Methodological Recommendations
for presented documentation for assessment of the efficacy, safety, and pharmacoeconomic parameters of medicinal products applying for inclusion in the Positive Drug List.

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I. Introduction

Efficacy and safety - definitions

Efficacy in the context of evidence based medicine is a capacity of a medicinal product or therapy/intervention to prove a positive impact on course or duration of disease (clinically measured effect) at dose tested in population of patients for which the medicinal product is intended and is tested.

During the marketing authorisation the assessment of safety of medicinal products as indicator of potential risk is done on basis of scientific guidelines, part of Notice to applicants. The marketing authorisation certifies that at the moment of assessment the benefit – risk ratio of the medicinal product is positive. Pharmacovigilance is defined as science and activities, related to the detection, assessment, understanding and prevention of adverse drug reactions or other problems resulting from drug use. Pharmacovigilance is a process that continues during the whole time while medicinal product is on the market and is used.

Pharmacoeconomics implements the principles and methods of health economics to drug policy (supply and demand, pricing and reimbursement of medicinal products).

The purpose of the pharmacoeconomic analysis is to determine, evaluate, and compare the costs and results from different alternatives in the treatment of diseases.

Pursuant to Article 30 of the Ordinance on the terms, rules and procedure for regulation and registration of the prices for medicinal products applied to be included in the Positive Drug List, assessment shall be performed according to the criteria of efficacy and therapeutic effectiveness, criteria for safety and pharmacoeconomic parameters.

These methodological recommendations have been drawn up with a view to achieve optimal assessment of candidate medicinal products. Therefore, applicants need to comply the analysis of the efficacy, safety and pharmacoeconomic analysis, with the requirements provided by these methodological recommendations.

II. Guidelines for the provision of data for assessment of efficacy and safety

The recommendations included in this Section II are aimed at providing general guidelines as to the provision of data needed for the assessment of the efficacy and safety of medicinal products that are candidates for inclusion in the PDL.

II.1. Guidelines for the provision of data to evaluate efficacy

Applicants shall submit analysis of the efficacy of the proposed indications of administration, which shall be substantiated by results from clinical trials using clinically significant endpoints for the intended use of the medicinal product. In certain clinical conditions, evidence for the long-term efficacy shall be submitted: survival rate and its prolongation; extension of the time to relapse/attack/worsening of the disease/disability, reduce mortality/improved quality of life, etc. Where applicable, should be provided strategy for assessment long-term efficacy and a risk management plan. Evidence of efficacy as monotherapy/first choice shall be an advantage of the candidate product. Evidence from additional comparative efficacy studies shall also be applied, if available. Submitted shall be interpretations relating to the method by which efficacy data supports the approved dosage in the respective population for indications applied for, as well as how benefits are to be optimised and risks minimised. Analysed shall be the factors that could result in decrease of efficacy or lack of efficacy and the measures undertaken therefore (e.g. data about the development in inhibitory antibodies during the administration of biological products).

Where a medicinal product is administered together with other medicinal products, data from conducted trials on their concomitant administration shall be presented. Annexed shall be pharmacokinetic/pharmacodynamic studies relating to medicinal interactions, if required/conducted. Non-randomised studies of the effects of therapy based on secondary databases could add the evidence from randomised clinical trials and prospective observations. Results from efficacy studies of combined medicinal products shall be submitted. It is necessary to submit information about the medical devices used during surgical procedures during administration, implantation or administration of the medicinal product, where these could affect the efficacy of the product.

II.2. Guidelines for the provision of safety assessment

Applicants shall submit a summary of the safety concerns including important potential risks and missing information relevant to the product at the time of submission. The pharmacovigilance plan for the product shall be summarised as to describe all additional pharmacovigilance measures, if required for marketing authorisation or for subsequent regulatory review.

