Additional file 1. Content of the questionnaire

Country of analysis: _____

Product type: Oncology Orphan ATMP Paediatric Other

Product name: _____

Active ingredient: _____

Regulatory status: Prior EMA submission / EMA submission completed / CHMP opinion favourable / EMA marketing authorisation favourable / In-country P&R negotiation

Type of authorisation (expected if not available): Normal/Conditional

Date of authorisation (expected if not available) (dd/mm/yyyy):

Start date of national P&R process (expected if not available) (dd/mm/yyyy):

Questions	Answers	Interpretation
Indication		
1. What is the authorised indication?	Description	Descriptive
2. Authorised indication	− First indication in monotherapy − First indication in combination − Extension of indication − New indication in monotherapy or in combination	Only to be considered in the P&R process in case of 1, 2 and 3
3. Is it foreseeable that the reimbursement decision restricts the authorised indication?	− Yes − No	Only to value the restriction as a reimbursement possibility of a higher price
4. Scope of indication potentially reimbursed	− Broad and clearly stated − Concrete and restricted, and clearly stated − Not clearly established	Only to integrate into the BI calculation and identify potential uncertainties for the payer
5. Are new indications for the product expected in the next 3 years after the marketing authorisation of the product?	− Yes − No	Estimates multi-indication as an element to be considered in medium-term negotiation

6. Is future competition expected in this indication?	– Yes, there is a high probability that there will be new therapeutic options in the next 3 years – Yes, but the products are at an early stage of development. – No.	Estimates the future competition
Priority of the therapeutic area		
7. Condition for which the product is intended (indication)	Description	Descriptive
8. The condition for which the product is intended can be classified as...	– Very severe – Severe – Moderate severity – Minor severity	Establishes the theoretical priority for the NHS
9. In terms of treatment needs, the therapeutic area or condition presents...	– Major unmet needs – Significant unmet needs – No significant unmet needs	Establishes the unmet need
PAT.1 Is the condition targeted by the product a priority for the NHS?	– **High priority** – **Medium priority** – **Low priority**	**Questions 8, 9**
Therapeutic need		
10. Therapeutic objective of the product	– Diagnosis – Intention to cure – Symptomatic (non-curative) reduction – Palliative care (*end-of-life*)	Additional information
11. Does the product meet important or relevant therapeutic needs?	– Yes, absolutely – Yes, partially – No, it does not cover important or relevant needs	Establishes the unmet need
12. The therapeutic positioning of the product is based on...	– Filling a therapeutic gap – Replaces other therapeutic alternatives (including non-pharmacological) – Combines with or adds to current treatment – New line or promising new therapeutic approach – Expands the range of therapeutic options available	Estimates the therapeutic positioning and BI

TN.1 Does the product target an area of unmet therapeutic need?	**– High need** **– Medium need** **– Low need**	**Questions 11, 12**
Clinical evidence available at the time of assessment		
13. The design of the study to be submitted/already submitted for marketing authorisation is...	Description	Descriptive Adds to the final and is a valid question for the uncertainties assessment
14. What is the primary endpoint of the study?	Description	Descriptive
15. Does the primary endpoint of the study meet the therapeutic objective?	– Yes, it is entirely appropriate as it is an endpoint related to the therapeutic goal – Yes, it is partially appropriate as it is an intermediate outcome, but related to the therapeutic objective – No, it is not adequate	Adds to the final and is a valid question for the uncertainties assessment
16. In terms of time to effect, when does the effect on the primary endpoint occur?	– Short term (<3 months) – Medium term (3 to 12 months) – Long term (>12 months)	It could be used in some model
17. Is the time horizon of the study appropriate to the therapeutic objective?	– Yes, it is entirely appropriate as it allows the effect of the endpoint on the therapeutic target to be assessed – Yes, it is partially appropriate as it allows the effect of intermediate variables on the therapeutic target to be assessed. – No, it is not adequate as it prevents assessment of the effect on the therapeutic target (intermediate or final endpoint)	Adds to the final and is a valid question for the uncertainties assessment
18. Can the population included in the study be extrapolated to our own?	– Yes, absolutely – Yes, partially – No	Adds to the final and is a valid question for the uncertainties assessment
19. Is the comparator used in the study appropriate?	– Yes, on the basis of available and accepted clinical evidence – Yes, but it is not the most widely used in actual clinical practice	Adds to the final and is a valid question for the uncertainties assessment

