**Applicant template for submission of full pharmacoeconomic assessments to the**

**National Centre for Pharmacoeconomics**

**International non-proprietary name:** ……………..

**Proprietary name:** ……………..

**Formulation(s):** ……………..

**Licensed therapeutic indication(s):** ……………..

**Submission checklist complete (Y/N):** ……………..

**Applicant company:** ……………..

**Name of applicant company representative:** ……………..

**Signature:** ……………..

**Date of submission:** ……………..

This document outlines the content and format of the written submission to the NCPE as part of a full pharmacoeconomic assessment. For further guidance on pharmacoeconomic methods, refer to HIQA Health Technology Assessment Guidelines ([www.hiqa.ie](http://www.hiqa.ie)), NCPE Requirements for conducting and reporting clinical evidence synthesis analysis and NCPE Guidelines for inclusion of drug costs in pharmacoeconomic evaluations ([www.ncpe.ie](http://www.ncpe.ie)).Commercial- or academic-in-confidence data should be highlighted throughout the document. This document may be updated periodically. Please refer to www.ncpe.ie to obtain the most recent version prior to submission.

Record of recent update:

|  |  |
| --- | --- |
| Version 1.5 | *12th July 2018* |
| Page 7 | Inserted:*‘The search date of the systematic review must be no more than six months prior to the date of submission of the HTA.’* |

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## Executive Summary

* An executive summary consisting of no more than two pages should preface the document encompassing an overview of the submission and the main findings of the economic evaluation.

## Disease and its management

#### Description of the disease/condition

* Provide a brief description of the disease/condition including an overview of the natural history of the disease, diagnosis, symptoms and clinical outcomes, causes or risk factors, disease-specific mortality etc.

#### Epidemiology of the disease/condition in Ireland

* State the incidence and prevalence of the disease/condition in Ireland, in the general population and among relevant subgroups.

#### Treatment guidelines and clinical pathway for patients in Ireland

* Describe how the disease/condition is managed in Ireland i.e. other available treatments, current standard of care (routine care) and best practice, supported by data confirming how this was established. Include both licensed and unlicensed therapies where applicable.
* Summarise Irish treatment/disease guidelines if available. Summarise other international guidelines which are followed in Ireland and describe any variation in disease management, supported by data confirming how this was established.
* Where evidence is based on expert opinion, provide a detailed description of the methods and results of the expert elicitation process (see Appendix 1).

## Intervention under assessment

#### Therapeutic indication

* State the regulatory approval status of the intervention. Specify the date of authorisation or CHMP opinion. Ensure that the European public assessment report (EPAR) is submitted in the reference file.
* State the therapeutic indication as approved by the EMA/HPRA, including relevant conditions or restrictions. Indicate if the licensed therapeutic indication in the EMA varies from other jurisdictions. State all other indications for which the intervention is currently licensed, or for which additional indications are anticipated in the future.
* Indicate if the intervention has an orphan designation from the EMA, and if the intervention is a generic/biosimilar medicinal product.

#### Description of the intervention

* State the international non-proprietary name (INN), proprietary name, formulation, licensed dose, frequency, route of administration and duration of use of the intervention.
* Indicate if specific tests or investigations are required for targeted therapy e.g. biomarker testing, companion diagnostics etc.
* Indicate if there are particular requirements for dispensing or administration of the intervention or if co-prescribed medicines are required.
* State the ATC code and drug class. Summarise the mode of action and pharmacology, clinically relevant interactions and pharmacokinetics.

#### Anticipated place in therapy

* State the anticipated place in therapy of the intervention with respect to other available therapeutic options, supported by data confirming how this was established. Identify relevant comparators for the economic evaluation.
* Where evidence is based on expert opinion, provide a detailed description of the methods and results of the expert elicitation process (see Appendix 1).
* Provide details of any current use of the intervention in Ireland e.g. as part of a clinical trial or early access programme, or in an unlicensed capacity.

#### Previous economic evaluations in Ireland of relevance to the current assessment

* Describe the outcome of any previous cost effectiveness assessments of this technology/comparator(s) in Ireland for this/other indication(s).

