for special medical purposes for which an increase in the reimbursement amount from the basic reimbursement amount is requested (bonus application as referred to under the provision of Section 25 and subsequent sections of Decree No 376/2011 Coll.)

Evaluation of cost-effectiveness is also required for:

5. Non-authorised medicinal products (so called *off-label* indications) pursuant to the provision of Section 39b, paragraph 3 of the Act on Public Health Insurance;
6. Highly innovative medicinal products pursuant to the provision of Section 39d of the Act on Public Health Insurance, in a procedure for determination or change of temporary and permanent reimbursement.

Furthermore, cost-effectiveness is to be evaluated in the following cases:

7. Determination of reimbursement as per the provision of Section 39c, paragraph 2(b) of the Act on Public Health Insurance;
8. Changes or amendments to the method of determining reimbursements – if, in the past, cost-effectiveness was not evaluated with regard to the currently used reimbursement determination method which did not require it, but at present the applicant applies applied for reimbursement determination using a method that requires such evaluation (e.g., when in the first administrative procedure, reimbursement price and conditions (RPC) were determined pursuant to the provision of Section 39c, paragraph 2(b) of the Act on Public Health Insurance, and newly, in the second administrative procedure, a change/determination of the RPC is requested pursuant to the provision of Section 39c, paragraph 2(a) of the Act on Public Health Insurance, which would result in an increase of the reimbursement of the intervention under review).

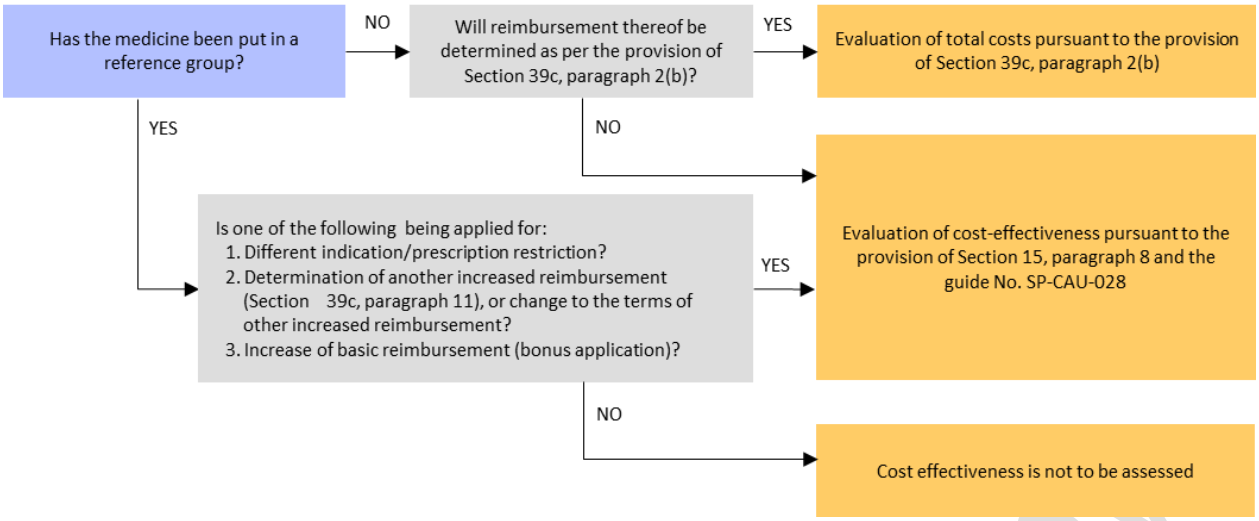

Figure 1 Cases in which cost-effectiveness pursuant to the Act on Public Health Insurance is / is not to be evaluated

Evaluation of cost-effectiveness as referred to under the provision of Section 39b, paragraph 2(c) of the Act on Public Health Insurance is to be submitted by the party to the procedure. The provision of Section 39f, paragraph 6 of the Act on Public Health Insurance, furthermore, specifies that in case of a procedure initiated upon request, the cost-effectiveness analysis is to be submitted by the applicant.

6.2. Definition of a cost-effective therapeutic procedure

Pursuant to the provision of Section 15, paragraph 8 of the Act on Public Health Insurance, there are three scenarios in which a therapeutic procedure may be considered cost-effective:

1. It provides the same or higher therapeutic effect with comparable costs (i.e. in case of determination of reimbursement pursuant to Section 39c, paragraph 2(b) of the Act on Public Health Insurance);
2. It provides at least a comparable therapeutic effect with lower total costs;
3. For therapies with higher costs and higher therapeutic effect the ratio costs/benefits is comparable (similar) to other therapeutic procedures reimbursed from the public health insurance funds.

While for items 1 and 2 the analysis-based determination of whether the procedure is cost-effective is rather simple, item 3 requires a comparison between the ICER value of the investigational intervention and ICER values of other (already reimbursed) interventions.

6.3. Type of Pharmacoeconomic evaluation, its methodology and its outcome measure

The selection of the basic methodology (type) of economic assessment should be conducted with regard to the identified differences in the benefits of treatment between the investigational intervention under review and comparator interventions and, moreover, taking into account the selection of the outcome measure.

The benefits of the investigational and comparator intervention are comparable

In the specific case, where the benefits of the intervention under review and comparator intervention are comparable based on available evidence, the author shall opt for the cost minimisation analysis (CMA) type of analysis to prove cost-effectiveness. The comparable level of benefits has to be clearly supported by appropriate evidence, through a direct comparative study of adequate robustness to assess the non-inferiority or equivalence in the main clinical parameters of efficacy and safety, meta-analysis of available clinical studies, or another suitable type of evidence.

Pursuant to the provision of Section 15, paragraph 8 of the Act on Public Health Insurance, it is possible to consider an intervention under review showing at least a comparable therapeutic effect cost-effective if, the use of the intervention generates lower total costs for the public health insurance system. The definition of cost-effectiveness when determining reimbursement pursuant to the provision of Section 39c, paragraph 2(b) of the Act on Public Health Insurance is slightly different – in this case, the basic reimbursement amount is determined as the amount of daily costs net of profit

margin and taxes, if cost-effective with respect to the time necessary for the individual therapeutic procedures. In such a case the definition set forth under the provision of Section 15, paragraph 8 of the Act shall apply: Cost-effective are such therapeutic procedures, which, with comparable costs, offer a comparable or higher therapeutic effect. Sensitivity analysis shall be submitted also in cases where CMA has been applied.

Assessment:

Where this type of analysis has been selected, the assessor shall check whether CMA has been used in accordance with the procedure outlined above, i.e. whether comparability has been discussed and evidenced, and whether the benefits in major clinical parameters may indeed be considered comparable. In case comparability has not been sufficiently evidenced, the Pharmacoeconomic evaluation using this methodology cannot be accepted. In such a case it is appropriate to use CUA-type analyses.

The benefits of the investigational and comparator intervention are different

In case of a disease which, including its sequelae or treatment, affects life expectancy or the quality of life, the clearly preferred method is CUA, with the benefit expressed in the form of QALY.

