**Summary of the Risk Management Plan (RMP)**

**for Tibsovo (ivosidenib)**

Product concerned (brand name): Tibsovo

Active substance: ivosidenib

Strength: 250 mg

Pharmaceutical form: film-coated tablets

Version number: 0.2

Manufacturing Authorization Holder: Servier (Suisse) SA

Date of final sign off: 13 October 2022

***Disclaimer:***

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Tibsovo is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Tibsovo in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Servier (Suisse) S.A. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tibsovo.

**Summary of risk management plan for Tibsovo (ivosidenib)**

This is a summary of the risk management plan (RMP) for Tibsovo. The RMP details important risks of Tibsovo, how these risks can be minimised, and how more information will be obtained about Tibsovo's risks and uncertainties (missing information).

Tibsovo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tibsovo should be used.

This summary of the RMP for Tibsovo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

# I. THE MEDICINE AND WHAT IT IS USED FOR

Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy.

Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

It contains ivosidenib as the active substance and it is given orally. The recommended dose is 500 mg (2 tablets of ivosidenib 250 mg) once daily at about the same time each day.

Further information about the evaluation of Tibsovo's benefits can be found in Tibsovo's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage <link to product's EPAR summary landing page on the EMA webpage.>

## II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Tibsovo, together with measures to minimise such risks and the proposed studies for learning more about risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Tibsovo is not yet available, it is listed under 'missing information' below.

## II.A List of important risks and missing information

Important risks of Tibsovo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tibsovo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

| **List of important risks and missing information** | |
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| Important identified risks | Differentiation Syndrome in patients with AML |
| | Electrocardiogram QT prolonged |
| Important potential risks | Embryo-foetal toxicity |
| Missing information | Use in patients with severe hepatic impairment<br>Use in patients with severe renal impairment |

## II.B Summary of important risks

| **Important identified risks: Differentiation Syndrome in patients with AML** | |
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| Evidence for linking the risk to medicine | Differentiation syndrome is a serious side effect that may occur in patients with acute myeloid leukaemia who have been treated with certain types of anticancer drugs, including ivosidenib. It is caused by a large, rapid release of cytokines (immune substances) from leukaemia cells that are affected by the anticancer drugs. Signs and symptoms of differentiation syndrome include fever; cough; trouble breathing; weight gain; swelling of the arms, legs, and neck; build-up of excess fluid around the heart and lungs; low blood pressure; and kidney failure.<br>In a clinical study of ivosidenib and azacitidine given in combination for the treatment of AML the percentage of subject in whom differentiation syndrome was reported was 14.1%. In the control group treated with azacitidine alone, the percentage of subject in whom differentiation syndrome was reported was 8.2%. Patients treated with ivosidenib were reported to have recovered with appropriate treatment.<br>The evidence is derived from clinical trials. Evidence from this source is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention. |
| Risk factors and risk groups | All patients treated with ivosidenib for IDH1 mutation-positive AML are potentially at risk of differentiation syndrome. There are no known factors that might predict the risk in these patients. |

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| Risk minimisation measures | *Routine risk minimisation measures:*<br>*SmPC section 4.2, 4.4 and 4.5 where advice is given for monitoring and management of differentiation syndrome along with its treatment and temporary interruption of ivosidenib.*<br>*SmPC section 4.4 and PL section 2 where warning is given in that differentiation syndrome may be life-threatening or fatal if not treated along with description of symptoms.*<br>*SmPC section 4.8.*<br>*PL section 4 where advice is given to seek urgent medical attention if patient experiences side effects/symptoms corresponding to differentiation syndrome.*<br>Legal status: Prescription only medicine.<br>Treatment to be initiated by experienced oncologist.<br>Additional risk minimisation measures:<br>None |
| **Important identified risks: Electrocardiogram QT prolonged** | |
| Evidence for linking the risk to medicine | QT prolongation may increase the risk of developing abnormal heart rhythms and may rarely lead to sudden cardiac arrest.<br>Nonclinical evidence indicates that ivosidenib can prolong QT interval in a reversible manner.<br>In a clinical study of ivosidenib and azacitidine given in combination for the treatment of AML the percentage of subject in whom QT prolongation was reported was 25.4%. In the control group treated with azacitidine alone, the percentage of subject in whom QT prolongation was reported was 12.3%.<br>In clinical studies of ivosidenib given for the treatment of cholangiocarcinoma the percentage of subject in whom QT prolongation was reported was 9.2%.<br>The evidence is derived from clinical trials and nonclinical studies. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention. |
| Risk factors and risk groups | The following may increase the risk of developing QT prolongation or its symptoms:<br>• A history of abrupt loss of consciousness, or of cardiac arrest<br>• Having a first-degree relative (parent, sibling) with abnormal heart rhythm or fast and chaotic heartbeats (long QT syndrome)<br>• Concomitant use of other medicines that may cause irregular heart rhythm or rapid heartbeats (prolonged QT intervals)<br>• Being female and on heart medication<br>• Excessive vomiting, diarrhoea or other conditions resulting in the loss of electrolytes. |
| Risk minimisation measures | Routine risk minimisation measures:<br>*SmPC section 4.3 and PL section 2 where contraindications are listed for patients with increase risk of QTc prolongation.*<br>*SmPC section 4.2 and 4.4 where guidance is given on regular ECG monitoring and management of QTc interval prolongation also reflected in the PL section 2.*<br>*SmPC section 4.2, 4.4 and 4.5. where advice is given for monitoring and management of concomitant administration of moderate or strong CYP3A4* |