	− No, it does not allow to estimate the value added in our environment	
20. Has the drug demonstrated statistically significant differences?	− Yes, for the primary endpoint − Yes, for secondary and/or exploratory endpoints − No, it has not shown differences for any relevant endpoint − No results available	ICB
21. What is the effect on the main variable?	− Important (<0.75) − Substantial (0.75-0.9) − Minor (0.9-1) − No data available for calculation	ICB
22. Does this drug improve overall survival?	− Yes, <3 months − Yes, 3 to 6 months − Yes, >6 months − Yes, it is potentially curative − No, it has only demonstrated a significant increase in progression-free survival >3 months − No results available	ICB
23. Does this drug improve safety in a statistically significant way?	− Yes, reduces severe adverse events (grade ≥3) − Yes, reduces mild to moderate adverse events (grade 1-2) − No, it does not reduce adverse events. − No conclusive results are available	Adds to the final and is a valid question for the uncertainties assessment
24. Does this drug improve health-related quality of life in a statistically significant way?	− Yes − No, it remains the same − No, it gets worse − No results available	Adds to the final and is a valid question for the uncertainties assessment
25. Are there valid results available for subgroups of patients?	− Yes, and the results are in line with the study design − Yes, but they were obtained in an exploratory study − No, there are results, but they are not valid − The results of subgroups are not considered relevant.	Adds to the final and is a valid question for the uncertainties assessment

26. Are there subgroups of patients with superior benefits?	– Yes – No – No valid analysis available	Adds to the final and is a valid question for the uncertainties assessment
CE.1 Is the evidence from clinical development (conducted or planned) of good quality?	**– The available evidence is of high quality and allows estimation of the therapeutic value of the product in our setting without uncertainties** **– The available evidence is limited, but it allows estimating value expectations, albeit with some uncertainties** **– The available evidence is very limited and does not allow estimating expectations of product value**	**Questions 15, 17, 18, 19, 25**
Incremental Clinical Benefit		
27. The improvement in incremental clinical benefit due to... (Please note that answers are not mutually exclusive)	– Efficacy – Safety – Compliance/adherence – Quality of life – It is not known exactly whether there is incremental clinical benefit	ICB
28. In terms of the treatment-eligible population, where does the incremental clinical benefit occur?	– In the whole population with the condition – In the whole population, but with greater benefit in some subgroups – It is not known exactly	ICB
ICB.1 Does the product bring added therapeutic value to the NHS in the therapeutic area for which it is intended?	**– High, compared to existing alternatives and with sufficiently strong evidence (substantially improves the benefit/safety of available alternatives) and with sufficiently strong evidence** **– Medium, slight improvement in benefit/safety over available alternatives, but not substantial and with sufficiently robust evidence.** **– Null, no incremental clinical benefit over available alternatives and with sufficiently strong evidence**	**Questions 20, 21, 22, 23, 24, 26**