Only in adequately justified cases where it is not possible to conduct CUA, it is permissible to use the CEA method, with the benefit expressed in the form of LYG (the disease, incl. its sequelae or treatment, affects life expectancy), or, where LYG cannot be used, it is possible to use a substantial and measurable criterion of the respective disease.

Other types of pharmacoeconomic analyses (CBA, CCA, etc.) are not permissible as cost-effectiveness evidence.

The procedure of the selection of suitable methodology of pharmacoeconomic evaluation and selection of the suitable outcome measure is outlined in Fig. 2.

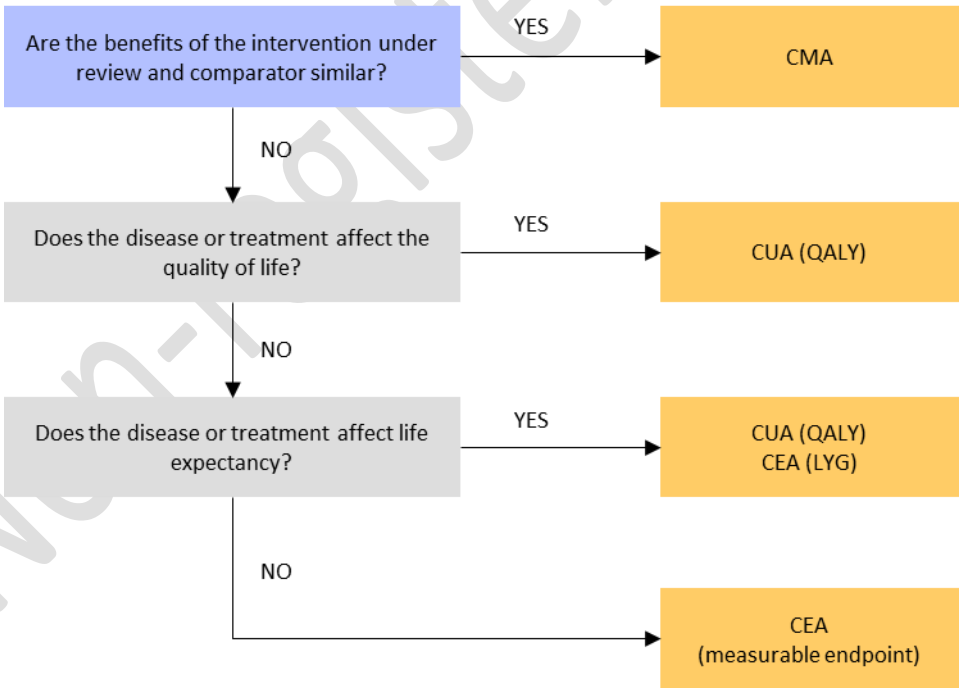

Figure 2 Decision-making tree for the selection of the type of analysis and outcome measure

Assessment:

When assessing the submitted analysis, the assessor shall focus on the selection of the outcome measure as per the aforementioned decision-making tree, check the available evidence regarding life expectancy and quality of life, and verify the justification of the selection of the type of pharmacoeconomic evaluation chosen by the author. In case of non-compliance of the selected cost-effectiveness analysis methodology and selection of the outcome measure it is not possible to consider the submitted pharmacoeconomic evaluation properly completed and its conclusion

representative.

6.4. Recommended procedures of Evaluation of cost-effectiveness

Good pharmacoeconomic practice and current issues in this field are addressed by research and regulatory organisations worldwide. With regard to the comprehensiveness and rapid development of this discipline, the Institute hereby provides an overview of recommended materials of acknowledged institutions which should be considered by the author of the cost-effectiveness analysis prior to the commencement of the evaluation proper as well as in its course. In addition to the current scientific literature, other sources include the following:

1. Good practice documents of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[1]
2. Recommendations of the NICE Decision Support Unit[2]
3. Recommended procedures of EUnetHTA[3]
4. Recommended procedures of the Czech Pharmacoeconomic Society (ČFES)[4]

6.5.Structure of the report on evaluation of cost-effectiveness

The author shall submit the pharmacoeconomic evaluation report structured in a manner allowing for the assessment of the methodology and procedures which were applied in the evaluation of costs and benefits. All of the input variables, procedures (incl. calculations) or statements have to be supported by appropriate evidence to allow for review. Concurrently, it must be obvious what data were taken from sources outside the Czech Republic.

The structure of the report describing the completed pharmacoeconomic evaluation usually consists of the following chapters:

- Objective of the of pharmacoeconomic evaluation (issue) and basic design of the analysis;
- Selection of the comparator intervention (comparator);
- Description of the investigational and comparator intervention;
- Perspective of the evaluation;
- Target population;
- Time horizon of the evaluation;
- Selection of the suitable type and methodology of pharmacoeconomic evaluation, selection of the outcome measure;
- Separate expression of the costs and benefits and their discounting, where appropriate;
- Determination of the result of pharmacoeconomic evaluation;
- Uncertainty of the result (sensitivity analysis, model validation);
- Conclusion and interpretation of results.

6.6. Objective of the of pharmacoeconomic evaluation

Definition and requirement:

Generally, pharmacoeconomic evaluation is conducted in order to elucidate whether the requested amount of reimbursement or increase in costs drawn from the public health insurance funds is adequate to the benefits which are anticipated in association with the use of the investigational intervention in clinical practice.

In the introduction to the report, the author should express a specific objective and purpose of the submitted evaluation. It should be clear from content of this chapter whether it is intended for the determination of the amount and terms of reimbursement, extension of existing terms of reimbursement, in what specific indication, for bonus or malus application, medicinal product/food for special medical purposes, etc.

Assessment:

[1] ISPOR: Good Practices for Outcomes Research and Use in Health Care Decisions. Available from: http://www.ispor.org/workpaper/practices_index.asp

[2] NICE Decision Support Unit: Technical Support Documents. Available from: http://www.nicedsu.org.uk/Technical-Support-Documents(1985314).htm

[3] EUnetHTA Guidelines: http://www.eunethta.eu/eunethta-guidelines

[4] ČFES: Recommended procedures of ČFES for health economic evaluations. Available from: http://farmakoekonomika.cz/

The assessor shall assess whether the objective of the evaluation is consistent with the data provided in the application for determination/change of the amount or terms of reimbursement and whether pharmacoeconomic evaluation is, in such a case, required as per the relevant provisions of the Act on Public Health Insurance and as detailed under section 6.1.

6.7.Analysis source data and submitted evidence

Definition and requirement:

Pharmacoeconomic evaluation should be based upon state-of-the art and valid professional evidence in compliance with the principles of evidenced-based medicine. In compliance with the provision of Section 45 of Decree No 376/2011, any key evidence referred to in the pharmacoeconomics evaluation shall be submitted to the Institute in full, otherwise the potential pharmacoeconomic evaluation cannot be considered reviewable. The hierarchy of evidence strength and validity and requirements for specific types of underlying studies are governed by internationally recognised standards.[5,6] Where source data are based on a study which has not been published to date, a report on the setup and results of this study shall be submitted in a similar scope so that it is possible to evaluate the key aspects. An example of the structure of such a document is presented by the Institute in the Annex.

