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STATE OF ISRAEL
Ministry of ?????? ??' ?
Health
Pharmaceutical ?????? ???
Administration

Guidelines for the submission of a request to include a pharmaceutical product in the national list of health services

The National Health Insurance Law, 1994

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1. General instructions for submission of a request to include a pharmaceutical product in the health services "basket":

1.1 A request to include a pharmaceutical product in the national list of health services ("basket") will include a comprehensive data file which will be submitted to the Pharmacoepidemiology and Pharmacoeconomics Department at the Pharmaceutical Administration of the Ministry of Health, according to the guidelines detailed herewith.

1.2 One data file will be submitted for all dosage forms, for all strengths and approved indications of the pharmaceutical product.

1.3 The data file will be submitted by the appointed pharmacist of the license holder of the pharmaceutical product.

1.4 All data and references will be in Hebrew and/or English. Official documents should be submitted in their original language.

1.5 Submission of the file on electronic media is both welcomed and recommended.

1.6 Inclusion of a pharmaceutical product in the health services basket is done on the basis of a predefined budget, according to decisions made by the public committee for the update of the basket appointed by the Minister of Health. The Pharmacoepidemiology and Pharmacoeconomics Department will consider each application and after assessment will pass its recommendations to the appropriate authorities. Therefore, a complete and detailed request does not guarantee the requested pharmaceutical product to be considered by the appropriate authorities for inclusion in the health services basket or implicates the Ministry of Health in any possible way.
However, the process of decision making is based on the data submitted in the request and hence the great importance of the request's content.

1.7 These guidelines contain a number of compulsory paragraphs (designated with an asterisk). The data appearing in these paragraphs is of crucial importance in the decision making process.

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1.8 The data submitted will be processed by the Pharmacoepidemiology and Pharmacoeconomics Department and presented to the public committee in a uniform format (For the 2002 update format see Appendix A)

2. Structure of the data file:

2.1 A request to include a pharmaceutical product in the national health services basket will be composed of three parts to be submitted according to section 3 of these guidelines:
Part I: Request forms and documents pertaining to details of the pharmaceutical product and a detailed summary of the data presented in parts II and III.
Part II: Clinical and epidemiological data.
Part III: Clinical-Economic evaluation.

2.2 The request will be submitted in a single binder separated by dividers.

2.3 On the back of the binder the name of the pharmaceutical product and the license holder's name, will be stated.

3. Dossier elements:

3.1 Part A - General:

3.1.1 Index

3.1.2 General description of the product (Form 1).

*3.1.3 One page summary of the disease's nature and the pharmaceutical product's relative benefits in comparison to the therapeutic alternatives that are included in the basket.

*3.1.4 The product's registration certificate (including full indications).

*3.1.5 Product monograph (if there is none - Full prescribing information (Physician leaflet)).

3.1.6 Detailed summary of the data presented in part II.

3.1.7 Detailed summary of the data presented in part III.

*3.1.8 An affidavit of the product's price in Israel (Form 2) - The product's price in Israel is defined as the selling price for the Sick Funds if the product is included in the basket.

3.2 **Part II – Clinical and Epidemiological data:**

3.2.1 **Clinical-Pharmacological profile:**
Briefly describe the general pharmacological profile of the pharmaceutical product's therapeutic class and the specific pharmaceutical product, according to the following points:

3.2.1.1 **The pharmaceutical product:**

- Recommended and commonly used treatment regimens with the product, including expected length of treatment.
- If the pharmaceutical product is indicated for use in combination with other pharmaceutical products, these combinations should be detailed, together with the required dosages.
- Summary of the adverse effects reported as part of the product's post marketing surveillance (summary of the last PSUR).
- Significant adverse effects, precautions / warnings and drug-drug interactions.
- Which changes have been made, if any, after receiving the marketing authorization (warnings, side effects, etc.)
- If the pharmaceutical product is being used in Israel under regulation 29 a(3), describe for which indications and how many patients are treated according to this approval.
- Detail other indications currently under research or any off label use of the pharmaceutical product, including all

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approved indications abroad (please state date of approval for each indication).

