

NDC CLINICAL CHECKLIST

|  |  |
| --- | --- |
| Date of NDC Meeting: |  |
| Full submission or resubmission: |  |

## REGISTRATION DETAILS

|  |  |  |  |
| --- | --- | --- | --- |
| **1.1 Medicine (generic name, strength, form [proprietary name])** | | | |
|  | | | |
| **1.2 Submitting company** | | | |
|  | | | |
| **1.3.1 Licensed indication under review** | | | |
|  | | | |
| **1.3.2 Does this medicine have a conditional marketing authorisation?** | | | |
|  | | | |
| **1.4 Other licensed indications (if relevant, to put the indication under review in context)** | | | |
|  | | | |
| **1.5 Any proposed positioning** | | | |
|  | | | |
| **1.6 Patient and Clinician Engagement (PACE) criteria** | | **Company submission** | **Assessment team validation** |
| End of life medicine (a medicine used to treat a condition at a stage that usually leads to death within 3 years with currently available treatments)? | | Yes/No | Yes/No/N/A |
| EMA designated orphan or a medicine to treat an equivalent size of population (<5 per 10,000) (full licensed indication) | | Yes/No | Yes/No/N/A |
| **1.6.1 Brief summary of assessment team validation, including need for escalation to the validation panel if required** | | | |
|  | | | |
| **1.6.2 Is it a GB designated orphan medicine? Provide date of designation and number.** | | | |
|  | | | |
| **1.7 Has it been validated as an ultra-orphan medicine (a medicine used to treat a condition with prevalence of <1 in 50,000 people)?** | | | |
|  | | | |
| **1.8 Was this medicine included in the Early Access to Medicines Scheme (EAMS)? Provide date and full indication if different to licensed indication.** | | | |
|  | | | |
| **1.9 Has this medicine been awarded an Innovation Passport allowing entry into the MHRA Innovative Licensing and Access Pathway (ILAP)? Provide the date and number of the Innovation Passport.** | | | |
|  | | | |
| **1.10.1 Date of licensing** | **1.10.2 Date of availability** | | |
|  |  | | |
| **1.11 Dose** | | | |
| *Complete details of the dose or dosing regimen for the indication under review specified in the SPC. Can refer to SPC for more information, e.g. dose reductions/interruptions. Ensure that the dosing regimen outlined in the SPC matches the dosing regimen detailed in the NPAF and the one used in the main study for this submission.*  *Include details of any restriction in who may prescribe the medicine, e.g. specialists only.*  *Reference the SPC.* | | | |
| **1.12 Companion Diagnostics** | | | |
|  | | | |
| **1.13 Disease context and potential comparator(s)** | | | |
|  | | | |
| **1.14 Relevant comparator(s). What might it replace in Scottish practice?** | | | |
|  | | | |
| **1.15 Indirect comparison: If an indirect comparison was presented was it appropriate and was it pivotal to the economic case? (Confirm with economist if not clear)** | | | |
|  | | | |
| **1.16 Type of economic case (e.g. cost minimisation analysis, cost utility analysis)** | | | |
|  | | | |

## SUMMARY

|  |
| --- |
| **2.1 Summary of submitting company’s clinical case** |
|  |
| **2.2 Key strengths of clinical evidence** |
|  |
| **2.3 Key uncertainties of clinical evidence** |
|  |
| **2.4 Key uncertainties in the available evidence with respect to the submitting company’s clinical case** |
|  |

## CLINICAL EVIDENCE

**Overview of Clinical Evidence**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Methodology | Patient nos. | Treatment Allocations | Source of funding |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

\*Key studies are highlighted in bold and will be appraised in detail

Detailed critical appraisal checklists for studies.