The category of the ongoing post-marketing safety studies shall be determined. Approved and implemented measures to minimise risks during the administration of the product shall be presented and analysed in the context of the possible increase of the public cost associated the implementation thereof. E.g., the requirement for periodic follow-up of hepatotoxicity aiming at avoiding hepatotoxicity, which increases the cost of a medicinal product action, while distribution of training materials or signal cards represents a risk of minimising action, which does not put additional costs for public and personal budget of the patient.

The cycle of submission of periodical safety reports of a medicinal product shall be submitted, together with a summarised information on the cumulative period of product marketing and summarised data about the exposition to the product.

Any important regulatory changes such as: undertaken urgent safety measures; arbitration (referral) procedures conducted; suspension of the marketing authorisation due to safety reasons, shall be presented including the reasons for implementing these and the resulting regulatory requirements arising from these. Submission of data of medical mistakes, abuse, improper use, overdose; use outside approved at product marketing authorisation and the adverse drug reactions arising from the handling of the product is necessary as in integral part of tracking product safety. The incidence of adverse drug reactions shall be submitted according to the latest approved SPC, indicating the date of approval. The incidence of adverse reactions is defined as follows:

Very common	(≥1/10);
Common	(>1/100 to < 1/10);
Uncommon	(≥1/1 000 to <1/100);
Rare	(≥1/10 000 to < 1/1 000);
Very rare	(<1/10 000) and
Not known	

The adverse drug reactions reported over the post-marketing period outside clinical trials, which have not been included in the summary of product characteristics, shall be reported as reactions with unknown incidence.

The positive benefit/risk ratio is subject to regulatory discretion and a prerequisite for a valid marketing authorisation. Any additional change in the benefit/risk ratio, irrespective whether it concerns additional benefits or additional risks shall be presented objectively and

accompanied by a clarification on whether new information has already been submitted for inclusion by a change to the marketing authorisation or, if it is not filed, there is a plan for submission to change.

For the purpose of pharmacoeconomic assessment, the information relating to the benefits of a medicinal product shall be presented separately for any approved indications and, if applicable separately for different population groups. Benefit shall be considered in the context of the characteristics of the disease to be treated/prophylacted/studied. It is necessary to provide information about the spread of the disease; its gravity and severity; the social importance of the disease; characteristics of the patients to be treated according to the disease, e.g. chronic illness, rare disease, etc.

It is necessary to provide information on the duration of benefits achieved and how it is measured in four surrogate indicators. Efficacy data of patients who are not eligible for alternative treatment, shall also be provided, if available. Product risks must be evaluated in terms of their clinical significance, severity and incidence of occurrence. For each of these, information about the reversibility of adverse effect and risk preventability shall be provided. Data on the efficacy of risk minimising actions shall be annexed, if available.

III. Purpose of the guidelines for the preparation of pharmacoeconomic analysis

These recommendations are intended to provide general guidance on how to prepare and present prarmacoeconomic analysis of medicinal products for the application for inclusion in the PDL, including the formation of price.

Pharmacoeconomic assessment needs to include, as minimum, the following information:

III.1. Short introduction of the medicinal product, the ATC code, should be stated the disease for the treatment of which the medicinal product is intended and is applied for inclusion in PDL.

Any economic evaluation shall be accompanied by a brief description of the disease and the available interventions, as well as by epidemiological data of the disease frequency and number of patients treated in Bulgaria, for whom the product would be applicable. It is recommended to indicate the international or Bulgarian pharmacotherapeutic guidelines where the international non-proprietary name is included. In cases where a medicinal product has more than one indication or is recommended for more than one patient groups, all indications and patient groups shall be indicated, where its use has been authorised or for which the medicinal product has applied for inclusion in the PDL.

Perspective of analysis: analyses shall be conducted in payer perspective, involving direct cost for public funds and patients co-payments. Economic analyses from the society perspective, including all costs, can be presented in addition, if considered relevant by applicant.

The number of patients to whom the economic evaluation refers shall be consistent with the target population according to clinical trials.