3.2.1.2 **The Therapeutic class:**

- Name of the therapeutic class and its classification according to the ATC classification system.
- Major pharmacological action of pharmaceutical products in this class.
- The rationale for using pharmaceutical products in this class.

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3.2.1.3 **Alternative treatment options:**
What are the major treatment options (drug and non-drug) currently existing in Israel for the same indication. For each treatment option specify if it is included in the basket, or not.
For each alternative medicinal treatment option summarize according to the following points: Brief pharmacological profile; mechanism of action; rationale for use of pharmaceutical products; efficacy and major side effects.
Please emphasize the aspects that differ significantly from the proposed pharmaceutical product.

It is recommended that the data presented will be in a tabular form.

3.2.1.4 Summarize briefly results from relevant clinical trials pertaining to the pharmaceutical product's efficacy for the relevant indication. Preferably use comparative studies in which the proposed pharmaceutical product is compared to other treatment options used for the same indication (see explanation in paragraph 3.2.5).

3.2.1.5 Attach any official treatment guideline/protocol for the requested indication/s (in Israel and / or other countries) in which the proposed product is part of. Highlight the relevant part concerning the proposed product.

*3.2.1.6 **Expert report:**

3.2.1.6.1 An expert report by at least one physician specializing in the field the pharmaceutical product is indicated for, should be submitted.

3.2.1.6.2 The expert report must be based on all the data presented in the request and refer to the following points:
- Efficacy and importance of the pharmaceutical product in comparison to alternative treatment for the same indication.

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- Personal experience with the pharmaceutical product.
- Definition of the pharmaceutical product's place in therapy (for example second/third line, specific patient groups to benefit the most from the treatment, etc.)

3.2.1.6.3 At the end of the report the following signed statement will appear:
"I am a physician, qualified to give this expert report on behalf of the requesting party. I give this expert report in support of a request to include this pharmaceutical product in the National Health Services list, according to the National Health Insurance Law, based on the entire file presented before me and my personal experience.

Herewith are details of my status and education:

I hereby declare that this is my name, that is my signature and the content of my expert report is true."

3.2.1.6.4 Expert reports that will not meet with the above mentioned criteria will not be taken under consideration.

3.2.2 **Pharmacoepidemiological data**

*3.2.2.1 Summarize briefly the disease state to which the pharmaceutical product is indicated for (pathophysiology and clinical course) and the typical gradual treatment regimen.

*3.2.2.2 The disease's epidemiology:
- Prevalence: number of patients in Israel.
- Incidence: number of new patients each year in Israel.

Include, where available, incidence and prevalence data from other western world countries.

*3.2.2.3 What is the market size (number of patients treated currently for the specific disease state) and its distribution for each of the treatment options detailed in section 3.2.1.3 (Use market surveys data, IMS, etc).

*3.2.2.4 Cite the Israeli sales figures of the requested pharmaceutical product from the last three years.

3.2.2.5 By how much is the target population expected to increase within the next three years following inclusion of the proposed pharmaceutical product in the basket.

*3.2.2.6 Is the requested pharmaceutical product included in a Sick Fund's formulary in Israel (If so, in which Sick Fund, date of inclusion in the formulary, rate of co-payment and type of insurance).

*3.2.2.7 Is the requested pharmaceutical product included in a formulary of a public insurer in other countries (state name of country and rates of co-payment).

3.2.3 **The new treatment equilibrium:**

3.2.3.1 As part of the treatment regimen what is the requested place of the pharmaceutical product.

3.2.3.2 How many patients are expected to switch from their current treatment to the proposed pharmaceutical product (based on clinical and/or economic considerations) after inclusion of the proposed pharmaceutical product in the health basket.

*3.2.3.3 Characteristics of the specific patient population which will benefit the most from receiving treatment with the proposed pharmaceutical product.

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3.2.3.4 After inclusion of the proposed pharmaceutical product in the health basket what is expected new market share for each treatment option (what percentage of the patients will be treated with each treatment option).

3.2.3.5 Is the market expected to grow after inclusion of the proposed pharmaceutical product in the health basket (will the number of treated patients increase)? If so, by how much.