	– **The available evidence does not allow adequate knowledge of the BCI provided (there are relevant uncertainties).**	
Budget impact of the product for the NHS or therapeutic area		
29. What is the estimated population potentially receiving the drug (prevalence)?	– <1/50,000 (ultra-rare) – >1/50,000 - 5/10,000 (rare) – >5/10,000 - 2/100 (prevalent) – >2/100 (very prevalent) – It is difficult to establish the number of eligible patients	Estimates the potential target population and uncertainties about the target population
30. What is the expected uptake of the molecule in the first 3 years after commercialisation among the potential population (market share)?	– <10% – 10%- <20% – >20% – Unknown	Estimates the potential prevalence of use and uncertainties in the target population
31. How is the drug used? It is applied...	– One time only – In a limited period of short duration (<3 months) – In a limited period of long duration (3 months - 1 year) – Chronic (>1 year) – Treatment duration unknown	Estimates the treatment duration and uncertainties about treatment cost
32. What is the individual dose regimen of the product?	– Concrete and clear, the dose is defined and the SmPC clearly indicates what to do in case of adverse events (low inter-individual variability). – Ambiguous, no clearly defined dose (high inter-individual variability) – The dose regimen is unknown	Estimates uncertainties about treatment cost
33. What is the requested price of the drug in relation to the therapies it replaces?	– Higher price (>10%) – Higher price (<10%) – Same price – Lower price – The treatment cost is unknown	Estimates the treatment costs and uncertainties about treatment cost
34. Does the addition of this drug reduce other non-pharmacological healthcare costs?	– Yes, there is evidence that it significantly reduces other healthcare costs (e.g. outpatient care, hospitalisation, etc.)	Estimates whether the treatment cost can be offset by other costs

	– No, there is no evidence of a significant reduction in other costs, or there is evidence but the reduction is insignificant. – There is no evidence on the impact	
BI.1 How is the budget impact for the NHS?	**– Null (or negative)** **– Low-medium** **– High** **– Very high**	**Questions 30, 31, 33, 34** **Approach to the budget impact of the product for the NHS**
BI.2 How is the BI of the product in the therapeutic area?	**– Null (or negative)** **– Low-medium** **– High** **– Very high**	**Questions 29 and BI.1** **Approach to the budget impact of the product in the specific therapeutic area**
BI.3 Are there uncertainties about the budget impact?	**– Null or low** **– Medium-high** **– Very high**	**- Questions 4, 29, 30, 31, 32, 33** **Approach to the uncertainties about the budget impact**
Incremental cost-effectiveness		
35. Is there reliable information from the ICER?	– Yes, and adapted to our environment (appropriate population and comparator) – Yes, it is methodologically correct, but it is not adapted to our environment – Yes, but it is not adequate from every point of view – There is no evidence	Only reports whether or not valid information exists
ICER.1 Is the product's ICER calculable and below the NHS willingness-to-pay threshold?	**– Dominant** **– ≤€20,000/QALY** **– >€20,000/QALY** **– Not known**	**Question 35** **Approach to whether the ICER result is acceptable based on available evidence (modifiable according to the thresholds defined in each application environment)**
ICER.2 Are there uncertainties in the available ICER?	**– No or very few** **– Yes, due to effectiveness** **– Yes, due to cost** **– Yes, due to effectiveness and cost**	**Questions CE.1 and BI.3** **Approach to the uncertainties in the available ICER data**
Uncertainties associated with the product		

U.1 Is the product's P&R decision affected by uncertainties?	**– No, there is little or no uncertainty** **– Yes, but not very relevant** **– Yes, very relevant**	**Questions CE.1, BI.3 and ICER.2** **Approach to the overall uncertainties of the product**
U.2 Which areas are affected by uncertainties?	**– None** **– Effectiveness (efficacy and safety)** **– Cost** **– Effectiveness and cost (ICER)**	**Questions BI.3 and ICER.2** **Approach to the dimensions affected by uncertainties**
Final assessment: perceived benefit to the NHS		
36. What is the perceived benefit of this product to the NHS, and does the risk of uncertainty outweigh the potential benefits?	– The NHS cannot afford not to reimburse this product (due to its benefit and priority) and must provide access as soon as possible. – The NHS cannot afford not to reimburse this product (due to its benefit and priority), but can delay or limit access. – The NHS can afford not to reimburse the product	Estimates a subjective compendium of the entire product.

Note: Questions highlighted in bold are aggregation questions.

Abbreviations: ATMP: Advanced Therapy Medicinal Products; BI: Budget Impact; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; ICB, Incremental Clinical Benefit; ICER: Incremental Cost-Effectiveness Ratio; NHS: National Health System; N/A: Not Applicable; P&R: Price and Reimbursement; QALY: Quality Adjusted Life Years; SmPC: Summary of product characteristics.