

**Applicant Submission Template**

|  |  |
| --- | --- |
| **Drug:** | INN/Brand® |
| **Therapeutic indication:** |  |
| **NCPE HTA number:** |  |
| **Applicant Company:** |  |
| **Submission checklist complete :** |  |
| **Applicant company representative:** | Name and email address |
|  | Signature |
| **Second company contact:** | Name and email address |
| **Date of submission:** |  |

**Version Control**

|  |  |  |
| --- | --- | --- |
| Version | Date | Description of key changes |
| 1.8 | 15/05/20 | 1. New Appendix 4 “Submission of commercial/academic-in-confidence information” 2. Additional guidance on supporting documentation required for economic model 3. Additional requirements for explanation of budget impact analysis inputs |
| 1.9 | 06/01/22 | 1. Updated to reflect the Framework Agreement on the Supply of Medicines to the Health Services 2021-2025 between the Irish Pharmaceutical Healthcare Association Ltd and the Department of Health and the Health Service Executive |
| 2.0 | 12/01/22 | 1. Changed wording from ‘IPHA rebate’ to ‘Framework Agreement rebate’. |

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)). (1-4)Inclusion of commercial- or academic-in confidence information should follow guidance outlined in Appendix 4 of this Template. This document may be updated periodically. Please refer to [www.ncpe.ie](http://www.ncpe.ie) to obtain the most recent version prior to submission.

Double-sided printing should be used when preparing the completed applicant template for submission. All pages in the submission, including appendices, should be numbered. While additional sub-headings may be included in the submission, do not otherwise alter the heading structure provided.

All files included in the submission should be named in accordance with the specified file-naming convention and saved in the specified format, as outlined in Table 1. The international non-proprietary name (INN) and NCPE HTA ID number (assigned to the assessment prior to the pre-submission meeting) should be included at the start of all filenames. Please do not use all capital letters or use underscores in the filename.

**Table 1 File naming convention and format**

|  |  |  |
| --- | --- | --- |
| Type of file | File naming convention | File format |
| Applicant template | <INN NCPE HTA Number Applicant Template>  e.g. Aspirin 1901 Applicant Template | .docx and .pdf |
| Cost-effectiveness model | <INN NCPE HTA Number CEM>  e.g. Aspirin 1901 CEM | .xlsx or similar |
| Budget impact model | <INN NCPE HTA Number BIM>  e.g. Aspirin 1901 BIM | .xlsx or similar |
| References | <INN NCPE HTA Number references>  e.g. Aspirin 1901 references | .ris |
| Submission checklist | <INN NCPE HTA Number Submission checklist>  e.g. Aspirin 1901 Submission Checklist | .pdf |

**Table of Contents**

[List of Figures 1](#_Toc40347082)

[List of Tables 2](#_Toc40347083)

[Abbreviations 3](#_Toc40347084)

[Executive Summary 4](#_Toc40347085)

[1. Disease and its management 5](#_Toc40347086)

[i) Description of the disease/condition 5](#_Toc40347087)

[ii) Epidemiology of the disease/condition in Ireland 5](#_Toc40347088)

[iii) Treatment guidelines and clinical pathway for patients in Ireland 5](#_Toc40347089)

[2. Intervention under assessment 5](#_Toc40347090)

[i) Therapeutic indication 5](#_Toc40347091)

[ii) Description of the intervention 6](#_Toc40347092)

[iii) Anticipated place in therapy 6](#_Toc40347093)

[iv) Previous economic evaluations in Ireland of relevance to the current assessment 7](#_Toc40347094)

[3. Clinical evidence 7](#_Toc40347095)

[i) Clinical efficacy evidence 7](#_Toc40347096)

[ii) Clinical evidence synthesis 9](#_Toc40347097)

[iii) Clinical safety 9](#_Toc40347098)

[4. The decision problem and model structure 10](#_Toc40347099)

[i) Population 10](#_Toc40347100)

[ii) Intervention 10](#_Toc40347101)

[iii) Comparators 10](#_Toc40347102)

[iv) Model structure 11](#_Toc40347103)

[v) Perspective 11](#_Toc40347104)

[5. Economic model inputs 12](#_Toc40347105)

[i) Treatment effectiveness 12](#_Toc40347106)

[ii) Health-outcomes 13](#_Toc40347107)

[iii) Resource use and costs 14](#_Toc40347108)

[iv) Discount rate 17](#_Toc40347109)