## Clinical evidence

*All clinical efficacy and safety evidence included in the submission must be selected following a systematic literature search to identify relevant data sources, and reported in accordance with* [*PRISMA*](http://www.prisma-statement.org/) *guidelines. The search date of the systematic review must be no more than six months prior to the date of submission of the HTA. Justify the selection of specific sources. Where evidence is based on expert opinion, provide a detailed description of the methods and results of the expert elicitation process (see Appendix 1).*

#### Clinical efficacy evidence

* Provide a brief overview of the clinical development programme supporting product registration. Summarise the programme under the headings in Table 1.

**Table 1: Summary of clinical development programme**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Methodology**  | **No. of Patients** | **Inclusion criteria** | **Treatments** | **Primary endpoints** | **Secondary endpoints** |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

* Describe the main studies from Table 1 in further detail. Studies directly comparing the intervention with the comparator(s) of interest to the decision-maker are of most relevance. Provide the rationale for selection of studies for detailed description. Describe each of the studies under the following headings *(may be tabulated as appropriate)*:
	+ Design and methodology
	+ Inclusion and exclusion criteria
	+ Treatments, allocation and retention
	+ Study endpoints

*Include both directly measured clinical outcomes and quality of life outcomes where measured. Justify the use of alternative endpoints. Discuss the validity of surrogate markers where included*

* + Analysis

*Describe data analysis methods including the statistical approach to missing data and to specific trial design features e.g. crossover, switching, responder enrichment etc.*

* + Population
	+ Results
	+ Quality assessment

*Use a validated quality assessment tool, including risk of bias. Results of the quality assessment may be included in an appendix*

* + Discussion of results and limitations

*Include a discussion of the relevance to the population for the indication under review*

* Provide details of supporting studies of relevance to the decision problem including randomised/non-randomised observational studies, phase IV post-marketing studies etc.
* Describe the application of treatment effects in the model.
* Describe the source of treatment effects for the intervention and comparator(s). If treatment effects were sourced from the studies described above, provide full details of any further analyses conducted to derive (relative) treatment effect estimates. If evidence from different sources was combined in an evidence synthesis analysis, complete Section 2.ii). If relevant evidence from different sources was available and *not* combined in an evidence synthesis analysis, justify this omission.

#### Clinical evidence synthesis

*Complete this section if evidence synthesis methods were used to combine multiple sources of evidence to estimate comparative effectiveness and/or safety e.g. a pairwise meta-analysis, indirect comparison or network meta-analysis. If not applicable, write “N/A”.*

Describe the clinical evidence synthesis under the following headings.Refer to the NCPE requirements for conducting and reporting clinical evidence synthesis analysis for detailed guidance.

* Background
* Objective
* Methods
* Results
* Discussion

#### Clinical safety

* Provide details of the adverse events occurring in the identified studies, in terms of absolute and relative statistical measures, specifying the population to which the results relate, and highlighting significant differences between the intervention and comparator(s).
* Summarise the key safety issues related to the intervention, and associated risk management requirements.
* Summarise the differences in safety profiles between the intervention and comparator(s), including results of any evidence synthesis analyses.

## The decision problem and model structure

#### Population

* Define the population included in the economic evaluation including subgroups if relevant. Provide justification if this does not reflect the licensed therapeutic indication.
* Populations or population subgroups should not be defined on the basis of response/non-response to treatment. This is more appropriately captured in the model using a treatment stopping-rule following response assessment.

#### Intervention

* Define the intervention included in the economic evaluation in terms of international non-proprietary name, proprietary name, formulation, dose, frequency, route of administration and duration of use. Provide justification if this does not reflect the licensed therapeutic indication.
* If treatment discontinuation is based on the observed duration of use in a clinical trial, or the application of a responder rule, describe the relevance of treatment discontinuation assumptions to clinical practice.