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3.2.4 **Pharmaceutical Products that will bear no added cost to the basket according to the <u>dossier submitter's assessment:</u>**
Attached to the full dossier will be a segment detailing the arguments as to why the inclusion of the proposed pharmaceutical product will bear no added cost to the health services basket. This part will be based on a comparison to therapeutic alternatives that are included in the basket.

In such a case, submission of a full dossier is necessary to ensure discussion of the requested pharmaceutical product as any other proposed product, in case there will not be an agreement as to the product not adding costs to the basket

3.2.5. **Supporting clinical information:**

*3.2.5.1 Attach a printout of the previous year's abstracts.

3.2.5.2 For each clinical trial summarize the following data elements:

- 3.2.5.2.1 Name of trial.
- 3.2.5.2.2 Location and trial date.
- 3.2.5.2.3 Publication citation/s.
- 3.2.5.2.4 Trial design, randomization and blinding procedures.
- 3.2.5.2.5 Inclusion and exclusion criteria.
- 3.2.5.2.6 Treatments to which the proposed pharmaceutical product was compared (including placebo).
- 3.2.5.2.7 Treatment and dosage regimens
- 3.2.5.2.8 Sample characteristics: demographics, sample size, disease severity and comorbidities.
- 3.2.5.2.9 Patient follow -up procedures: if intention to treat, were drop-outs followed ?
- 3.2.5.2.10 Clinical and other outcomes measured and their statistical significance.
- 3.2.5.2.11 Compliance behavior.
- 3.2.5.2.12 Concordance of the achieved outcomes in the trial's sample and the actual expected outcomes in the target population (considering differences of treatment protocol, treatment populations, comorbidities,

compliance, follow-up, etc.). If such a difference exists, propose a model to link the trial's results with the expected outcomes in Israel while detailing the justification to the model's assumptions.

3.2.5.3 If meta analyses have been undertaken, these should be summarized with particular emphasis on the inclusion criteria for studies analyzed.
Justify the relevance of the analysis to the target population.

3.2.5.4 Where a retrospective study has been undertaken (utilizing pharmacy and medical claims databases) the study should be summarized and should include, in addition to the above information, the research question or hypothesis tested, rationale for the study design, choice of data source, techniques used to assess data quality, rationale for chosen statistical or econometric procedure and techniques used to avoid issues such as selection bias.

3.3 **Part III: Economic evaluation**

3.3.1 An economic evaluation of the proposed pharmaceutical product must be submitted (See instructions in Appendix B: Instructions for performing an economic assessment).

3.3.2 An economic evaluation conducted abroad should be adapted to Israeli settings. In such cases the request will include both evaluations.

3.3.3 The economic evaluation will be performed according to one of the accepted models, taking into account the following elements:

3.3.3.1 Estimated target population.
3.3.3.2 Savings in healthcare resources (hospitalization, physician visits, etc.).
3.3.3.3 Savings in medical technologies.
3.3.3.4 Comparison to cost of alternative registered treatments in Israel.
3.3.3.5 Cost of treatment.

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Form 1

General description of the pharmaceutical product

Name of the product: _____

Registered dosage form in Israel (including dosage forms, strength/concentration, package type and quantity/size and registration number):

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____

Active ingredients (Generic names) and their quantity in dosing units:

1. _____
2. _____
3. _____
4. _____

Registered indications in Israel (including date of approval of each indication):

1. _____
2. _____
3. _____

Pharmacological classification of the product (according to ATC):

1. Name of the product's pharmacological class: _____

2. Known or assumed mechanism of action of the product: _____
_____
_____
_____

Other countries in which the product is registered and the registered indications in each country (if different from the registered name in Israel):

____

Is the product indicated for use in combination with any other product ?

____

General:

Name of license holder:

____

License holder’s address (in Israel and abroad): ____

Name of the appointed pharmacist: ____

Pharmacist’s License number: ____________________

Affidavit:

To my knowledge and professional responsibility, I, the undersigned, declare herewith that all the data submitted in this request are correct.