[v) Parameter Summary 17](#_Toc40347110)

[6. Results of incremental cost-effectiveness analysis 18](#_Toc40347111)

[i) Incremental analysis of costs and outcomes 18](#_Toc40347112)

[ii) Analysis of Uncertainty 18](#_Toc40347113)

[7. Budget Impact Analysis 19](#_Toc40347114)

[i) Eligible population and market share 19](#_Toc40347115)

[ii) Gross drug-budget impact 19](#_Toc40347116)

[iii) Net drug-budget impact 20](#_Toc40347117)

[iv) Additional costs and cost-offsets 20](#_Toc40347118)

[v) Analysis of Uncertainty 21](#_Toc40347119)

[8. HTAs and reimbursement status in other jurisdictions 21](#_Toc40347120)

[9. Conclusion 21](#_Toc40347121)

[10. References 21](#_Toc40347122)

[11. Appendices 22](#_Toc40347123)

[12. Electronic model 22](#_Toc40347124)

[Appendix 1 26](#_Toc40347125)

[Appendix 2 28](#_Toc40347126)

[Appendix 3 30](#_Toc40347127)

[Appendix 4 34](#_Toc40347128)

[References 37](#_Toc40347129)

## List of Figures

## List of Tables

## Abbreviations

## 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/hybrid 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 drugs 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 the intervention/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 review to identify relevant data sources, and reported in accordance with* [*PRISMA*](http://www.prisma-statement.org/) *guidelines. The search date of the systematic literature review must be no more than six months prior to the date of submission of the HTA. Justify the selection of specific sources. Wherever possible, clinical evidence should be based on an analysis of pre-specified endpoints when trial follow-up is complete, in accordance with national HTA guidelines.* *(4) Where marketing authorisation has been granted on the basis of interim analysis of clinical trial data, ensure that results from the most recent data cut(s) are also provided. The submission of supplementary data after the initial submission date may result in realignment of timelines in line with the submission of new data. 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 2.

**Table 2 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 search to identify relevant data sources. The date of the systematic search must be no more than six months prior to the date of submission of the HTA. Inputs relating to treatment effects and health outcomes should be selected following a systematic literature review, with search results reported in accordance with PRISMA guidelines. For all other inputs, a description of the systematic search employed to identify relevant studies should be included. 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 literature review 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.
* All outcomes which impact on patients’ HRQoL should be included. 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 literature review 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.
* All outcomes which impact on costs or healthcare resource use should be included. Justify the inclusion or exclusion of selected costs in the model.

*Intervention and comparator costs*

* Please refer to the Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluation when completing this section. (<http://www.ncpe.ie/submission-process/hta-guidelines/guidelines-for-inclusion-of-drug-costs/>).
* Complete the Table 3 templates below including the relevant prices to wholesaler and total prices to the HSE for the intervention and comparator(s) per pack and per unit time, as applicable. Additional columns may be added in cases where there are multiple strengths or packs. 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.
* Full details of the total drug cost to the HSE for the intervention and comparator(s) should be provided in Appendix 3, including price to wholesaler, wholesale margin, fees, rebates, VAT and pharmacy fees. Figures included in Table 3 below should correspond with those included in Appendix 3, the cost effectiveness model (exclusive of VAT) and the budget impact model (inclusive of VAT, where applicable).
* Specify the rate of Framework Agreement rebate applicable.
* State whether value-added-tax (VAT) is payable on the intervention/comparator(s).
* The cost per year should account for any assumptions regarding vial sharing, broken bulk dispensing and weighted average dosing assumptions where patients require different doses.
* Describe and provide the rationale for any assumptions regarding the dose of the intervention/comparator(s), treatment cycle length and the duration of treatment/rate of discontinuation applied in the model.
* Please write out calculations in full. Alternatively, submit the completed table in a spreadsheet where interim calculations can be clearly seen.
* 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).