Source data for the analysis, including used calculations, intermediate steps and considerations should be presented in a straightforward manner with appropriate comments. The same applies in the case that new evidence is presented together with an application for a change to / amendment of the content of the submission or in response to a call for cooperation, where any changes to the previous version must be commented on.

Expert panel

Opinion of an expert panel represents a special type of source data intended for the description of clinical practice and for pharmacoeconomic evaluations. Where an expert panel has been established, the author of the pharmacoeconomic evaluation should submit the following information to allow for review:

1. Its nominal membership, specifying the position or expertise of the members;
2. Date when it was held and venue thereof;
3. List of questions or questionnaires which were presented to the members of the panel to be answered;
4. The content of the positions provided by individual experts or results of statistical evaluation, if the panel had 3 or more members (e.g. specification of mean and limit values).

The composition of members of the expert panel should correspond to the treatment of the disease in clinical practice, it should involve doctors from healthcare facilities where a significant number of patients with the disease in question may be anticipated with regard to the proportionate distribution in the Czech Republic, who are experienced in the treatment of such patients. The number of members and composition of such expert panels should reflect the situation in the incidence of the respective disease and should be appropriately justified.

Table 1 Example of presentation of basic data on the expert panel

Date of meeting:	Venue:		
Panel membership:	Expert 1, Site 1 Expert 2, Site 2 Expert 3, Site 3		
Issue	Mean / median	Lowest value	Highest value
Number of visits per month	3.3 / 4.0	2.0	4.0

[5] EUnetHTA Guidelines: http://www.eunethta.eu/eunethta-guidelines

[6] NICE Decision Support Unit: Technical Support Documents. Available from: http://www.nicedsu.org.uk/Technical-Support-Documents(1985314).htm

Per cent of i. v. administration	10% / 3%	2%	25%

Assessment:

The assessor shall check whether the pharmacoeconomic evaluation has been based upon the state-of-the art and valid professional evidence in compliance with the international principles of evidence-based medicine. Potential risk of bias shall be assessed. Concurrently, it shall be verified whether the evidence has been submitted in full, otherwise the submitted evaluation cannot be considered properly completed.

6.8.Selection of comparator intervention (comparator)

Definition and requirement:

Comparator interventions (comparators) are therapeutic procedures which are recognised as common for the therapy of the respective disease of the target patient group in the concerned stage of the disease and for its treatment line and are, concurrently, reimbursed from the health insurance funds of the Czech Republic. Where several relevant comparators have been identified, the comparison should be completed separately with each of them. Furthermore, the selection of the comparator must be properly justified.

A reimbursed therapeutic procedure hence means that it is a medicinal product/food for special medical purposes or other therapeutic procedure which is reimbursed from health insurance funds. Please note that a suitable comparator may enter the reimbursement system also in the course of the administrative procedure held for the investigational intervention.

Common therapeutic procedure means that it is a routinely used procedure for the target group in the given indication.

Generally, for the main comparator in the base case scenario, the Institute discourages the use of those medicinal products/foods for special medical purposes which are:

1. Reimbursed within the scope of institutional care on the basis of a drug flat rate, if there is any doubt as to their similar position in clinical practice as that of the investigational intervention;
2. Reimbursed in the regimen referred to under the provision of Section 16, paragraph 1 of the Act on Public Health Insurance, if another comparator is available which is reimbursed through the standard reimbursement mechanism. If the comparator is a medicinal product/food for special medical purposes reimbursed via this special reimbursement mechanism, it is necessary to prove in the administrative procedure that reimbursement is routinely realised in this manner, what the costs of such a treatment are, and to what percentage of patients such a procedure is applied;
3. Temporarily reimbursed medicinal products/foods for special medical purposes for the base case scenario, as cost-effectiveness did not have to be proven for these products, restricted duration of the temporary reimbursement applies, and there are uncertainties regarding the determination of permanent reimbursement.

With a view to the aforementioned, a permanently reimbursed comparator should be used in the basic scenario. In respect of an alternative scenario, however, the Institute recommends to use also an intervention reimbursed pursuant to the provision of Section 39d of the Act on Public Health Insurance in the temporary reimbursement regimen.

Assessment:

The assessor shall evaluate both Czech and foreign recommended treatment procedures, the summary of the product characteristics (SPC) and the terms of reimbursement, whether the individual treatment methods (pharmacological as well as non-pharmacological) are used, reimbursed, under what conditions and whether they are relevant comparators for the proposed objective of the analysis (determination or change of the terms of reimbursement). He/she shall therefore check whether the comparator intervention was selected correctly.

6.9.Description of the investigational and comparator intervention

Definition and requirement:

The description of the intervention under review and comparator intervention should contain all the information relevant for the proper pharmacoeconomic evaluation. This comprises, in particular, a description of the efficacy, safety and other properties, if affecting the benefits or costs of the intervention (dosing, rules for starting, discontinuing and terminating treatment, etc.). Furthermore, it shall contain a description of the population from underlying studies and an evaluation of comparability with the target population proposed in the terms of reimbursement (section 6.11 refers).

Assessment:

The assessor shall check whether the data from clinical evidence may be applied to the target population for which the evaluation has been completed.

Table 2 Example of presentation of basic data on interventions

Intervention	Act. subst. 1	Act. subst. 2	Act. subst. 3
Dosing	3 mg	10 mg/kg	Highest value
Dosing frequency	Daily	Day 1 of a 21-day cycle	4.0
Treatment termination	Lifelong administration, termination 10% per year due to ADR	Until progression, see PFS curve	Until progression, see PFS curve
Reference	Ref. 1	Ref. 2	Ref. 3

6.10. Perspective of evaluation

Definition and requirement:

The only perspective permissible for the purposes of evidencing cost-effectiveness as referred to under the provision of Section 15, paragraph 8 of the Act on Public Health Insurance is that of the health insurance companies of the Czech Republic (payer for reported medical care). Other costs may be quantified for information, but must be presented completely separately.

Assessment:

The assessor shall check whether the chosen perspective was that of the payer for medical care and whether the costs and benefits included are consistent with this perspective. The choice of another perspective or a unclear separation of irrelevant (e.g. indirect) costs cause inaccuracy of the pharmacoeconomic evaluation.

6.11.Target population

Definition and requirement:

For the purposes of this procedure, target population is defined as a population of patients who are considered to be the recipients of the investigational intervention in clinical practice in the Czech Republic. The target population must be fully consistent with the required terms of reimbursement of the intervention under review and its characteristics must be in accordance with the available clinical evidence and recommended procedures.

To allow for complete reviewability, the description of the target population should be completed using basic demographic characteristics (age, gender, etc.), characteristics associated with the disease (stage of the disease, severity, presence of comorbidities, risk factors, etc.) and other specific features of the population in question (previous therapy/its failure, anticipated treatment adherence, poor tolerability, presence of non-responders, etc.), which may influence efficacy and safety. Both the general and specific characteristics of the target population should match the patient population from the underlying study as much as practicable – any potential differences must be clearly justified, discussed, and reflected in the pharmacoeconomic evaluation, e.g. in the sensitivity analysis.

Where it is possible to identify significant differences in benefits (in terms of efficacy or safety) or costs in patient subgroups specifically defined by their characteristics, a separate evaluation of these subgroups should be submitted as well. Such differences may arise not only from the results of the underlying study with the given investigational intervention, but also due to different baseline risks based on empirical studies.