Choice of alternatives for comparison – Where there are several therapeutic approaches (including non-pharmacological treatment and no treatment), these shall be listed. The therapeutic approaches used as comparative alternatives shall be chosen on the basis of the most commonly used therapy or first line therapy. To have international comparability it is recommended as a definition of comparator to indicate the perceived "best standard treatment", as recommended most EU Member States.

The following therapeutic alternatives can also be used: treatment used in current clinical practice; the most commonly used therapy; the most commonly used alternative medicinal products; reimbursed therapies with the same or equivalent therapeutic indications. If a new medicinal product belongs to an existing pharmacotherapeutic group, the comparator product shall be the most commonly used product within the group (the so-called “golden standard”), or the one that will most probably be affected by the introduction of the new product. If the new medicinal product belongs to a new pharmacotherapeutic group, the comparator product shall be the most commonly used medicinal product for the same indications.

Non-pharmacological treatment and no-treatment shall be acceptable alternatives only where this is the most commonly used method in therapeutic practice or where there are no other alternatives for treatment of the indicated patients. Doses and duration of comparative treatment shall be those recommended in the summary of the product characteristics and the therapeutic guidelines.

In all cases, the choice of alternatives shall provide evidence from randomised clinical trials (RCTs) or studies of actual therapeutic practice, where direct or indirect comparisons with the selected alternatives have been conducted in terms of efficacy, safety or effectiveness.

Therapeutic benefit of the candidate product, e.g. improved safety, improved compliance to the therapy compared to other alternatives measured with specific clinical indicators derived from the RCT or from research in real therapeutic settings shall be clearly justified.

III.2. Systematic description of clinical trials conducted with a candidate medicinal product paying particular attention to its short-term and long-term clinical and social outcomes that could have important economic importance (e.g. increasing life expectancy, decrease of mortality, improvement in quality of life, decrease of the use of other health resourses such as GP or specialist visits, hospitalisations, adverse drug reactions, disability, reduction of incidence of disease recurrence reduction in the incidence or severity of disease complications, frequency of successfully treated patients, reduction of temporary disability, etc.). Data from clinical trials shall present the purpose and type of research; compared alternatives in the clinical trial, including placebo, if it is the second arm of the study; measures of clinical change (clinical indicators, quality of life, long-term results, etc.); outcomes and differences in clinical parameters during the study and the authors' conclusions.

The presentation of the data can be performed in a tabular form to facilitate analysis. The table shall present the accurate data of the clinical outcomes of the administrated medicinal product in involved subjects – both short-term as regards changes in clinical parameters and long-term as regards the quality of life. Tabular and text information shall include reference description of published clinical trials or such that are in the course of being conducted.

In case of changes in the quality of life of the patients, it shall be indicated by which instruments the assessment has been performed and which parameters of the quality of life have been affected. Provided that there is evidence of decrease in the recurrence and severity of adverse drug reactions, these shall be discussed in terms of possible reduction of treatment cost.

If meta-analyses or systematic reviews of data efficacy and safety were published, they need to be commented. When using a network meta-analysis or indirect comparison of therapies results should be considered in terms of data relevance and their applicability in the decision making in the healthcare system.

Conducted long-term studies of effectiveness (as opposed to clinical trials exploring efficacy before the marketing authorisation) and meta-analyses or systematic reviews of clinical trials shall be discussed separately.

When conducting pharmacoeconomic analysis, data from clinical trials or comparative studies between therapeutic strategies shall derive from direct clinical comparison, as this is considered as studies with the highest degree of reliability. In the absence of direct comparison, studies including indirect comparison can be used; it is only allowed in the absence of any original studies for direct comparison.

Subgroup analysis shall be used when there is a significant subgroup of patients for which treatment might be more or less cost-effective compared with other patients. This shall be subject to the same requirements.

III.3. Description of conducted pharmacoeconomic analyses in other countries.

Where there are health economic evaluations or pharmacoeconomic analysis conducted with a candidate medicine for other health systems, these shall also be described – purpose and type of study; compared alternatives in the clinical study; health outcome measurements (clinical indicators, quality of life, long-term results, etc.); used methods and models and authors' conclusions.