Table 3a Total intervention drug cost to the HSE (Drug cost and pharmacy fees)

|  |  |  |
| --- | --- | --- |
|  | Price to wholesaler | |
| Price to wholesaler\* |  | |
| Strength |  | |
| Pack size |  | |
|  | Total cost per pack including wholesale mark-up, rebates and pharmacy fees (except where stated)§ | |
|  | Excluding VAT | Including VAT |
| Per pack (excluding pharmacy fees) |  |  |
| Per year† (including pharmacy fees) |  |  |
| \*The price to wholesaler for the intervention must match the price on the pricing application form (PAF)  §Total cost must correspond with Total cost in Appendix 3  †Where the treatment course is less than one year, this may be replaced by the cost per treatment course | | |

Table 3b Total comparator drug cost to the HSE (Drug cost and pharmacy fees)

|  |  |  |
| --- | --- | --- |
|  | Price to wholesaler | |
| Price to wholesaler\* |  | |
| Strength |  | |
| Pack Size |  | |
|  | Total Cost per pack including wholesale mark-up, rebates and pharmacy fees (except where stated)§ | |
|  | Excluding VAT | Including VAT |
| Per pack (excluding pharmacy fees) |  |  |
| Per year†(including pharmacy fees) |  |  |
| \*The price to wholesaler for the intervention must match the price on the pricing application form (PAF)  §Total cost must correspond with Total cost in Appendix 3  †Where the treatment course is < 1 year, this may be replaced by the cost per treatment course | | |

*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. The discount rate is set by the Department of Finance (4% since August 2019). A range of discount rates should be applied in sensitivity analysis (0%-10%). (5)

#### 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 (mean total costs and outcomes) 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.
* 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.
* Ensure that all relevant information has been submitted, in the appropriate format, to allow the NCPE Review Group to re-run analysis and reproduce results.
* Present the price-ICER relationship over a range of prices, calculated using both probabilistic and deterministic analysis. If a commercial-in-confidence discount is in place for the comparator(s), present the price-ICER relationship over a range of prices for both the comparator and the intervention.

## 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

* The NCPE Budget Impact Model Template (available at [www.ncpe.ie](http://www.ncpe.ie)) is the preferred format for submission of Budget Impact Models. The NCPE Template is available to guide applicants in the calculation of the eligible patient population, drug acquisition costs and cost offsets, presentation of results and analysis of uncertainty.
* The prices of the intervention and comparator(s) should be consistent with those provided in Section 3.ii and Appendix 3, including VAT where applicable.
* 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.
* A clear explanation of how estimates of eligible population, treated population and market share were calculated should be provided, including details of all calculations and underlying assumptions.
* Based on the eligible population and predicted market share, state the estimated gross drug-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). Partial calendar years are not acceptable in budget impact models due to uncertainty in the exact date or month of introduction to the market.
* 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 sensitivity analysis for each parameter/scenario, 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. Please include, amongst others, the BENELUXA countries of Belgium, Netherlands, Austria and Luxembourg.

## Conclusion

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

## References

* Format all references in the Vancouver style, 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 primary data source should be referenced rather than secondary sources such as other economic evaluations which have used the data. The relevant line/table/section should be highlighted within the primary reference source.
* Submit electronic full-text copies and an RIS formatted file of all references. Website links alone are not sufficient due to the potential for web addresses to change over time. Screenshots should be provided as “full-text” copies in these cases. The number of full-text references should match the number of references in the submission.

## Appendices

* Appendix 1 should be submitted if any evidence in the submission is based on expert opinion. Information provided in this appendix should follow the “NCPE Guidance on the use of expert opinion as supporting evidence in the applicant submission”, located at the end of this document.
* Appendix 2 should describe all systematic literature reviews conducted as part of the submission. Information provided in this appendix should follow “NCPE Guidance on conducting and reporting on the systematic literature search used to identify evidence on clinical efficacy and safety evidence, in addition to economic model inputs”, located at the end of this document.
* Appendix 3 should describe all drug cost calculations for the intervention and comparator(s). Information provided in this appendix should follow NCPE “Guidance for Inclusion of Drugs Costs in Pharmacoeconomic Evaluations”.
* Appendix 4 includes a Confidential Information template which must be completed if the submission contains confidential information.
* Summary of product characteristics, EPAR, additional information and other supporting documentation may be submitted as appendices, as appropriate.
* Each individual appendix should appear as an individual heading within the main table of contents or within a separate table of contents for appendices alone.