Assessment:

The assessor shall evaluate whether the target population in the proposed indication matches the population monitored in clinical studies and evaluated in the pharmacoeconomic evaluation. Only in such a case may the results of the evaluation be relevant for the respective target population or target subgroup, where applicable.

6.12. Time horizon

Definition and requirement:

The time horizon is a period over which the costs and benefits associated with the disease and its treatment are evaluated. The time horizon should be long enough to allow for a reliable and justified conclusion regarding the evaluation of the differences in costs and benefits of the compared interventions depending on the available evidence. Costs and benefits must be always measured over the same time horizon for the intervention under review as well as comparator intervention.

The time horizon should primarily correspond to the anticipated duration of effect (i.e. achieved differences in the efficacy, safety or costs between the interventions), duration of the disease taking into account state-of-the-art knowledge and experience from clinical practice of the individual interventions. It should, moreover, correspond to the life expectancy of the target group. Where the selected time horizon exceeds the time of monitoring in the pivotal study, the observed data may be extrapolated as appropriate.

Assessment:

The assessor shall determine whether the costs and benefits were measured over the same time horizon and whether the duration of the time horizon was adequately chosen and properly justified. Incorrect completion of this part leads to an incorrect result of the pharmacoeconomic evaluation.

6.13.Methods of measuring quality of life

Definition and requirement:

For the purposes of pharmacoeconomic evaluation, quality of life is commonly measured through standardised methods – using questionnaires (particularly generic ones) or direct methods. A pharmacoeconomic evaluation always has to apply the same method of measuring quality of life to all (clinical) conditions, as individual methods are not mutually comparable and result in varying partial values of utility. The recommended questionnaire is the EQ-5D, or, where applicable, specific questionnaires which may be converted to the values of the EQ-5D questionnaire (using regression, so called mapping algorithm).

Transferability of the value of utility:

The most accurate results are achieved by the use of utility identified in the Czech Republic on the basis of evaluation as per validated scoring tables for the Czech Republic (not available at the time of publication of this document). If the local values of utilities from the Czech Republic are not available, it is recommended to use utilities from Great Britain. The reasons for this procedure are usually the good availability of British utilities and comparability of results among administrative procedures, as at present, it is the British values which are mostly used.

Table 3 Example of presentation of used utility values

Condition	Utility value	Method of determination	Reference no.
1	0.85	EQ-5D (UK)	10
2	0.79	EQ-5D (UK)	10

Assessment:

The assessor shall check particularly the sources and nature of the used utility values. Where the same method for the measuring of the quality of life has not been applied to all input utility values, the pharmacoeconomic evaluation cannot be considered correctly performed, as the differences in the utility values will not be relevant (may arise solely from the difference in the applied methodology, rather than from the true difference in the utility of the individual medical conditions).

6.14. Determination and quantification of costs

Definition and requirement:

With regard to the selected payer perspective, the author of pharmacoeconomic evaluation should identify all costs relevant for the respective disease.

Relevant costs shall mean solely direct costs – medical as well as non-medical, if demonstrably covered by health insurance.

The costs are derived from the amount of reimbursement from health insurance (so called unit costs) and the frequency of their resource use. The calculation of costs should be performed and described in a manner allowing to review how the costs were determined. In case the submitted analysis implies that with dosage related to an average patient, a non-usable leftover of the packaging of the medicinal product/food for special medical purposes arises, it is appropriate for the author to reflect these costs in the base case scenario as well.

If the author selects as the comparator intervention a medicinal product/food for special medical purposes, in respect of which a revision of reimbursement or another administrative procedure regarding determination or change of RPC is[7] or soon is to be[8,9] held, one of the alternative scenarios should also reflect reimbursement identified in the concerned revision or administrative procedure.

If it is known from other administrative procedures that the reimbursement of the comparator intervention was influenced by a price agreement or risk-sharing agreement, the sensitivity analysis should present also a simulation of the results with the costs for the comparator in the potential range (such as 50%, 75%, and 90% of comparator cost, i.e. a 10-50% reduction of reimbursement).

The relevant sources for pricing the used care are, in particular:

1. List of prices and reimbursements of medicinal products/foods for special medical purposes ("SCAU") published by the Institute on a monthly basis;[10]
2. The current version of Decree No 134/1998, as amended, on the list of medical services (LMS) and their point values[11]
3. Decree on the determination of point values, amounts of reimbursement of reimbursed services and regulatory restrictions for the year in question, including amendments thereto[12]
4. DRG relative weight index[13][13]

Table 4 Example of presentation of applied values of pharmacoeconomic costs for a continuous use of a medicinal product

Item	Dosage	Reimb./pack	Costs per year (CZK)	Reference no.
Medicinal product 20X10 MG	10 mg daily	10,000.00	182,500.00	SCAU of 1/9/2016

Table 5 Example of presentation of applied costs per procedure

[7] An overview of administrative procedures from which it is possible to retrieve information on pending and completed administrative procedures is published by the Institute on its website (Úvod / SÚKL / Úřední deska / Informace o průběhu správních řízení / Přehled správních řízení): http://www.sukl.cz/sukl/prehled-spravnich-rizeni

[8] An informative overview of changes to reimbursements is published by the Institute on its website (Úvod / Přehledy a seznamy / Přehledy cen a úhrad léčiv / Informativní přehled změn úhrad): http://www.sukl.cz/zmeny-uhrad-rozhodnute-v-reviznich-rizenich

[9] A general overview of groups of medicinal products in respect of which an in-depth revision of the reimbursement system is to be initiated is published by the Institute on its website (Úvod / Léčiva / Ceny a úhrady léčiv / Informace o správních řízeních / Hloubková revize systému úhrad): http://www.sukl.cz/leciva/previdelna-revize-systemu-uhrad

[10] A list of prices and reimbursements of medicinal products/foods for special medical purposes is published by the Institute on its website (Úvod / SÚKL / Úřední deska / Přehledy cen a úhrad léčiv / Seznam léčiv a food for special medical purposes hrazených ze zdravotního pojištění): http://www.sukl.cz/sukl/seznam-leciv-a-pzlu-hrazenych-ze- zdrav-pojisteni

[11] The Decree is amended by the Ministry of Health of the Czech Republic on an annual basis; individual versions are published e.g. on the website of the Ministry (Hlavní stránka / Zdravotní pojištění / Vyhlášky): http://www.mzcr.cz/Odbornik/obsah/vyhlasky_999_3.html

[12] The Decree is usually amended by the Ministry of Health of the Czech Republic on an annual basis; individual versions are published e.g. on the website of the Ministry (Hlavní stránka / Zdravotní pojištění / Vyhlášky): http://www.mzcr.cz/Odbornik/obsah/vyhlasky_999_3.html

[13] The relative weight index is published on the website of the Ministry (Hlavní stránka / Zdravotní služby / DRG / Meto- dické materiály): http://www.mzcr.cz/Odbornik/dokumenty/metodicke-materialy-2014_8590_1058_3.html

Procedure code	Procedure name	Points	Time	Minute overhead rate	Per point reimbursement	Cost per procedure
42021	COMPLEX EXAMINATION	473	60	3.01	1.03	673.21 CZK

Table 6 Example of presentation of applied healthcare utilisation

Item	Percentage of patients	Average duration	Unit cost	Total costs
Hospitalisation	10%	5 days	1 200 CZK/day	600 CZK

Assessment:

The assessor shall check the structure and types of costs considered. He/she shall focus on the identification of other costs which should be relevantly included. If there are provably other types of costs which – if included – could adversely affect the result of pharmacoeconomic evaluation, the presented pharmacoeconomic evaluation cannot be considered properly performed.