#### Comparators

* List all the relevant comparators included in the economic evaluation in terms of international non-proprietary name, proprietary name, formulation, dose, frequency, route of administration and duration of use. Provide justification if these details do not reflect the licensed therapeutic indication(s), posology and method of administration.
* Provide the rationale for the inclusion (and exclusion) of relevant comparators identified in Sections 2.iii) and 3.iii).

#### Model structure

* Describe the type of model used, time horizon and cycle length. State if a half-cycle correction was applied. Provide the rationale for these model choices.
* Describe the model structure and provide a model diagram.
* If a state transition model was used, describe the model health states, patient pathways through the model and clinical outcomes.
* Provide the rationale for the model structure in terms of the natural course of the disease/condition and the clinical relevance/importance of model outcomes to patients.
* If progression through the model is based on a surrogate marker, provide the rationale and evidence base for use of the marker.
* Describe all methods and assumptions used to derive baseline model transition probabilities including a description of the systematic search employed to identify relevant sources*.* Present the transition probability matrix.
* Justify the relevance of the model to the Irish population in question.
* A comprehensive suite of quality assurance checks should be conducted and reported, to ensure the internal and external validity of the model. Provide details and results of all model verification, external validation and quality assurance exercises.
* In tabular format, clearly detail and justify all assumptions regarding the model structure.

#### Perspective

* The perspective of the analysis should be that of the Health Service Executive (HSE) in Ireland. A wider, societal perspective may be presented as a scenario analysis. State the perspective of the primary analysis and of any secondary analyses conducted.

## Economic model inputs

*Select economic model inputs following a systematic literature search to identify relevant data sources, and report search results in accordance with PRISMA guidelines. Justify the selection of specific sources. Where evidence is based on expert opinion, provide a detailed description of the methods and results of the expert elicitation process (see Appendix 1). Model inputs should be derived from an Irish population, where available. All parameter values should be presented together with measures of precision e.g. mean value and 95% confidence interval.*

#### Treatment effectiveness

* Describe the mechanism by which the intervention alters the disease course in the model.
* Describe the application of treatment effects in the model.
* Describe the source of treatment effects for the intervention and comparator(s) in the model, including a description of the systematic search employed to identify relevant sources.
* If treatment effects were determined by patient-level data, analysed using non-parametric or parametric survival analysis methods, present a range of models within the written submission and electronic model and systematically assess model fit*.* Provide the corresponding summary outcomes predicted by the models e.g. mean overall survival, mean progression free survival etc, and compare with equivalent outcome results from clinical trials.
* If treatment effects were extrapolated over the model time horizon, describe the persistence or durability of treatment effects of both the intervention and comparator(s). Provide the rationale and evidence to support the extrapolation of treatment effects.
* Provide details of all analyses conducted to derive and extrapolate treatment effects.
* Clearly detail and justify all assumptions regarding treatment effectiveness.
* Tabulate the mean parameter values and ranges applied in probabilistic analyses and deterministic sensitivity analyses, including justification for the chosen ranges and probability distributions.
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in treatment effectiveness.

#### Health-outcomes

* Describe the health outcomes captured by the model in terms of the expected health-related benefits and harms represented by model health states and/or events. The preferred evaluation type is a cost-utility analysis with the outcomes expressed in quality-adjusted life years (QALYs).The EQ-5D-3L descriptive system is the preferred method of measuring health-related quality of life (HRQoL), with utilities derived from an EQ-5D-3L valuation set from a representative sample of the general population. Additional outcomes such as life years gained may also be presented.
* Justify the inclusion or exclusion of selected benefits and harms (adverse events) in the model.
* Describe the sources of HRQoL utility data used in the model, including a description of the systematic search employed to identify relevant studies. Provide the rationale for the choice of data sources.
* If HRQoL outcomes were measured during the clinical development programme, describe the methods and results of the analysis. Provide rationale for inclusion/omission of trial results in the model.
* Provide details of all analyses conducted to estimate utility values including details of the population, the timepoint of measurement, response rates, the instrument and valuation methods, the approach to missing data and mapping technique if used. Discuss the relevance of the population from which estimates were derived to the Irish population in question.
* Clearly detail and justify all assumptions regarding the application of utility values in the model.
* Tabulate the mean parameter values and ranges applied in probabilistic analyses and deterministic sensitivity analyses, including justification for the chosen ranges and probability distributions.
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in health-related benefits and harms.