## 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. Ensure that all relevant information has been submitted, in the appropriate format, to allow the NCPE Review Group to re-run analysis and reproduce results.
* Supporting documentation, e.g. a Technical Specification Report if available from the model developers, should be submitted along with the economic models (not necessary for the NCPE BIM template). The information in supporting documentation should include but not be limited to, guidance for model-users on how to use/adapt the model, and detail on the basic functioning, background calculations, and underlying assumptions of the model structure. At a minimum, a document should 1) define the role and describe the content of each tab of the Excel spreadsheet, and 2) list and describe all of the macros used in the model and define their relationship to the various tabs of the spreadsheet.
  1. ***Cost-effectiveness model***
* The applicant must submit a fully executable electronic copy of the cost-effectiveness model, ensuring that the model structure and all parameter values are as specified in the written submission.
* 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 NCPE Budget Impact Model Template (available at [www.ncpe.ie](http://www.ncpe.ie)) is the preferred format for submission of Budget Impact Models. The NCPE Template is available to guide applicants in the calculation of the eligible patient population, drug acquisition costs and cost offsets, presentation of results and analysis of uncertainty. If a Budget Impact Model other than the NCPE Template is used, the NCPE Template should be consulted for best practice guidance.
* The budget impact model should be fully programmable so that the NCPE Review Group can easily examine the impact of a change in any of the parameters to the budget impact.
* Tabulate all parameters used in the model in consecutive rows on a single worksheet. Include the reference source and measures of uncertainty where available.
  1. ***Spreadsheet Best Practice***
* 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.
* Workbooks, cells, and tabs should all be unhidden and modifiable.
* Value restrictions should not be placed on cells.
* Tabs should be appropriately named and correspond with those in the Technical Specification Document.
* Key cells and ranges should be named in order to provide clarity.
* Formulae that have been copied down for multiple rows should not change in the middle of a column, without clear indication.
* Nested IF statements or cells with nested min/max functions should be kept to a minimum. The exact values used in each possible scenario should be made clear to the Review Group.
* Any irrelevant or unused tabs or inputs in the model should be removed.
* Ensure the integrity of all calculations employed in each model before submission.
  1. ***VBA programming guidelines***
* Code that is not being used in the model should not be included in the submitted model.
* Code should be as concise and efficient as possible.
* All VBA procedures that are being used for a button should all be in the same module where possible. Functions and other commands that are being used for multiple buttons should be kept together in a separate module.
* There should be a brief description at the beginning of each procedure to explain what it is intending to do.
* Commenting should be included throughout each procedure.

## Appendix 1

**NCPE Guidance on the use of clinical 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**. Expert opinion may be a qualitative expression of an individual’s judgement, or a quantitative expression of judgement used to define point estimates of key model parameters and characterise uncertainty (6). In the case of quantitative data, appropriate mathematical aggregation methods should be used. All studies or exercises used to obtain expert opinion should be well-designed to minimise bias and reported with clarity and transparency. Applicant submissions which include data based on expert opinion should provide details of the process used to obtain the data **including the following elements** (6, 7):

1. A description of the criteria used for selecting the experts.
2. The numbers of experts approached.
3. The details of experts who participated.
4. The date(s) on which the expert opinion was obtained.
5. A declaration of potential conflicts of interest from each expert whose opinion was sought.
6. The background information that was provided to the experts on the study and its consistency with the evidence provided in the submission.
7. Detailed method used to collect opinions e.g. either individually or through a meeting.
8. The medium used to collect opinions e.g. direct interview, questionnaire, telephone.
9. The questions asked (including a copy of the questionnaire or outline of the interview).
10. The numbers of responses received for each question.
11. The responses received for each question.
12. The analytic approach used to collate the opinion, including the variability in opinion. This is of particular importance where quantitative expert opinion has been used to inform a model input parameter, in which case all of the data used to derive the parameter in addition to a description of the mathematical method or process used to aggregate the data is required.

## Appendix 2

**NCPE Guidance on conducting and reporting on the systematic literature search used to identify evidence on clinical efficacy and safety evidence, in addition to economic model inputs.**

Studies for the efficacy and HRQoL inputs of the model should be identified and selected following a systematic review of the published peer-reviewed and grey literature, in addition to any relevant unpublished data available to the applicant. Provide a clear description of the data sources used, and the search strategies used for all electronic databases.Database searches must be conducted within **six months** of the date of HTA submission. Applicant submissions should provide details of the search process **including the following elements**:

1. A breakdown of each of the PICOS elements (i.e. population, interventions, comparators, outcomes, study design) used in the search. The elements should correspond with the decision problem outlined in the Applicant Submission
2. Details of all electronic databases searched including years of coverage and the platform used
3. Details and justification of any date limits applied to the search strategy
4. Details and justification of any other limits applied to the search strategy (study/publication type, languages etc)
5. References for any validated search filters used in the strategy
6. Date that searches were undertaken
7. The full search strategies used, including the number of hits per line, for each individual database.
8. Details of sources searched to identify grey literature (conference proceedings, trial registries)
9. Details of the search strategies or key words used to identify grey literature
10. Details of study selection criteria including inclusion and exclusion criteria
11. A PRISMA flow chart that details the number of studies identified and excluded from electronic databases and grey literature sources
12. Details of studies excluded at the full text review stage (with reasons for exclusion)
13. Complete reference list of included studies

Where applicants are undertaking a clinical evidence synthesis more detailed reporting is required, refer to the document “NCPE requirements for conducting and reporting clinical evidence synthesis analyses” for further guidance.

