**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

**Response to stakeholder organisation comments on the draft remit and draft scope**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit and proposed process**

| Section | Stakeholder | Comments [sic] | Action |
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| Appropriateness of an evaluation and proposed evaluation route | AMMF – the Cholangiocarcinoma Charity | No comments | No action required |
| | Servier Laboratories | Servier believe that Ivosidenib fulfils all criteria for the HST route:<br>**The condition is very rare defined by 1:50,000 in England**<br>The overall incidence of cholangiocarcinoma is increasing with currently around 2800 people diagnosed each year in the UK, although it is not always clear which subtype the cancer is[1] . Coding issues within the UK make differentiation between subtypes difficult but each subtype has distinct risk factors, molecular pathogenesis, therapeutic options, and prognosis. Literature states that iCCAs represent approximately 34% of CCA cases[2], giving an incidence of 952 in the UK.<br>IDH1 mutations are found in approximately 12.5% of intrahepatic cholangiocarcinoma[3] | Thank you for your comments. This issue was discussed by the topic selection oversight panel which decided that this appraisal would be routed as a technology appraisal. Please see HST checklist for more details. |

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| | | Therefore, using 2020 mid-year England population estimate, 56,550,000 this gives an incidence of 0.11:50,000<br>**Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications.**<br>Ivosidenib is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated as targeted therapy for the treatment of adult patients with a susceptible IDH1 mutation with locally advanced or metastatic intrahepatic (icca) cholangiocarcinoma who have been previously treated.<br>The patient numbers eligible for Ivosidenib are expected to be around 107 (IDH1 mutation present in 12.5% of iCCA cases and 90% receive a 1st line treatment[4]) in this indication.<br>Other indications are in relapsed and refractory acute myeloid leukaemia (AML) and as first line monotherapy in AML, although this is only approved in the U.S. There is no intent to pursue a license in these U.S approved indications outside of the U.S.<br>Servier has two ph3 positive studies in CCA 2/3L monotherapy and AML 1L who are ineligible for intensive chemotherapy, for which registration is under review in Europe and will also be sought in the UK.<br>Therefore the patient numbers eligible for Ivosidenib are 135 in this indication.<br>247 with IDH1 mutation<br>55% of these ineligible for intensive chemotherapy[5-7]<br>**The very rare condition significantly shortens life or severely impairs its quality**<br>No specific screening methods are available to reliably detect CCA early enough, and most CCA cases are found only after the cancer has | |

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| | | advanced to an incurable stage[8]. Most patients (~70%) are diagnosed at late stages of disease progression due to lack of specific symptoms[9]<br>Advanced stage diagnosis results in 30% of CCA patients being eligible for tumor resection[10] and poor survival outcomes among patients with CCA have been reported across multiple analyses covering various patient subgroups and clinical settings[11]<br>CCA patients experience aggravating symptoms and half of all untreated patients fail to survive past three to four months from presentation of symptoms[12]<br>The incidence-based mortality rate of CCA per 1,000,000 person-years reported in the UK was 2.66 in 2001 and 4.93 in 2017[13]<br>Due to delayed diagnosis and poor prognosis of CCA, a significant clinical, humanistic and economic burden is imposed on patients. The burden of CCA symptoms on daily lives, work productivity, quality of life, mental health, and sexual function is hugely debilitating[14].<br>**There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.**<br>Patients with cholangiocarcinoma continue to experience substantial unmet need for treatments that improve survival. First-line standard of care in locally advanced or metastatic CCA is combination chemotherapy (gemcitabine + cisplatin); however, 2nd line standard of care is ill-defined in the national and international guidelines and FOLFOX (folinic acid, fluorouracil and oxaliplatin) is often used due to the limited availability of treatment option[15].<br>FOLFOX has a ph3 study in Biliary Tract Cancer (BTC), not CCA but the incremental benefit over best supportive care is <1mth and hence its clinical value is limited. Its use/recommendation in clinical guidelines (as of today) illustrates the lack of other satisfactory options. | |