#### Resource use and costs

* Describe all costs captured by the model including intervention and comparator costs (drug acquisition, administration, monitoring etc.), adverse event, health state and other costs. Direct costs relevant to the healthcare payer should be included in costs from the HSE perspective. Non-healthcare/wider societal costs, productivity losses associated with informal care, absenteeism from work etc. may be included in sensitivity analysis.
* Justify the inclusion or exclusion of selected costs in the model.

*Intervention and comparator costs*

* State the price to wholesaler (ex-manufacturer price) of the intervention (per pack) exclusive of tax. The price of the intervention must correspond with the Price Application Form submitted to the Corporate Pharmaceutical Unit, HSE Primary Care Reimbursement Service. Alternative prices may be included in a sensitivity analysis. State the price to wholesaler (ex-manufacturer price) of the comparator(s).If a Patient Access Scheme (PAS) or confidential discount is in place for a comparator, include a plausible range of prices in sensitivity analysis. State whether value-added-tax (VAT) is payable on the intervention/comparator(s).
* Include a table using the headings described in Table 2 outlining the price per year (or treatment course as applicable) of the intervention and comparator(s) detailing price to wholesaler, wholesale margin, fees, rebates and final reimbursement price under the relevant reimbursement scheme (exclusive of VAT). For further guidance refer to the Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluation (<http://www.ncpe.ie/submission-process/hta-guidelines/guidelines-for-inclusion-of-drug-costs/>).

**Table 2. Price per patient per year (or per treatment course) for the intervention and comparator(s).**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Strength** | **Pack size** | **a. Price to wholesaler (PTW)** | **b. Pharmacy purchase price**  | **c. Plus pharmacy fee\*** | **d. Less Rebate 5.25% on PTW** | **Total reimbursement price per pack** | **Cost/ patient/ year or treatment course** |
|  |  |  |  |  |  |  | **b+c-d** |  |
|  |  |  |  |  |  |  |  |  |

\*For drugs reimbursed under the GMS/DPS or LTI scheme include a €5 dispensing fee.

\*For drugs reimbursed under the HTDS include a monthly patient care fee of €62.03.

* Describe and provide the rationale for any assumptions regarding the dose of the intervention/comparator(s) and the duration of treatment/rate of discontinuation applied in the model.
* Where applicable the length of treatment should be determined from the mean treatment duration as opposed to the median. If the source informing the mean duration of treatment is not fully mature this should be noted in the submission.
* Describe the measurement and valuation of administration and monitoring costs associated with the intervention and comparator(s).

*Health state, adverse event and other costs*

* Describe the sources of resource use and unit cost data used in the model, including a description of the systematic search employed to identify relevant studies. Provide the rationale for the choice of data sources.
* If resource utilisation was measured during the clinical development programme, describe the methods and results of the analysis, and discuss the relevance of the trial protocol to standard practice in Ireland. Provide rationale for inclusion or omission of trial results in the model.
* Describe the methods of converting costs from a different year or reported for a different country, if relevant.
* Clearly detail and justify all assumptions regarding the application of resource use and cost data in the model.
* Tabulate the mean parameter values and ranges applied in probabilistic analyses and deterministic sensitivity analyses, including justification for the chosen ranges and probability distributions.
* Outline the approach taken to sensitivity analysis and scenario analysis in order to explore uncertainty in resource use and costs.

#### Discount rate

* State the discount rate applied to costs and benefits/harms, and the range of discount rates applied in sensitivity analysis (0%-10% in one-way sensitivity analysis).

#### Parameter Summary

* Tabulate all parameters used in the model including values, range/confidence intervals and probability distributions applied in probabilistic analyses and deterministic sensitivity analyses, and sources. Cross-reference parameter details to relevant sections in the written submission, and indicate the location of parameters in the electronic model
* Indicate that each parameter has been included in both probabilistic and deterministic analysis. Justify the exclusion of any parameter from probabilistic or deterministic analysis.