## Appendix 3

Drug cost calculations

* Please refer to the Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluation when completing these tables (<http://www.ncpe.ie/submission-process/hta-guidelines/guidelines-for-inclusion-of-drug-costs/>).
* Please complete the tables below describing the components of the total price to the HSE for the intervention and comparator(s) per pack and per year (or per treatment course, if shorter than one year). (Table 1a-b) The cost per year/treatment course should account for any assumptions regarding vial sharing, broken bulk dispensing and weighted average dosing assumptions where patients require different doses.
* Describe and provide the rationale for any assumptions regarding the dose of the intervention/comparator(s), treatment course length and any assumptions regarding the duration of treatment/rate of discontinuation applied in the model.
* The NCPE Budget Impact Model Template (available at [www.ncpe.ie](http://www.ncpe.ie)) is available to guide applicants in the calculation of accurate drug acquisition costs.
* Please write out calculations in full. Alternatively, submit the completed table in a spreadsheet, or as part of the NCPE Budget Impact Model Template, where interim calculations can be clearly seen.
* Please add additional columns for multiple strengths and/or comparators.

**Table A3a Intervention drug cost and pharmacy fees**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug cost per pack** | | | |
|  | | Calculations | Strength and Pack Size |
|  |
| A | Price to wholesaler |  |  |
| B | Wholesale mark-up |  |  |
| **C** | **Reimbursement Price** |  |  |
| D | Framework Agreement rebate^ |  |  |
| E | VAT |  |  |
| **F(i)** | Total drug cost to the HSE per pack excluding pharmacy fees but **including VAT** |  |  |
| **F(ii)** | Total drug cost to the HSE per pack **excluding VAT** and pharmacy fees |  |  |
| **Pharmacy fees per year (or treatment course)\***  *(For Hospital Drugs this section may be omitted)* | | | |
|  |  | Calculations | Value |
| G | Pharmacy fees per year (treatment course) |  |  |
| H | Non dispensed patient care fee per year (treatment course) (High Tech only) |  |  |
| I | VAT on pharmacy fees |  |  |
| J (i) | **Total pharmacy fee per year (treatment course) including VAT** |  |  |
| J(ii) | **Total pharmacy fee per year (treatment course) excluding VAT** |  |  |
| **Total Drug cost per year (or treatment course)\*** | | | |
| K(i) | **Total Drug Cost per year (treatment course) including Pharmacy Fees and VAT** |  |  |
| K(ii) | **Total Drug Cost per year (treatment course) including pharmacy fees and excluding VAT** |  |  |
| †*Footnote indicating duration (and clear justification) if cost per year has been replaced with cost per treatment course (i.e. for interventions modelled to continue for a discrete duration* | | | |

\* Where the treatment course is < 1 year, the drug cost and pharmacy fees per year may be replaced by the cost per treatment course

^ specify the rate of Framework Agreement rebate applicable

**Table A3b Comparator drug cost and pharmacy fees**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug cost per pack** | | | |
|  | | Calculations | Strength and Pack Size |
|  |
| A | Price to wholesaler |  |  |
| B | Wholesale mark-up |  |  |
| **C** | **Reimbursement Price** |  |  |
| D | Framework Agreement rebate^ |  |  |
| E | VAT |  |  |
| **F(i)** | Total drug cost to the HSE per pack excluding pharmacy fees but **including VAT** |  |  |
| **F(ii)** | Total drug cost to the HSE per pack **excluding VAT** and pharmacy fees |  |  |
| **Pharmacy fees per year (or treatment course)\***  *(For Hospital Drugs this section may be omitted)* | | | |
|  |  | Calculations | Value |
| G | Pharmacy fees per year (treatment course) |  |  |
| H | Non dispensed patient care fee per year (treatment course) (High Tech only) |  |  |
| I | VAT on pharmacy fees |  |  |
| J (i) | **Total pharmacy fee per year (treatment course) including VAT** |  |  |
| J(ii) | **Total pharmacy fee per year (treatment course) excluding VAT** |  |  |
| **Total Drug cost per year (or treatment course)\*** | | | |
| K(i) | **Total Drug Cost per year (treatment course) including Pharmacy Fees and VAT** |  |  |
| K(ii) | **Total Drug Cost per year (treatment course) including pharmacy fees and excluding VAT** |  |  |