_________________________ ________________________________ ______________

Name of the appointed Stamp and signature of the appointed Date

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Pharmacist pharmacist

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Form 2

Affidavit of the product's price

Dosage forms				
Strength				
Package type and quantity Price per package (for institutions)*				
Number of estimated patients				

*Price for institutions – The product's price is defined as the selling price for the Sick Funds if the product is included in the basket

_____	_____	_____
Name of the license holder or a corporate manager who is the license holder	Stamp and signature of the license holder or the corporate manager who is the license holder	Date

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Appendix A: Submission format to the public committee

Name of the technology: Rank:

Technology description

Active ingredient:

Manufacturer: Importer:

Strength: Dosage form:

Treatment regimen:

Approved indications:

Included in the basket:

Not included in the basket:

Requested indications for inclusion in the basket:

The technology will be used in which surroundings: Community / Hospital / Etc.

Technology's efficacy:
The active ingredient

The disease and its treatment

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Benefits of the pharmaceutical product in comparison with other products indicated for the same indication (including references)

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Safety & Adverse effects:

The treatment's common side effects (5% and above) are

Serious adverse effects are

Experience in Israel:

The product is registered in Israel since/was approved for registration in 2002/is in the process of registration.
The product is included in the National List of Health Services since ____ for the treatment of.

Personal accounts by recommending physicians of their experince with the product in Israel.

Experience abroad:

The product is registered in .

Treatment alternatives included in the basket:

Pharmaceutical

Other technologies

Treatment alternatives not included in the basket:

Pharmaceutical

Other technologies

Indications approved abroad:

Limitations:

Warnings / Precautions

Contra-indications

Significant Drug & Food Interactions

Place of the pharmaceutical product in the disease's treatment regimen:

Epidemiology:

The number of patients in Israel:

Estimated Use of the technology:

Extra information:
a. Israeli data

b. Data from abroad

The expected change following inclusion in the basket:

Current market distribution of treatment options

Expected market distribution following inclusion of the product in the "basket"

Compliance data

Expected market change – increased utilization, market expansion, etc.

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Costs:

Price per package based on the manufacturer/importer's affidavit:

Price in the world:

Cost of annual treatment per patient:

Cost of alternatives included in the basket:

Net cost of treatment (including VAT):

Total net cost to all patients:
Total number of patients X Annual cost per patient =

Number of patients treated in 2001:
a. according to the Sick funds:

b. according to the manufacturer/importer

Public funding:

In Israel:
The pharmceutical product is included in the basket of the Sick funds in Israel according to the following:
Clalit Health Services - % reimbursement
Leumit - % reimbursement
Meuhedet - % reimbursement
Maccabi Health Services - % reimbursement

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Abroad:
The pharmceutical product is included in the basket of public insurers in the following countries:

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Summary

The product is _____ indicated for the treatment of

Brief description of the indication.

There are _____ patients suffering from _____, _____ of which are expected to use the proposed product.

Brief Comparison to treatment alternatives.

The annual cost of treating ___ patients is _____ NIS.

Recommendations:

The pharmaceutical product was recommended for inclusion in the basket by:

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Appendix B: Instructions for performing an economic assessment

The pharmceutical product is included in the basket of the Sick funds in Israel according to the following:

1. **Assessment clinical outcomes**:

1.1 Define the clinical outcomes (including indices of quality of life) indicative of a successful treatment. Intermediate or final outcomes may be used. If intermediate outcomes are selected then the analysis should be supported by evidence to show how these outcomes are linked quantitatively to final outcomes.

1.2 What are the desired values for the outcomes mentioned above, which define a treatment as successful.

1.3 What is the number of patients in Israel that achieve the wanted clinical outcome with the current treatment options. (Defined as the sum of the product of the percentage of patients achieving the wanted outcome in each of the existing treatment options and the number of patients treated with each treatment option, in a given year).

1.4 What is the expected impact of the proposed pharmaceutical product on the disease's treatment outcomes (the value received in section 3.3.4.1.3 after taking into consideration the new treatment equilibrium).