## Results of incremental cost effectiveness analysis

#### Incremental analysis of costs and outcomes

* Calculate and present total costs and outcomes, incremental costs and outcomes and incremental cost-effectiveness ratios (ICERs) using both probabilistic and deterministic analysis, for the full population and relevant subgroups. If more than one comparator is included, present ICERs for each comparator compared with standard-of-care or baseline, followed by a fully incremental analysis with exclusion of treatments subject to dominance and extended dominance.
* Justify the number of replications conducted in probabilistic analysis.
* Explain any differences between the ICERs calculated using probabilistic and deterministic analysis.

#### Analysis of Uncertainty

* Present the results of the probabilistic analysis using a scatter-plot of simulated cost and effect pairs on the incremental cost-effectiveness plane, and using cost-effectiveness acceptability curves and tables illustrating the probability of cost effectiveness at a range of willingness to pay thresholds including €20,000 and €45,000/QALY\* *(see footnote at end of template).*
* Present the results of deterministic sensitivity analyses and scenario analyses, in tabular format and using a tornado diagram. Conduct analyses for the full population and relevant subgroups. Discuss the key drivers of cost effectiveness.
* Present the price-ICER relationship over a range of prices, calculated using both probabilistic and deterministic analysis.

## Budget Impact Analysis

#### Eligible population and market share

* State the estimated eligible population over the next five years and the proportion of market share predicted for the intervention, supported by data confirming how these estimates were established. Eligible population should comprise both the incident (newly diagnosed) and prevalent population.

#### Gross drug-budget impact

* Tabulate the price of the intervention and comparator(s) inclusive of wholesale margin, fees, rebates and VAT if applicable, per pack and per year (or treatment course as applicable). The price of the intervention must correspond with the Price Application Form submitted to the Corporate Pharmaceutical Unit, HSE Primary Care Reimbursement Service. Alternative prices may be included in a sensitivity analysis. If a Patient Access Scheme (PAS) or confidential discount is in place for a comparator, include a plausible range of prices in sensitivity analysis.
* Based on the eligible population and predicted market share, state the estimated gross budget impact (i.e. inclusive of fees, margins, rebates and VAT as applicable) in year 1, 2, 3, 4, and 5 (ensure at least five full calendar years are included). It is necessary to ensure that a full 5 year budget impact is included (i.e. Year 1 to be the 1st rolling 12 months. On occasion, individual companies may seek to only include partial calendar years. Such budget impact submissions are not accepted as the exact date or month when a therapy is introduced can be open to significant uncertainty.
* The gross budget impact estimates should only include the drug acquisition cost. Other costs, such as costs of administration or concomitant medication may be presented in section 7 (iv).
* Where applicable the length of treatment should be determined from the mean treatment duration as opposed to the median. If the source informing the mean duration of treatment is not fully mature this should be noted in the submission.

#### Net drug-budget impact

* Describe the potential drugcosts and cost-offsets anticipated from the increased utilisation and/or displacement of other drugs. Present the net *drug-budget* impact analysis taking account of potential drug cost-offsets in year 1, 2, 3, 4, and 5.
* The net budget impact estimates should only include the drug acquisition cost. Other costs, such as costs of administration or concomitant medication may be presented in section 7 (iv).

#### Additional costs and cost-offsets

* Describe the potential for additional costs and cost-offsets which may impact the wider healthcare budget e.g. drugs, administration, monitoring, adverse event costs etc., supported by data confirming how these estimates were established. Present the net healthcare budget impact analysis taking account of potential wider healthcare costs in year 1, 2, 3, 4, and 5.

#### Analysis of Uncertainty

* Explore the impact of parameter uncertainty on the budget impact analysis using deterministic one-way sensitivity for each parameter/scenario analysis, providing clear rationale for the range of values applied.

## HTAs and reimbursement status in other jurisdictions

* Describe the reimbursement status of the intervention in other European countries, including the level of reimbursement, any restrictions on reimbursement, and any patient access schemes which may apply.
* Indicate the outcome/status of HTAs of the intervention in other European countries.