In case costs were considered and included on an aggregate basis contrary to the health insurance payer perspective, the submitted pharmacoeconomic evaluation cannot be considered correct.

6.15.Discounting

Definition and requirement:

Discounting as a method of future cost and benefit adjustment to their current market value is to be used where a time horizon exceeding 1 year is used. The recommended discount rate is 3% p.a. both for costs and benefits. For sensitivity analysis, it is recommended to provide scenarios without a discount rate (0%) and a scenario with a 5% discount rate.

Assessment:

The assessor shall check the discount rate used and its impact on the result.

6.16. Pharmacoeconomic model

Definition and requirement:

The model allows for available evidence synthesis and for the assessment of variable and to-date not fully evaluated disease development scenarios in association with the use of the intervention under review and comparator intervention. Models should be created for the environment of the healthcare system of the Czech Republic, or adapted thereto.

The basic setup of the model (base case scenario) should reflect current clinical practice of the disease in question as much as practicable and it should be based upon the most relevant available evidence and justified key assumptions. Where other potential assumptions exist, their influence upon the result should form part of the sensitivity analysis. The selection of the structure and setup of the model must be adequately described, as well as detailed results achieved through the modelling, so that it is possible to assess the validity of the compiled model.

The use of a health economic model (hereinafter referred to as the "model") is recommended where necessary:

1. to extrapolate results from the selected population of the pivotal clinical study (a phase III RCT, etc.) to a wider population in clinical practice;
2. to extrapolate data for a longer timespan corresponding to the selected time horizon than the duration of monitoring in the underlying study;
3. to combine data of various nature (benefits in efficacy, benefits in safety, impact upon quality of life) or from multiple sources of available evidence;
4. to obtain, though modelling, an outcome measure more representative for the disease in question (QALY or LYG).

Where similar terms of reimbursement are requested not only in the Czech Republic, but also in other EU Member States, and the Institute is presented with evidence differing from the evidence presented in those Member States, specific reasons for such course of action together with significant differences in the submissions should be provided.

6.16.1.Submitted or open access model

In order to facilitate and speed up the course of the administrative procedure, the Institute recommends that a functional health economic model be submitted or remote access thereto be provided. A submitted model (a file in Microsoft Excel, TreeAge, etc.) may be considered confidential commercial information (CCI) as referred to under the provision of Section 39f, paragraph 11 of the Act on Public Health Insurance (for more details on CCI please refer to section 6.20).

In case there is another input value or setup which has not been used adequately, the submission of the model will allow the assessor to verify the influence of such a fact upon the result more quickly and it will speed up the course of assessment of the submitted evidence.

The availability of the health economic model will facilitate assessment in those cases where the input value – specifically costs of the comparator – changes upon the issue of a decision from a parallel administrative procedure (e.g. abbreviated reimbursement revision), which is conducted with a relevant comparator intervention, or in cases where a price agreement or risk sharing agreement regarding the comparator intervention exists.

Assessment:

The assessor shall verify the input data and basic setup of the model with regard to the submitted report on the pharmacoeconomic evaluation. He/she shall check whether the model, in its base case setup, provides the result presented by the author of the analysis. Should the assessor find that any of the input parameter values has been selected inappropriately with regard to the available evidence, he/she shall review the influence of such a value on the result of the analysis. If the change of the value does not significantly influence the result, taking into account the results of sensitivity analysis, the assessor shall state this fact in his/her assessment. If the value exhibits a significant influence on the result of the analysis, the assessor shall elaborate a call for cooperation to verify such procedure by the applicant. Any steps taken and findings coming from the submitted model shall be recorded by the assessor in a protocol which shall form part of the dossier (e.g. as an attachment to the call for cooperation), in order to safeguard the transparency of the course of action taken.

6.16.2.Non-submitted model

Where the pharmacoeconomic model has neither been submitted nor access provided thereto, the author of the analysis shall elaborate on and detail all of the substantial data, key assumptions and source data entering the model. The methodology of the model must be described in detail and a clear explanation of how the variables have been processed and statistically evaluated must be provided – i.e. individual calculation steps, equations applies, etc. shall be specified to safeguard transparency and reproducibility of the modelling. It may concern the following data:

1. Average values, 95% confidence intervals of continuous variables, standard errors of the mean;
2. Results of regression analysis, including the specification of values of individual coefficients;
3. Results of correlation analysis, including the specification of values of individual coefficients;
4. Results of parameterisation of survival analysis curves for the purposes of extrapolation, including the specification of each parameter necessary to construct survival curves;
5. Specific values or parameters and setup of sensitivity analyses (both one-way and probabilistic)

In such a case, CCI as referred to under the provision of Section 39f, paragraph 11 of the Act on Public Health Insurance may only be considered such data which meet the conditions set forth by law (section 6.20 refers).

Assessment:

The assessor shall verify any relevant data, including the applied methodology, the design of the model and used procedures and calculations. In case the evidence has not been submitted, the model has not been described in a manner ensuring transparency and reproducibility of the modelling, or facts not reflected in sensitivity analysis have arisen in the course of the administrative procedure, the submitted pharmacoeconomic evaluation cannot be considered properly performed.

6.16.3. Validation of the pharmacoeconomic model

Definition and requirement:

External validation of the model

If there are data from clinical practice or prospective research (e.g. on the impact of treatment on mortality and other relevant clinical endpoints in a longer time horizon), it is appropriate to submit them for verification of the results of the model.

Internal model validation

The submitted model should be also suitably internally validated, i.e. in the sense that under the same conditions the model provides the same and reliable results. The author of pharmacoeconomic evaluation should hence specify how the internal validation was performed (e.g. specify the statistical methods for the evaluation of extrapolation). Internal validation is necessary for microsimulation models, where, for example, the number of repetitions may substantially influence the result of pharmacoeconomic evaluation.

Assessment:

The assessor shall check the method by which the model was validated. Absence of internal validation in cases, where it is indispensable, is a major shortcoming resulting in impossibility to review the pharmacoeconomic evaluation.

6.16.4. Data extrapolation

Definition and requirement:

Data from a clinical study and from clinical practice may be extrapolated provided a suitable function is used (e.g. Weibull, exponential, log-normal, Gompertz); the selection of the curve has to be properly justified by a visual check of curve adhesion to actual data and their foreseeable continuation for all methods, by the submission of the results of Akaike information criterion (AIC) and Bayesian Schwarz´s information criterion (BIC), and other statistical tests (e.g. development of a risk function in time, residue analysis). When selecting a suitable method for the extrapolation itself (i.e. for the shape/form of the curve beyond the time horizon of the study), such curve shall be preferred which suitably holds the trend identified from the data. Together with the results of the basic scenario, also results (incl. those of the probabilistic sensitivity analysis) for other theoretically acceptable fits shall be submitted.