\* Where the treatment course is < 1 year, the drug cost and pharmacy fees per year may be replaced by the cost per treatment course

^ specify the rate of Framework Agreement rebate applicable

## Appendix 4

**Submission of commercial/academic-in-confidence information**

In the interests of transparency of NCPE recommendations, all efforts should be made to ensure that information included in the Applicant Submission can be included, without redaction, in NCPE Assessment Reports and is publishable in NCPE summaries. It is recognised, however, that certain information, for commercial or academic reasons, may be requested to be considered confidential, either by the Applicant, or other parties contributing to the Assessment. This type of data should be kept to a minimum in submissions. If confidential information is included in an Applicant Submission, it should be highlighted as such in all relevant documents, in accordance with the following convention: yellow for commercial-in-confidence, blue for academic-in-confidence. Submissions which include confidential information **must include a completed Table A4.1**, identifying all confidential information contained in the submission, the specific reason for identifying information as confidential, and the date/milestone on which the data may no longer be regarded as confidential. All information included in Table A4.1 will be reviewed by the NCPE Review Group. Any information which is not considered to warrant confidentiality will be highlighted by the NCPE Review Group at the time of Preliminary Review. Any information accepted as confidential by the NCPE Review Group, and subsequently included in the NCPE Assessment Report, will be highlighted as such. Confidential information will not be included in the NCPE Assessment Summary.

*Types of information which* ***may*** *be considered confidential*

Detailed information must be provided to justify the identification of information as confidential in Table A4.1. It is insufficient to simply label information as “commercial-in-confidence” or “academic-in-confidence”. The following broad types of information may be considered confidential.

* Information which is not in the public domain, the publication of which may have a significant impact on the commercial interests of the Applicant.
* Scientific research findings which are not in the public domain, the publication of which may jeopardise the ability of the author(s) to publish the findings as a scientific paper.
* Price discounts/rebates submitted as part of PAS proposals.
* Cost-effectiveness model and budget-impact model outputs, estimated under the terms of a PAS.

*Types of information which* ***may not*** *be considered confidential*

* Information which is already in the public domain.
* Drug price (as outlined in Table 3)\*.
* Cost effectiveness input parameters except where the information is considered confidential under the circumstances described above.
* Cost-effectiveness results including. ICERs, incremental costs and QALYs, probabilities of cost effectiveness etc\*.
* Budget impact estimates including estimates of eligible patient population, treated patient population, gross drug-budget and net drug-budget impact\*.

*\*With the exception of prices, and cost-effectiveness and budget-impact model outputs, calculated/estimated under the terms of a PAS.*

**Table A4.1: Confidential information included in the Applicant Submission**

|  |  |  |
| --- | --- | --- |
| **Page and line number** | **Specific reason for confidentiality**  ***(identifying information as “commercial” or “academic” is insufficient”)*** | **Date/milestone after which information may not be regarded as confidential** |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

## References

1. Health Information and Quality Authority. Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. Dublin, Ireland: HIQA, 2018. .

2. Health Information and Quality Authority. Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland. Dublin, Ireland: HIQA, 2018.

3. Health Information and Quality Authority. Guidelines for Stakeholder Engagement in Health Technology Assessment in Ireland. Dublin: 2014.

4. Health Information and Quality Authority. Guidelines for the Economic Evaluation of Health Technologies in Ireland. Dublin, Ireland: HIQA, 2018.

5. Department of Public Expenditure and Reform. Circular 18/2019: Update of the Public Spending Code (PSC): Central Technical References and Economic Appraisal Parameters. Dublin, Ireland: Department of Public Expenditure and Reform; 2019. Available from: <https://assets.gov.ie/20001/35c13bbd055a4a09961a4ec59c93c798.pdf>.

6. Iglesias CP, Thompson A, Rogowski WH, Payne K. Reporting Guidelines for the Use of Expert Judgement in Model-Based Economic Evaluations. PharmacoEconomics. 2016;34(11):1161-72.

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