## Conclusion

* Provide an overview of the main findings of the submission.

## References

* Format all references in a standardised style (based on Harvard or Vancouver), and list at the end of the submission. Verify that all in-text references correspond to the final reference list prior to submission.
* Where a reference is used to support specific evidence e.g. data point, parameter, other piece of information, the relevant line/table/section should be highlighted within the reference.
* Submit electronic full-text copies and an RIS formatted file of all references.

## Appendices

* Additional information, details of search strategies, summaries of product characteristics and other supporting documentation may be submitted as appendices, as appropriate.

## Electronic model

* Microsoft Excel is the preferred software for NCPE submissions. Contact the NCPE in advance of submission if alternative software packages are considered for submission.
	1. ***Cost-effectiveness model***
* The submitted model should be accompanied by a Technical Specification Document, providing sufficient detail to facilitate model evaluation and reproduction..
* Submit a fully executable electronic copy of the cost-effectiveness model, ensuring that the model structure and all parameters values are as specified in the written submission.
* In Microsoft Excel, please ensure that all intermediate calculations between the input parameters and the final matrices (transitions, patients, costs, QALYs etc) are clearly shown on the spreadsheets.
* In Microsoft Excel models, all parameter values directly feeding into the deterministic and probabilistic calculation of costs and benefits should be listed in consecutive rows on a single worksheet.
* Disaggregated probabilistic results i.e. all simulated cost and effect pairs, should be presented in the model, in addition to summary measures.
	1. ***Budget Impact Model***
* The budget impact model should be fully programmable so that the NCPE can easily examine the impact of a change in any of the parameters to the budget impact.
* Tabulate the price of the intervention and comparator(s) inclusive of wholesale margin, fees, rebates and VAT if applicable, per pack and per year (or treatment course as applicable).
* If incidence and prevalence estimates are applied to population estimates, the excel model should start from this point.
* Tabulate all parameters used in the model in consecutive rows on a single worksheet. Include the reference source and measures of uncertainty where available.
* In Microsoft Excel, please ensure that all intermediate calculations between the input parameters and the final matrices (patients, costs, offsets) are clearly shown on the spreadsheets.
* Ensure the integrity of all calculations employed in the model before submission.

*\*Note on the QALY threshold*

The €20,000 and €45,000/QALY thresholds are specified in the *Framework Agreement on the Supply of Medicines to the Health Services 2016- 2020 between the Irish Pharmaceutical Healthcare Association Ltd and the Department of Health and the Health Service Executive*. The duration of this agreement is four years from 1st August 2016. Applicants should incorporate any relevant changes which may apply after the term of the current agreement.

## Appendix 1

**NCPE Guidance on the use of expert opinion as supporting evidence in the applicant submission**

Data inputs should be based on empirical data from randomised trials or nonrandomised studies. Where such data is lacking, expert opinion may be needed to supplement or support observed data. Expert opinion represents low level evidence and if used in a submission, **its inclusion should be justified**. Data collection should be systematically planned, documented and analysed, and reported in a transparent way. Applicant submissions which include data elicited through expert opinion should provide details of the elicitation process **including the following elements**:

1. A description of the criteria used for selecting the experts.
2. The numbers of experts approached.
3. The number of experts who participated.
4. A declaration of potential conflicts of interest from each expert whose opinion was sought.
5. The background information that was provided to the experts on the study and its consistency with the evidence provided in the submission.
6. Detailed method used to collect opinions e.g. either individually or through a meeting.
7. The medium used to collect opinions e.g. direct interview, questionnaire, telephone.
8. The questions asked (including a copy of the questionnaire or outline of the interview).
9. Numbers of responses received for each question.
10. The analytic approach used to collate the opinion, including the variability in opinion.

**References:**

Hunger et al. Using Expert Opinion in Health Technology Assessment: A Guideline Review. Int J Technol Assess Health Care. 2016 Jan;32(3):131-9

Australian Government Department of Health. Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (PBAC Guidelines), version 5.0.