Assessment:

The assessor shall assess whether the method of the completed extrapolation was described and properly justified and whether the uncertainty associated with the applied extrapolation procedure has been discussed.

6.17.Result of pharmacoeconomic evaluation

Definition and requirement:

The result of pharmacoeconomic evaluation shall be expressed in adequate detail, to allow for assessment thereof. Individual cost categories shall be specified separately therein, in particular, pharmaceutical costs of the investigational intervention shall be clearly separated. In case of benefits in the CUA or CEA types of analysis, it shall be stated in what conditions the benefits are obtained, always in terms of life-years gained (LYG) and quality-adjusted life-years (QALY). The incremental cost-effectiveness (ICER) shall be calculated using the following formula:

$$ICER = \frac{COSTS_{II} - COSTS_{CI}}{BENEFITS_{II} - BENEFITS_{CI}}$$

where II is the investigational intervention and CI is the comparator intervention. ICER expresses the number of financial units in Czech crowns which need to be incurred from health insurance funds to obtain one more unit of benefit.

Table 7 Example of presentation of results of analysis

	Scenario 1		
Costs	Investigational	Comparator 1	Difference

Pharmaceutical, of investigational medicinal product Pharmaceutical, other Symptomatic treatment Visits to doctor Diagnosis Hospitalization			
Total costs			
QALY			
Condition 1 Condition 2 Condition 3			
Total QALY			
LYG			
Condition 1 Condition 2 Condition 3			
Total LYG			
ICER (CZK/QALY)			

Results presented in a clear and detailed form are required also in the case of relevant alternative scenarios, of an updated analysis submitted together with the application for submission content amendment and also in the case when a response to the call for cooperation is submitted.

Where the setup or results of analyses submitted has changed over time (e.g. in the analysis submitted for the determination of permanent reimbursement as opposed to the analysis submitted for the determination of the initial temporary reimbursement), the reasons for such differences should be briefly described.

Assessment:

The assessor shall check how the results have been presented. If the results have been presented in a form which does not enable proper discussion and interpretation thereof and adoption of the decision on cost-effectiveness of the investigational intervention, the submitted pharmacoeconomic evaluation cannot be considered properly performed. A mere presentation of the result expressed as total costs/total benefits and the ICER value is not considered sufficient.

6.18.Uncertainty of the result of sensitivity analysis

Definition and requirement:

Sensitivity analysis forms an integral part of any pharmacoeconomic evaluation and should include any input parameter or assumption which may influence the result of the pharmacoeconomic evaluation for the purposes of identification of sources of inaccuracies and uncertainty, their subsequent quantification and assessment of the impact upon the value of the result. The preferred method of quantification of uncertainty in pharmacoeconomic evaluation is one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA).

One-way sensitivity analysis and scenario analysis

An integral part of one-way sensitivity analysis is a table containing all of the tested parameters, specifying the input values in the base case scenario and input values (minimum and maximum) into the OWSA, including the source of this range (confidence interval, etc.).

The scenario analysis should present results after change to the accepted assumptions, i.e. scenarios

using another extrapolation method, another method used for the elimination of cross-over, disregarding of a certain condition, etc.

The result of the one-way sensitivity analysis is thereafter presented in the form of a table and a tornado diagram.

Probabilistic sensitivity analysis

Within the scope of a probabilistic sensitivity analysis, the author shall present a list of input variables, incl. selected distributions and parameters. The results are illustrated by means of a cost-effectiveness scatter plot and a cost-effectiveness acceptability curve. Together with the charts, the probability of the intervention being cost-effective with the limit of 1.2 million CZK/QALY shall be also specified. This limit shall be used also in cases where additional information about the result, such as net-monetary benefit, value of information, etc. are presented.

Table 8 Example of presentation of the setup of one-way and probabilistic sensitivity analysis

Input name	Average value	Standard error,	Values in one-way sensitivity analysis		Values and setup in probabilistic sensitivity analysis			Ref.
		95% CI	Lower limit	Upper limit	Parameter 1	Parameter 2	Distribution	
Age Probabilistic shift from condition 1 to condition 2 OS hazard ratio PFS hazard ratio Utility in condition 1 Utility in condition 2 Costs in condition 1 Costs in condition 2								
…								

Assessment:

The assessor shall focus on the method of identification and quantification of uncertainty and its subsequent correct evaluation in the sensitivity analysis. Unless the evaluation concerns the entire uncertainty that has a particularly negative impact upon the result of the sensitivity analysis, the submitted pharmacoeconomic evaluation cannot be considered correctly performed, as it is not possible to assess whether the results presented in the base case scenario are reliable.

6.19. Transferability in pharmacoeconomic evaluation

Definition and requirement:

Results of a foreign pharmacoeconomic evaluation are generally non-transferable. Nevertheless, their adaptation to the conditions of the Czech Republic is possible, if reflecting the nature of the therapeutic practice, intensity of resource utilisation, amount of costs, definition of the target population and other key assumptions specific for the environment of the current clinical practice in the Czech Republic. Results of valid clinical and empirical studies are transferable if comparable in terms of the Czech target population. Utility values are considered transferable by the Institute, but the source must be always quoted and the conditions stipulated under section 6.13.

The baseline characteristics of the target population (epidemiological and mortality endpoints), unit and total costs are not transferrable. In case official Czech statistics are not available, the epidemiological and mortality endpoints may be supported by the opinion of the relevant professional society.

Data about healthcare resource utilisation and endpoints extremely sensitive to the particular local environment and treatment methods with a rather unclear interpretation value, such as compliance (or its clearly documented relation to the substantial parameters of the given disease on the clinically

significant change level) are partially transferable.

Where any data are transferred from foreign conditions, the author of the pharmacoeconomic evaluation should also discuss when and under what conditions it is possible to transfer such data.

Assessment:

The assessor shall check how the transferability was discussed in the pharmacoeconomic evaluation. In case non-transferable data were transferred, the pharmacoeconomic evaluation cannot be considered correct (whether too large an uncertainty is generated under the conditions of the Czech Republic).

6.20.Confidential commercial information

6.20.1. Evidence that cannot be classified as confidential commercial information

Pursuant to the provision of Section 39f, paragraph 11(c), (e), (f), and (j) of the Act on Public Health Insurance, the following, *inter alia,* cannot be classified as confidential commercial information (CCI): quantifiable and evaluable anticipated results and reasons for pharmacotherapy, dosage, results of available clinical trials, pharmacoeconomic evaluations, particularly cost-effectiveness analysis and budget-impact analysis, basic data on the costs of existing treatment or pharmacotherapeutic options with the estimate of impact upon health insurance funds, estimated consumption and number of patients treated with the assessed medicinal product.

The Institute shall not classify as CCI other publicly available information (such as data contained in the SPC, publicly available evaluations of foreign HTAs or regulatory agencies, data available and public in other administrative procedures, data from indices and lists of procedures or legislation), and, equally, shall not classify as CCI generally known mathematical or statistical relations or other commonly known and used procedures, as such information and data do not represent "facts not normally accessible in the relevant business circles", and hence do not comply with the definition of CCI set forth under the provision of Section 504 of Act No 89/2012, the Civil Code.