If the provided health technology assessments or pharmacoeconomic analyses have been made by state institutions for the purposes of another national healthcare system, their opinion – positive or negative including motives – shall be clearly stated. All decisions of state institutions in Europe such as NICE, HAS, NSC, IQWIG, DACEHTA, POLTHA, KCE, etc. (positive or negative) shall be described with the relevant references and the appropriate document containing the final assessment and conclusion shall be annexed.

In case of a positive decision, the reimbursement status of the respective product in Europe, indications, restrictions and level of reimbursement, a summary of recommendations for reimbursement, if reimbursement is valid for any indications or for specific indications only, shall be described.

III.4. Cost for treatment with a candidate product.

Treatment cost shall be presented in a tabular form – cost per course of treatment per patient and for all potential patients who would use the medicinal product. Where possible, costs can be presented by DDD for the course of treatment.

Costs of the therapy shall be calculated according to the ceiling price of wholesaler/retailer level incl. VAT. If the product is applied for 100% reimbursement for Annex 1, the costs shall be calculated on wholesaler price incl. VAT. In the cases of application according to Annexes 2 and 3, the costs shall be calculated on wholesaler price incl. VAT. In the case of application for reimbursement less than 100%, the costs for the NHIF and for the patients shall be calculated in a separate table at retailer prices incl. VAT.

III.5. Cost of treatment with other medicinal products used for the therapy of the disease and/ or indication.

Costs of treatment shall be presented in a tabular format including cost of a therapeutic course of one patient and of all potential patients to whom the medicinal product could be administered. Where possible, costs can be presented in terms of DDD for a course of

treatment. Costs of the therapy shall be calculated on the retailer ceiling price incl. VAT. If the product applies for 100% reimbursement according to Annex 1, costs shall be calculated on the wholesaler price incl. VAT. In case of applications for Annexes 2 and 3, costs shall be calculated on wholesaler price incl. VAT.

Clinically comparable alternatives of the candidate product as well as the accepted standard treatment according to the therapeutic guidelines or national standards shall also be included. It is of particular importance to define the medicinal products that most probably be replaced by the candidate product. Calculation of costs with competing alternatives shall be performed under observation of the requirements to prices described in point III.5 of this recommendation.

III.6. Presentation of the analytic technique.

The analysis shall be performed by the methods of pharmacoeconomic analysis (cost-effectiveness, cost-utility, cost-minimisation in comparing alternatives with identical outcomes). Cost-benefit method can be used in the evaluation of vaccination programs and products.

As guidelines for the implementation of pharmacoeconomic analyses can be used the guidelines of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and other methodological materials for pharmacoeconomics.

As main pharmacoeconomic analysis shall be conducted a cost-effectiveness and result should be expressed in incremental cost-effectiveness ratio.

The presentation of the indirect costs and outcomes these shall be calculated and discussed separately from the direct medical costs and outcomes. At presenting and discussing the long-term costs and benefits over a period longer than one year, these shall be discounted. Recommended discount rate is 5%.

The cost of treatment with the candidate product shall correspond to those calculated as per point III.5 adding all other costs associated with its administration such as clinical tests, treatment of possible adverse drug reactions, etc. Price of additional health services, such as clinical tests, hospital stay, and adverse reactions shall be derived from official sources in Bulgaria. Preferably shall be the prices agreed between health care providers and NHIF. If such are not available, tariffs of hospitals for paid services or other sources can be used.