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| | *inhibitors (leads to increase in plasma concentrations of ivosidenib) and medicines that prolong QT interval.*<br>*SmPC section 4.4 where warning is given that QTc interval prolongation has been reported following treatment with ivosidenib. Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic monitoring of ECGs and electrolytes, during treatment with ivosidenib.*<br>*SmPC section 4.8.*<br>*PL section 2 and 4 where warning is given that ivosidenib can cause a serious condition known as QTc interval prolongation which can be life threatening. Advice is given to seek urgent medical attention if patient experiences side effects/symptoms corresponding to QTc interval prolongation*<br>*PL section 2 where patient is advised to talk to the doctor if the patient has heart problems or have problems with abnormal electrolytes levels or patient is taking any medicines that affects the heart, along with advice on regular ECG monitoring.*<br>Legal status: Prescription only medicine.<br>Treatment to be initiated by experienced oncologist<br>Additional risk minimisation measures:<br>None |
| **Important potential risk: Embryo-foetal toxicity** | |
| Evidence for linking the risk to medicine | Embryo-foetal toxicity refers to the potential to injure the developing child in the womb.<br>Evidence for embryofoetal toxicity is based on non-clinical studies, which may be relevant for humans. In the absence of evidence of the effects on the foetus in humans, embryofoetal toxicity is considered an important potential risk for ivosidenib. In non-clinical embryo-foetal toxicity studies, ivosidenib was associated with maternal toxicity and spontaneous abortions, decreased foetal body weights, delayed bone formation and variation in organ development (small spleen). Ivosidenib was also found to cross the placenta. Based on these studies, ivosidenib could cause foetal harm when administered to women during pregnancy. |
| Risk factors and risk groups | Sexually active women of childbearing potential and male patients whose partners are women of childbearing potential are at risk of the consequences of embryofoetal toxicity. Women of childbearing potential and males with partners of childbearing potential not using effective contraception during treatment with ivosidenib and for at least 1 month after the last dose are at risk. Patients treated with oral contraceptives not using a barrier method of contraception are also at increased risk, as ivosidenib may decrease the effectiveness of oral contraceptives. |
| Risk minimisation measures | Routine risk minimisation measures:<br>*SmPC section 4.4, 4.6 and PL section 2 where warning is given that woman of childbearing potential should have a pregnancy test done prior to start of therapy and the women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with ivosidenib and for at least 1 month after the last dose.*<br>*SmPC section 4.4, 4.5, 4.6 and PL section 2 where caution is advised that ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended.* |

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| | *SmPC section 4.6 where advice is given that ivosidenib is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception; if a patient (or female partner of a treated male patient) becomes pregnant during treatment or during the one-month period after the last dose, they should be informed of the potential risk to the foetus.*<br>*PL section 2 where advice is given that ivosidenib is not recommended during pregnancy as it may harm the unborn baby. Furthermore, patient should consult doctor if the patient is pregnant, thinks she might be pregnant or is planning to have a baby, before taking ivosidenib.*<br>Legal status: Prescription only medicine.<br>Treatment to be initiated by experienced oncologist<br>Additional risk minimisation measures:<br>None |
| **Missing information: Use in patients with severe hepatic impairment** | |
| Risk minimisation measures | Routine risk minimisation measures:<br>*SmPC section 4.2 and 4.4 where warning is given that the safety and efficacy of ivosidenib have not been established in patients with severe hepatic impairment (Child Pugh classes C) therefore ivosidenib should be used with caution and this patient population should be closely monitored.*<br>*SmPC section 4.8.*<br>*PL section 2 where advice is given to talk to the doctor if the patient has any liver problem before taking ivosidenib.*<br>Legal status: Prescription only medicine.<br>Treatment to be initiated by experienced oncologist<br>Additional risk minimisation measures:<br>None |
| Additional pharmacovigilance activity | Organ impairment substudy of AG120-C-001. |
| **Missing information: Use in patients with severe renal impairment** | |
| Risk minimisation measures | Routine risk minimisation measures:<br>*SmPC section 4.2 and 4.4 where warning is given that the safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR < 30 ml/min/1.73 $m^2$) therefore, ivosidenib should be used with caution and this patient population should be closely monitored.*<br>*PL section 2 where advice is given to talk to the doctor if the patient has any kidney problem before taking ivosidenib.*<br>Legal status: Prescription only medicine.<br>Treatment to be initiated by experienced oncologist<br>Additional risk minimisation measures:<br>None. |
| Additional pharmacovigilance activity | Organ impairment substudy of AG120-C-001. |

## II.C Post-authorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tibsovo.

### II.C.2 Other studies in post-authorisation development plan

There is one organ impairment substudy of the AG120-C-001 study, planned to investigate the use of ivosidenib in patients with severe hepatic or renal impairment:

**Organ impairment substudy of AG120-C-001**

**Purpose of the study:**

To evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with haematologic malignancies with an IDH1 mutation with moderate hepatic impairment, severe hepatic impairment or severe renal impairment.