The report on the cost-effectiveness analysis usually largely contains the aforementioned data which cannot be classified as CCI pursuant to the provision of Section 39f, paragraph 11 of the Act on Public Health Insurance. Should the submitted document contain information that should be hidden upon request of the applicant and that meets the conditions of CCI, it has to be clearly identified or provided in an annex which alone will be classified as CCI.

6.20.2. Evidence which may be classified as confidential commercial information

Additional analyses and data processing as well as data not published to-date, health economic models alone, proposals and agreements on discounts concluded between health insurance companies and marketing authorisation holders, proposals and agreements on risk sharing or on various schemes influencing costs or cost-effectiveness (such as managed-entry agreement or patient access scheme) may be classified as CCI.

6.20.3. Procedure for the presentation of evidence classified as confidential commercial information

Any evidence classified as CCI or as containing CCI should be submitted to the Institute in a suitable form facilitating appropriate handling thereof.

For this reason, if it is possible to submit the CCI in a special document (e.g. draft agreements on risk-sharing or price agreements), such evidence should be presented in a clearly labelled special file.

If some of the information cannot be extracted from the document (such as the bulk of to-date unpublished data on subpopulation efficacy in the report on cost-effectiveness analysis), it is suitable to submit one document clearly labelled as a document containing CCI, and another document in which selected information that is not to be published will be blackened or deleted.

General information on the submission of documents classified as CCI is published also on the website of the Institute.[14]

[14] "Předkládání dokumentů vedených v režimu obchodního tajemství" (*Submission of Documents Classified as CCI)*, an article published on 1 March 2017 (Úvod / Léčiva / Ceny a úhrady léčiv / Doplňující informace / Předkládání dokumentů vedených v režimu...): http://www.sukl.cz/leciva/obchodni-tajemstvi- cenova-a-uhradova-regulace

7. ANNEXES

Annex 1: Example of the structure of a report on the setup and results of a previously unpublished study

Annex 2: Analysis of administrative procedures with evaluation of cost-effectiveness

Example of the structure of a report on the setup and results of a previously unpublished study

Minimum required data

1. Basic data on the study
    a. Study phase and design
    b. Study objectives
    c. Data collection period
    d. Time horizon of monitoring
    e. Data collection locations
    f. Description of the investigational and comparator intervention (incl. dosage and method of administration, etc.)
2. Statistical methods
    a. Description of all applied statistical methods and a rationale of their selection
    b. List of applied software
    c. Procedure for the handling of missing values
    d. Description of censoring in the analysis of overall survival analysis and progression-free survival or time to progression, and potential bias affecting the results as a consequence of censoring
3. Patient population
    a. Inclusion and exclusion criteria
    b. Size of the studied population (incl. a flow-chart indicating the numbers of patients who took part in the monitoring, how many patients received the investigational medicinal product, how many patients were excluded from the analysis and for what reasons, etc.[15]
    c. Basic demographic characteristics
    d. Relevant data on the clinical condition of the patients
    e. Relevant data on the previous treatment of the patients
4. Efficacy outcomes
    a. The results of primary as well as other objectives for each group (predefined by the protocol)
    b. For quantitative data results: mean, median, standard deviation, and a 95% confidence interval or interquartile range
    c. For qualitative data results: absolute frequency and relative frequency (percentage share), for ordinal data also median
    d. For survival analysis: itemised numbers of patients in risk, number of censored patients and its impact upon the result
    e. Number of missing values in each parameter
    f. Differences between groups are to be verified by an appropriate statistical test.
5. Safety outcomes
    a. The results of primary as well as other objectives for each group
    b. A list of all expected and unexpected adverse events, their number and the number of patients who experienced the adverse event in question
    c. For each adverse event, specify its severity and treatment method
    d. Number of missing values in each parameter
    e. Potential differences between groups are to be verified by an appropriate statistical test (as per item Statistical methods).
6. Critical assessment and conclusion
    a. A description of any shortcomings of the monitoring and existence of potential bias
    b. A discussion on their impact upon evidencing the therapeutic efficacy, safety, and cost-effectiveness

[15] See CONSORT Statement 2010 Flow Diagram available from http://www.consort-statement.org/.

Analysis of administrative procedures with evaluation of cost-effectiveness

1. Introduction

Cost-effectiveness is defined by the provision of Section 15, paragraph 8 of Act No 48/1997, on Public Health Insurance, as amended (hereinafter referred to as the "Act on Public Health Insurance"), cost-effective procedures being specifically considered to be such procedures which:

- at comparable costs provide the same or higher therapeutic effect consisting of prolonged life expectancy, improved quality of life, or improvement of a substantial and measurable criterion of the respective disease; or
- with at least comparable therapeutic effect imply lower total costs for the health insurance system; or
- **at higher costs and with higher therapeutic effect this ratio is comparable to other therapeutic procedures reimbursed from public health insurance funds.**

In association with the gradual development of the Institute´s decision-making practice depending on the legislative requirements, following a professional discussion, a cost-effectiveness (CE) threshold has been established and applied in the long term. The CE threshold has been derived from the WHO-CHOICE recommendation, as at the time when the amendment to the Act on Public Health Insurance came into force (implemented by Act No 261/2007, on Public Budget Stabilisation, as amended, effective from 1 January 2008), no incremental cost-effectiveness ratios from the period prior to the effect of the amendment were known. The WHO-CHOICE methodology recognised highly cost-effective therapeutic procedures, achieving ICER in the amount of 1x GDP/per capita/year/QALY (i.e. approx. 300 thousand CZK/QALY), furthermore, a threshold for cost-effective therapeutic procedures in the amount of 3x GDP/per capita/year/QALY (i.e. approx. 1 million CZK/QALY) was recommended.

As the Act on Public Health Insurance does not specify the links between cost-effectiveness and the WHO-CHOICE methodology, the Institute conducted a research of administrative procedures assessing cost-effectiveness after 2013, when the Institute´s methodology SP-CAU-028 for the evaluation of cost-effectiveness was published, which introduced the standard of quality for the conduct and presentation of analyses, which means that since 2013, accepted analyses may be considered compliant with these standards and their results valid and reviewable.

2. Objective

To analyse administrative procedures in which cost-effectiveness was evaluated, with the aim to fulfil the requirement of the provision of Section 15, paragraph 8, sentence two of the Act on Public Health Insurance and to establish a ratio of costs and benefits of therapeutic procedures reimbursed from the public health insurance funds.

3. Methodology

Administrative procedures have been identified in respect of which cost-effectiveness was evaluated using the following criteria so as to meet the requirement set forth by Section 15, paragraph 8, sentence two of the Act on Public Health Insurance, and these were administrative procedures concerning such medicinal products for which a higher therapeutic effect was reported and which generated higher costs, and hence the ICER could be calculated for them.