**DESCRIPTION of study A**

### EFFICACY

|  |
| --- |
| **3.1 DESCRIPTION OF THE STUDY DESIGN** |
| *Sample text (adapt or add additional text as required):*  STUDYNAME is/was an international, multicentre, randomised, open-label/double-blind, parallel group, phase III/phase II study which evaluated the efficacy and safety of ARM1 compared with ARM2 in X patients with CONDITION.  The study design comprised a X-week run-in, Y-week treatment period and Z-week extension/follow-up.  Patients were recruited across X centres from X countries between MONTH YEAR and MONTH YEAR. |
| **3.2 DESCRIPTION OF THE STUDY POPULATION** |
| **3.2.1 Does the study population (or a subgroup) represent the indication under review or proposed positioning (if applicable)?** |
| *Sample text (adapt or add additional text as required):*  The study included patients of all ages however the marketing authorisation has only been granted in adults (XX% of the study population).  *Ensure that the dose used in the study matches the dose in the SPC and NPAF. If it is not the same, has the submitting company justified why a different dose was used in the study?. Likewise, for medicines given in combination, ensure that the dosing for each medicine is correctly specified in the NPAF and SPC* |
| **3.2.2 Key inclusion and exclusion criteria** |
| *Sample text (adapt or add additional text as required):*  The key inclusion criteria were:  The key exclusion criteria were: |
| **3.3 DESCRIBE THE STUDY TREATMENTS** |
| *Sample text (adapt or add additional text as required):*  Patients were randomised equally/2:1 to receive DRUG1 DOSE ROUTE FREQUENCY (n=X) or DRUG2 DOSE ROUTE FREQUENCY (n=X). Treatment was to continue until… (May need to mention concomitant medication also).  Randomisation was stratified according to STRATIFICATION FACTOR (STRATA 1 or STRATA2)… |
| **3.4 DESCRIPTION OF THE STATISTICAL METHODOLOGY/PLAN** |
| **3.4.1 What was the primary outcome(s) and was it clearly defined?** |
| *Sample text (adapt or add additional text as required):*  Overall survival was defined as the time between date of randomisation and death due to any cause.  Progression Free Survival (PFS) was defined as the time between date of randomisation to the date of first progression (independently or investigator assessed using RECIST v1.1 criteria) or death due to any cause, whichever occurred first. |
| **3.4.2 Were any methods used to enhance the accuracy of the measurements e.g. central review, multiple measurements, training of assessors?** |
|  |
| **3.4.3 What population was used in the analysis?** |
| *Sample text (adapt or add additional text as required):*  Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomisation.  Safety analyses were performed in all patients who had received at least one dose of study medicine. |
| **3.4.4 Was the study appropriately powered? If not, explain. Provide brief details of the power calculation and which outcomes, and subgroups if appropriate, were included in the power calculation to control for type II error.** |
|  |
| **3.4.5 Did the study include a hierarchical testing strategy to control for type I error? If so please define the order of testing.** |
| *If a hierarchical statistical testing strategy was applied in the study then this should be noted here. Standard wording:*  A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported). |
| **3.4.6 Did the methodology account for the possibility of missing data for assessment of primary and any relevant key secondary outcomes?** |
|  |
| **3.4.7 What was the duration of the study and follow-up?** |
| *Sample text (adapt or add additional text as required):*  The study was stopped at the first/second interim analysis when X PFS events had occurred with median follow-up of X months. A final analysis is planned after X overall survival events. |
| **3.5 RESULTS** |
| **3.5.1 Was there a CONSORT diagram and were all patients accounted for?** |
| *Sample text (adapt or add additional text as required):*  A CONSORT diagram/table of disposition was provided in figure/table X of the company submission and this was confirmed from the key publication/EPAR. This accounted for all patients. |
| **3.5.2 What proportion of patients completed the study and was there any crossover?** |
|  |
| **3.5.3 What were the baseline characteristics of patients in the population of interest? Were there any differences between treatment groups?** |
| *Sample text (adapt or add additional text as required):*  Overall, the baseline characteristics across both treatment groups were well matched and presented in Table X of the company submission. For the total study population (n=X), patients had a median age of X (range X to X years)…*and other characteristics relevant to disease*  In STUDYNAME, there were some/notable differences between the ARM1 (n=X) and ARM2 (n=X) groups at baseline including: |
| **3.5.4 Provide details of the primary outcome giving all relevant information to how the results were presented.** |
| *When appropriate, under primary or secondary outcome results, the following standard wording should be used in any description of hierarchical testing:*  A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported)*.* |
| **3.5.5 Provide details of relevant subgroup analyses that support the licensed indication or proposed positioning.** |
|  |
| **3.5.6 Describe briefly any relevant secondary outcomes?** |
|  |
| **3.5.7 Provide details of patient reported outcomes.** |
| *Sample text (adapt or add additional text as required):*  Health Related Quality of Life (HRQoL) was assessed using X questionnaires: (including definitions and scoring range). These instruments were used at screening, every X weeks for the first X months and then every X weeks thereafter. (Report brief results). |
| **3.6 EXTENSION STUDY** |
| **3.6.1 Was there a relevant extension study? Provide brief details/results.** |
|  |
| **3.7 ANY ADDITIONAL IMPORTANT DETAILS** |
|  |