2. **Assessment of the cost to health services providers** :

2.1 Identify the resources used for the proposed indication for each of the treatment options currently existing (including the treatment itself, resources used to support therapy and resources used to treat side effects and treatment failures).

2.2 Estimate the cost to the Sick Funds for each unit of the resources mentioned in the previous section. As to the cost of the proposed pharmaceutical product itself, a signed affidavit of the pharmaceutical product's price in Israel must be submitted (Form 2). The pharmaceutical product's price in Israel is defined as the maximal selling price for the Sick Funds if the pharmaceutical product will be included in the basket.

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2.3 Assess the overall annual cost of treatment of the proposed indication to the Sick Funds (A model based on cost of resources and clinical outcomes mentioned before, may be used).
It is preferable to use the Ministry of Health's ambulatory services' price list when pricing a non-medicinal treatment of the disease (the price-list can be downloaded from the Ministry's website: http://www.health.gov.il/taarifon/index.htm)

2.4 Assess the cost of resources which will be used to treat the disease-state, in the first three years following the inclusion of the proposed pharmaceutical product in the health basket. In this assessment consider the size of the market and the expected new market shares.

2.5 What is the net impact of inclusion of the proposed pharmaceutical product in the health basket on the total cost of treating the disease-state to the Sick Funds.

3. **Cost effectiveness evaluation**
A comprehensive evaluation of the expected benefit to the treated population, after inclusion of the proposed pharmaceutical product in the health basket, will be submitted which will include the following elements:

3.1 Overall assessment of the impact of the proposed pharmaceutical product on the cost of treatment of the target population in the first three years following the inclusion of the proposed pharmaceutical product in the health basket.

3.2 Overall assessment of the proposed pharmaceutical product's impact on the treatment's outcomes.

3.3 Impact of the uncertainty of the different data on the strength of the above assessment (sensitivity analysis of the evaluation)

4. **Supporting pharmacoeconomic information:**

4.1 For each pharmacoeconomic study/trial summarize the following data elements:
4.1.1 Name of trial, date and location, length of trial.
4.1.2 Publication citation/s.
4.1.3 Research question.

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4.1.4 Type of pharmacoeconomic study.
4.1.5 Study perspective.
4.1.6 Study design.
4.1.7 The treatment to which the pharmaceutical product was compared and the reasons it was chosen.
4.1.8 Inclusion and exclusion criteria.
4.1.9 Sample characteristics: demographics, sample size, disease severity and comorbidities.
4.1.10 Treatment protocol.
4.1.11 Resource utilization and unit costs.
4.1.12 Outcomes selected.
4.1.13 Principal findings and their statistical significance.
4.1.14 Relevance to the treated population in Israel.

4.2 Cite studies which analyze the economic impact of the use of the proposed pharmaceutical product that are relevant to the information requirements of the public committee.
Please pay attention to the fact that most pharmacoeconomic studies that appear in the scientific literature analyze the economic impact in terms of incidence. These studies compare the costs of the different treatment options in a single patient from the stage of diagnosis throughout the course of the disease. Since the public committee deals with allocating an annual budget to the Sick Funds, the Israeli guidelines request information which will assist the committee in assessing the impact of the proposed pharmaceutical product on the annual cost of treatment to the Sick Funds, to treat all the patients in Israel in a defined period of three years following inclusion of the proposed pharmaceutical product in the health basket. Therefore, it is of great importance that the economic data and the supporting pharmacoeconomic studies submitted to the committee, examine the impact of inclusion of the proposed pharmaceutical product in the health basket in terms of prevalence and not in terms of incidence.

4.3 As supporting data, one may use pharmacoeconomic evaluations based on clinical trials. In such cases, it must be examined whether the extrapolation or the model are relevant to the Israeli settings (patient characteristics' wise: comorbidities, compliance, type and quantity of resources used, cost data).

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4.4 When citing a pharmacoeconomic evaluation based on an epidemiological study or retrospective data (and not on a prospective clinical trial), detail carefully the study's design, different factors which might influence the study's results (confounding variables) and the techniques used to overcome them, the methodology used when the economic evaluation or the model were performed, statistical analysis of the results, and the relevance of the results to the local settings.

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