Table: Criteria for the selection of administrative procedures in compliance with the provision of Section 15, paragraph 8 of the Act on Public Health Insurance

Criterion	No. of administrative procedures
Required evaluation of cost-effectiveness	355
Commenced after 31 December 2012*	301

Became final	155
Application not withdrawn	137
Temporary reimbursement not required	117
Submitted valid cost-effectiveness analysis	72
ICER/CMA value specified	65
Higher costs and higher benefits of the investigational intervention (ICER > 0)	30

*Evaluation as per the SP-CAU-028 methodology effective as of 1 January 2013

4. Result

Of the 30 analysed administrative procedures in which at least one ICER value was available, in 17 cases (57%) the ICER value was less than 600 thousand CZK/QALY and in 29 administrative procedures (97%) it was lower than 1.2 million CZK/QALY. In one case a value greater than 1.2 million CZK/QALY was presented for one of the scenarios; for another relevant scenario, the value was again less than 1.2 million CZK/QALY.

Table: Overview of results of administrative procedures

Result of cost-effectiveness analysis (ICER) in thous. CZK/QALY	No. of administrative procedures
<0*	-
0–299	5
300–599	12
600–899	6
900–1 200	6
> 1200**	1**

* not including dominant and cost-saving results (CMA)

** 2 scenarios presented, the worse result was used

The cumulative curve of the results of cost-effectiveness analysis from the analysed administrative procedures then implies a clear trend; specifically that the absolute majority of ICER values does not exceed the threshold of 1.2 million CZK/QALY.

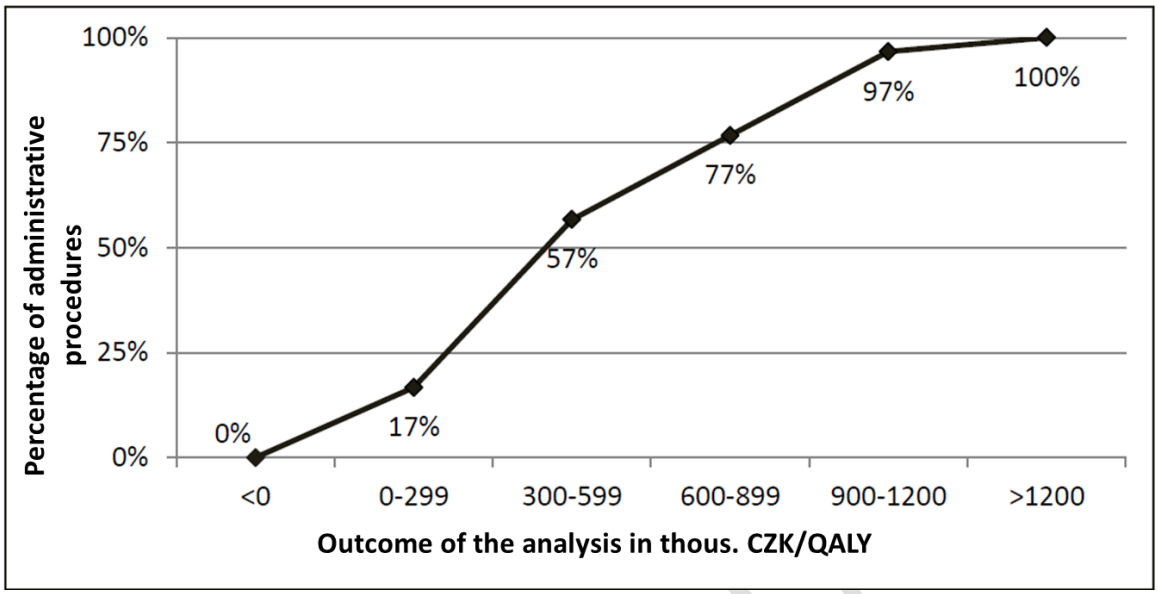

Chart: Percentage of administrative procedures in relation to the cost-effectiveness (ICER) outcome

5. Conclusion

In compliance with the requirement stipulated by Section 15, paragraph 8, sentence two of the Act on Public Health Insurance, administrative procedures concerning therapeutic procedures which brought a higher therapeutic effect at higher costs were analysed.

A significant proportion of the administrative procedures (57%) achieved more favourable results of up to 600 thousand CZK/QALY compared to the acceptable threshold of 1.0–1.2 million CZK/QALY.

The analysis of completed administrative procedures implied that for 97% of therapeutic procedures, this ratio was less than 1.2 million CZK/QALY, and it is necessary to mention that the remaining 3% concerned only one administrative procedure in which, furthermore, the second ICER value in the relevant scenario was less than 1.2 million CZK/QALY. Therapeutic procedures with the cost/benefit ratio under the threshold of 1.2 million CZK/QALY may be considered cost-effective, as they meet the condition set forth by the provision of Section 15, paragraph 8, sentence two of the Act on Public Health Insurance.

6. Impact upon decision-making practice and course of the administrative procedure

In compliance with the decision-making practice of the Institute, the threshold of 1.2 million CZK/QALY shall continue to be applied as the common acceptable threshold in deciding about cost-effectiveness, in compliance with the provision of Section 15, paragraph 8 of the Act on Public Health Insurance. With a view to the aforementioned analysis, it is obvious that the Institute has been applying this threshold in the long term when deciding about cost-effectiveness and a vast majority of the cost/benefit ratios in routine administrative procedures (i.e. those which did not consider several criteria) were less than this threshold. Particularly in borderline cases where the outcome of the analysis will range between 0.9–1.2 million CZK/QALY uncertainties associated with the input data and, subsequently, sensitivity analysis results, will be taken into account to a higher degree.

In exceptional and justified cases, the Institute, having assessed any available and relevant evidence provided in the dossier, will, on a case-by-case basis, continue to take account of other criteria in compliance with the relevant statutory provisions.

7. <u>List of Analysed Administrative Procedures</u>

Table: List of analysed administrative procedures which met selection criteria referred to under section 3.

Administrative procedure	Name of the medicinal product
SUKLS25055/2013	ZEMPLAR
SUKLS39396/2013	EDURANT
SUKLS73511/2013	FORXIGA
SUKLS81620/2013	BETMIGA
SUKLS100546/2013	MOZOBIL
SUKLS134176/2013	CERTICAN
SUKLS134806/2013	VIDAZA
SUKLS143051/2013	JETREA
SUKLS157419/2013	bortezomib
SUKLS178517/2013	VICTRELIS
SUKLS204787/2013	LUCENTIS
SUKLS207032/2013	AVASTIN
SUKLS224333/2013	INLYTA
SUKLS2459/2014	AUBAGIO
SUKLS9055/2014	STRATTERA
SUKLS19726/2014	INCIVO
SUKLS24796/2014	HUMIRA
SUKLS41605/2014	MODIGRAF
SUKLS77313/2014	XOLAIR
SUKLS89711/2014	SOVALDI
SUKLS95799/2014	SYNAGIS
SUKLS95804/2014	LEVACT
SUKLS111059/2014	BOTOX
SUKLS162874/2014	GAZYVARO
SUKLS177406/2014	BRILIQUE
SUKLS210691/2014	SPIRIVA RESPIMAT
SUKLS85/2015	PYLERA
SUKLS90762/2015	XULTOPHY
SUKLS102913/2015	LUCENTIS
SUKLS30346/2016	COSENTYX