### SAFETY

|  |
| --- |
| **3.8 DESCRIPTION OF ADVERSE EVENTS** |
| **3.8.1 Describe the overall adverse event profile.** |
| *Sample text (adapt or add additional text as required):*  In the \*NAME OF STUDY\* study at data cut-off \*DATE\*, the median duration of treatment in the \*ARM1\* group was X months and in the \*ARM2\* group was X months. Any treatment-emergent adverse event (AE) was reported by X% (n/N) of patients in the \*ARM1\* group and Y% (n/N) in the \*ARM2\* group and these were considered treatment-related in X% and Y% respectively. In the \*ARM1\* and \*ARM2\* groups respectively, patients reporting a grade 3 or higher AE were X% versus Y%, patients with a reported serious AE were X% versus Y%, patients with a dose reduction due to treatment emergent AEs were X% versus Y%, the proportion of AEs that led to dose interruptions were X% versus Y% and patients discontinuing therapy due to an AE was X% versus Y%. (delete as appropriate). |
| **3.8.2 Describe any relevant comparative overall adverse event information including incidence of any important treatment related adverse events.** |
| *Sample text (adapt or add additional text as required)*  The most frequently reported treatment-related/emergent AEs of any grade with an incidence >X% in the \*ARM1\* group versus the \*ARM2\* group were: nausea (X% versus Y%), anaemia (X% versus Y%), fatigue (X% versus Y%), etc… Further details are presented in Table X of the company submission with details of treatment-related AEs presented in Table X. |
| **3.8.3 Give details of any treatment related deaths during the study or at follow up.** |
|  |
| **3.8.4 Detail any important safety aspects that may be specific to this medicine including rare and/or life-threatening treatment related adverse events.** |
|  |

## ADDITIONAL RELEVANT INFORMATION

|  |
| --- |
| **4.1 Give brief details of any relevant additional information including supportive studies that have augmented the data available for the indication under review in this submission.** |
|  |

## SUMMARY OF CLINICAL EFFECTIVENESS

|  |
| --- |
| Clinical context |
| **5.1 Provide brief description of pharmacology for the medicine under review and any background details that may have a bearing on the use of this medicine e.g. is this medicine first in class for this indication or are there any other special circumstances?** |
|  |
| **5.2 Comment on the potential place in therapy of the medicine under review within the disease context and with respect to key comparators and any unmet need.** |
|  |
| Internal Validity |
| **5.3 Was the primary outcome appropriate? Consider whether it was:**   * **a direct health outcome or a surrogate outcome?** * **appropriately assessed/scored or is there any risk of bias in measurement?** * **assessed at an appropriate time-point?** |
|  |
| **5.4 Comment on any limitations of the study methodology, considering:**   * **lack/issues of randomisation** * **lack/issues of blinding** * **population analysed (ITT versus per protocol)** * **high overall levels of missing data, crossover, subsequent treatment or differences between treatment groups, including remaining imbalances in baseline patient or disease characteristics** * **statistical issues (lack of power for relevant outcomes, adjustment for multiplicity)** |
|  |
| * 1. **Was there anything in the way the results were reported that should be taken into consideration including:**   + **wide confidence intervals**   + **small relative differences presented as significant**   + **insufficient treatment duration**   + **relevant (long-term) outcomes not available**   + **relative not absolute risk**   + **subgroup analysis supporting proposed positioning/indication under review or other factor(s)?** |
|  |
| External Validity |
| **5.6 Are there any issues with the study population that might affect the generalisability of the study results to the Scottish population? Consider whether:**   * **the inclusion/exclusion criteria reflect patients eligible for treatment in practice?** * **the baseline characteristics of study patients reflect patients eligible for treatment in practice?** |
|  |
| **5.7 Are there any issues with the medicine under review, comparator and/or concomitant treatments used in the study(ies) that may differ from Scottish clinical practice?** |
|  |
| Clinical Benefit |
| **5.8 Provide a brief summary of the key study (or studies) outcome(s). Consider the following:**   * **Were the results consistent for the medicine under review in the evidence provided?** * **Were the results were statistically significant and/or clinically meaningful considering the magnitude of the treatment effect?** * **Was the duration of treatment sufficient to provide clinically relevant results and are these sufficiently mature?** |
|  |
| **5.9 Provide an overview of the safety profile of the medicine under review.** |
|  |
| **5.10 Would the introduction of this intervention have advantages or disadvantages for the service or patient? Are there any practical issues for the patient or carer? Are there any service implications?** |
|  |
| Additional Information |
| **5.11 Give details of any other important information specific to this medicine.** |
|  |
| **5.12 If the company has suggested a proposed positioning for the medicine, does the evidence provided support this positioning? Provide any comments on how the proposed positioning can be worded as a restriction in the event that the medicine is accepted for restricted use by SMC.** |
|  |
| **5.13 If the medicine has a GB conditional marketing authorisation could the specific obligations address the key uncertainties in the clinical evidence highlighted above?** |
|  |
| **5.14 If this is an EAMS medicine, will ongoing clinical studies help address the key uncertainties in the clinical evidence?** |
|  |
| **5.15 If this medicine has an Innovation Passport, will the evidence generation address key uncertainties in the clinical evidence?** |
|  |
| **5.16 If the medicine has been validated as an ultra-orphan, include brief details of impact beyond direct health benefits.** |
|  |

## APPENDIX 1 – PUBLISHED GUIDELINES

|  |
| --- |
| **Published guidelines relevant to the indication under review.** |
|  |

## APPENDIX 2 – PREVIOUS SMC ADVICE

|  |
| --- |
| **Detail previous SMC advice relevant to the indication under review.** |
|  |

## APPENDIX 3 - REFERENCES

|  |
| --- |
| **List of references used in critical appraisal.** |