Clearly defined outcome measures shall be previously described in the section referred to in point III.2. The choice of measure of the therapeutic outcome shall be reasonably justified and consistent with the accepted in clinical and pharmacotherapeutic guidelines indicators to monitor disease progression. If more than one measure of outcome has been

chosen, more than one calculation can be performed. In conducting incremental analysis should include all medicinal products used to treat the disease under item III.2 and application-related cost, according to official prices. While conducting incremental analysis, all medicinal products used for the treatment of a disease referred to in point III.2, as well as the costs associated with the treatment thereof calculated at official prices. As a minimum, the cost of pharmacological therapy shall be weighed against the cost of available alternatives. Pharmacoeconomic analysis shall indicate whether the medicinal product is cost effective using the methodology of WHO-CHOICE (as products with high efficiency value are those in which the cost-effectiveness ratio is less than the annual GDP per capita) - **Highly cost-effective;** as products with value efficiency are those in which the cost-effectiveness ratio is between one and three times the annual GDP per capita - **Cost-effective; Not cost-effective –** for products in which the cost-effectiveness ratio is more than three times annual GDP per capita. The result must be presented as GDP in Bulgarian currency and in purchasing power standard (adjusted by purchasing power parity - PPP) according to official data published in the National Statistical Institute.

III.7. Modelling

Modelling should be applied if the available data are insufficient to allow assessment of the cost-effectiveness or cost-utility ratio.

When calculating the ratio, the following models of the type "decision tree" or Markov's model can be implemented. Modelling shall state the following data:

- type of model and its choice shall be justified;
- the time horizon of the model. It shall include the time of onset of major clinical outcomes;
- probabilities used in the model;
- use of diagrams to describe the model will enable a better perception;
- cohort of patients included in the model;
- measures of therapeutic outcome and costs shall comply with the recommendations set out in sections III.2 and III.4;
- interpretation of the modeling results. It shall be indicated the period of time the candidate medicinal product is cost-effective and what is the incremental ratio for additional therapeutic outcome.

III.8. Sensitivity analysis

Sensitivity analysis is an assessment of the extent of dependence of outcomes and costs on probabilistic or deterministic variables. The assessment shall include a sensitivity

analysis of the values of key parameters, where parameters used must be justified and special attention shall be paid to the most significant ones in terms of final outcomes. Depending on the type of method used and the presence of a pharmacoeconomic model, a stochastic sensitivity analysis can be applied by Monte Carlo simulation or Tornado diagram. In the sensitivity analysis, the intervals of variation of the variables shall be justified.

III.9. Analysis of budget impact

Conducting budget impact analysis shall be applied in the presence and use of clear data of the probably affected population, changes in therapy and type of additional costs and benefits in the treatment with the candidate product. Analysis of the budget impact shall be performed in compliance with the methods of Mauskopf et al., as described in the literature. It shall include data from current therapeutic practice and anticipated changes that would occur in the budget from the introduction of a medicinal product in the reimbursement practice.

If the administration of a medicinal product requires additional clinical examinations or tests, these shall also be submitted and described in order to assess the total costs of administration of the medicinal product.

If a marketing authorisation holder has an analysis conducted for other healthcare systems, he shall discuss the data about the costs and outcomes in the light of the Bulgarian healthcare system. It is possible that alternatives which are cost effective in other countries, to be unacceptable for Bulgaria at the available prices of healthcare services.

IV. Specific medicinal product groups

Health technology assessment as regards the reimbursement of orphan drugs varies throughout separate countries, and the role of pharmacoeconomic analysis also varies. Assessment of effectiveness needs relevant information regarding the cost-effectiveness of clinical trials for orphan drugs - this information is often incomplete or missing. This assessment shall meet different criteria than those applicable for the medicinal products for treatment of common diseases, such criteria can be:

- Submission within a specified period of time, not longer that one year, of additional evidence of the benefits from the administration of the medicinal product.
- Submission of models (Markov etc.) to support decision making.
- Assessment on the basis of: seriousness, severity of a rare condition; availability of an alternative; what is the cost for the patient provided that the medicinal product is not reimbursed.
- Ethical considerations.

- Assessment of the budget impact of the new orphan drug.
- It is not necessary full pharmacoeconomic analysis for orphan drugs, which have great social benefit, but are not cost effective and their use is indicated for serious conditions, for which there is no effective alternative therapy.

V. Conclusion

Clear and unambiguous conclusion about the benefits of the candidate product, the clinical significance and its place in therapy.

References:

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