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| | | In recent years, there has been a paradigm shift towards targeted therapies for the treatment of CCA[16]. This shift is articulated through updates of international and local clinical guidelines, recommending to use targeted treatments over FOLFOX if mutations are confirmed<br>Pemigatinib is the only approved targeted therapy based on findings from biliary tract / CCA trials, and is only indicated for patients with FGFR2 mutations in locally advanced or metastatic CCA[17]. Pemigatinib has recently been approved in the UK[18].<br>Other targeted therapies, such as larotrectinib and entrectinib, are now recommended in the French, German and NCCN guidelines[19-21] and many more are being investigated[22].<br>Ivosidenib is a first-in-class targeted treatment that provides a significant clinical benefit in patients with IDH1 mutated CCA[23] | |
| Wording | AMMF – the Cholangiocarcinoma Charity | No comments | No action required |
| | Servier Laboratories | Yes | Thank you for your comment |

| Section | Stakeholder | Comments [sic] | Action |
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| Additional comments on the draft remit | AMMF – the Cholangiocarcinoma Charity | No comments | No action required |
| | Servier Laboratories | No comments | No action required |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | AMMF – the Cholangiocarcinoma Charity | Broadly, this is accurate. | Thank you for your comment |
| | Servier Laboratories | Accurate and complete | Thank you for your comment |
| Population | AMMF – the Cholangiocarcinoma Charity | Yes | Thank you for your comment. |
| | Servier Laboratories | Yes | Thank you for your comment. |
| Subgroups | AMMF – the Cholangiocarcinoma Charity | No comments | No action required |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Servier Laboratories | No. Servier request that the whole population is considered | Thank you for your comment. |
| Comparators | AMMF – the Cholangiocarcinoma Charity | Yes, the only treatments currently available have been listed. Although there really are no other specific treatments for a cholangiocarcinoma patient with an IDH1 mutation. | Thank you for your comment. The committee will consider relevant comparators during the course of the appraisal. |
| | Servier Laboratories | FOLFOX is only used within routine practice for the overall population, not specifically those with an IDH1 mutation. Therefore, we perceive the correct comparator to be BSC. However, in the absence of any targeted comparator, FOLFOX could be accepted. Folinic acid is listed separately. Folinic acid ( Leucovorin) is routinuely given with 5FU as it modulates it's activity so FOLFOX will include this. It is not used as a stand alone agent in this setting so should not be a separate comparator | Thank you for your comment. The comparators in the scope are intended to be inclusive of those that are thought to be used in clinical practice. The scope is inclusive to allow for all appropriate comparators to be considered, if deemed relevant. The final scope has been amended to reflect that folinic acid is not used as a stand alone agent. |

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| Outcomes | AMMF – the Cholangiocarcinoma Charity | Yes | Thank you for your comment. |
| | Servier Laboratories | Yes | Thank you for your comment. |
| Equality | AMMF – the Cholangiocarcinoma Charity | No comments | No action required |
| | Servier Laboratories | No equality issues | Thank you for your comment. |
| Other considerations | AMMF – the Cholangiocarcinoma Charity | Under Economic Analysis, it is stated, "…The economic modelling should include the costs associated with diagnostic testing for IDH1 gene mutation in people with advanced cholangiocarcinoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test."<br><br>With so little in the treatment armoury for CCA, with the advent of targeted therapies such as ivosidenib, molecular profiling should be available for all those diagnosed with CCA – at diagnosis or during 1st line treatment. This is essential so that all those eligible for such treatments can be considered in a timely manner.<br><br>Whilst the costs of molecular profiling are undoubtedly a consideration, | Thank you for your comment. The NICE methods guide (section 4.8.1) states that the costs of companion diagnostics which are not routinely used in clinical practice should be included in cost-effectiveness assessments. The committee will consider whether testing for IDH1 gene mutations |

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| | | AMMF strongly advocates that it should be available to all CCA patients who could be eligible for a targeted therapy. | are considered routine practice during the course of this appraisal. |
| | Servier Laboratories | No comment | No action required |
| Questions for consultation | AMMF – the Cholangiocarcinoma Charity | No comment | No action required. |
| | Servier Laboratories | The scope states that the economic modelling should include the costs associated with diagnostic testing for IDH1 gene mutation in people with advanced cholangiocarcinoma who would not otherwise have been tested and a sensitivity analysis should be provided without the cost of the diagnostic test. However, IDH1 testing is already part of the genetic test directory so funding should be in place. Therefore, Servier believes the base case should not include cost of testing<br><br>Ivosidenib is not considered by Servier to be a candidate for managed access | Thank you for your comment. The committee will consider whether IDH1 gene mutation screening is part of routine practice and whether or not to include the costs of such tests. |
| Additional comments on the draft scope | AMMF – the Cholangiocarcinoma Charity | None | No action required. |

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| | Servier Laboratories | None | No action required |

**The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope**