Summary of the Risk Management Plan
for
LYTGOBI (Futibatinib)

Taiho Oncology Europe GmbH

Neuhofstrasse 12
6340 Baar
Switzerland

RMP version number: 1.2

Document date: 02 May 2023

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 LYTGOBI 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 authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of LYTGOBI in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic.

Taiho Oncology Europe GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of LYTGOBI.

Summary of risk management plan for Lytgobi (futibatinib)

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

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

This summary of the RMP for Lytgobi 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).

Important new concerns or changes to the current ones will be included in updates of Lytgobi's RMP.

I. The medicine and what it is used for

Lytgobi is authorised for treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement (see SmPC for the full indication). It contains futibatinib as the active substance and it is given by oral route of administration.

Further information about the evaluation of Lytgobi's benefits can be found in Lytgobi's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lytgobi, together with measures to minimise such risks and the proposed studies for learning more about Lytogobi's 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 PSUR 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 Lytgobi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lytgobi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Lytgobi. 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	
Important identified risks	Serous retinal detachment
Important potential risks	Embryo-foetal toxicity/teratogenicity
Missing information	None

II.B Summary of important risks

Identified risk: Serous retinal detachment	
Evidence for linking the risk to the medicine	Retinal toxicities, including central serous retinopathy and serous retinal detachment, represent class effects of MEK inhibitors (Francis, 2017; Urner-Bloch, 2016; Weber, 2016). FGFR acts upstream of the MEK kinase in the FGF-MAPK pathway and as such, FGFR inhibition leads to inhibition of the MAPK pathway and development of ocular toxicities (van der Noll, 2013). Ocular toxicities were observed in clinical trials with various FGFR inhibitors (Alekseev, 2021; Goyal, 2021; Morales-Barrera, 2020), including the clinical development programme for futibatinib where Grade 1 and Grade 2 events of central serous retinopathy associated with retinal toxicities occurred in 6.2% of iCCA patients.
Risk factors and risk groups	The specific risk factors and risk groups have not yet been established for futibatinib.

Identified risk: Serous retinal detachment	
Risk minimisation measures	**Routine Risk Minimisation Measures:** – SmPC sections 4.2, 4.4, and 4.8 – PL sections 2 and 4 Dose modifications for serous retinal detachment are provided in SmPC section 4.2. Recommendation for routine ophthalmological examination is included in the SmPC section 4.4 and PL section 2. Subject to restricted medical prescription **Additional Risk Minimisation Measures:** None

References: Alekseev O, Ojuok E, Cousins S. Multifocal serous retinopathy with pemigatinib therapy for metastatic colon adenocarcinoma. Int J Retina Vitreous 2021, 7(1): 34.
Francis JH, Habib LA, Abramson DH, Yannuzzi LA, Heinemann M, Gounder MM, et al. Clinical and Morphologic Characteristics of MEK Inhibitor-Associated Retinopathy: Differences from Central Serous Chorioretinopathy. Ophthalmology 2017, 124(12): 1788-98.
Goyal L, Kongpetch S, Crolley VE, Bridgewater J. Targeting FGFR inhibition in cholangiocarcinoma. Cancer Treat Rev 2021, 95102170.
Morales-Barrera R, Suárez C, González M, Valverde C, Serra E, Mateo J, et al. The future of bladder cancer therapy: Optimizing the inhibition of the fibroblast growth factor receptor. Cancer Treatment Reviews 2020, 86102000.
Urner-Bloch U, Urner M, Jaberg-Bentele N, Frauchiger AL, Dummer R, Goldinger SM. MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: Long-term ophthalmic effects. Eur J Cancer 2016, 65130-8.
Weber ML, Liang MC, Flaherty KT, Heier JS. Subretinal Fluid Associated With MEK Inhibitor Use in the Treatment of Systemic Cancer. JAMA Ophthalmol 2016, 134(8): 855-62.
Abbreviations: FGF=fibroblast growth factor; FGFR=fibroblast growth factor receptor; iCCA=intrahepatic cholangiocarcinoma; MAPK=mitogen activated protein kinase; MEK=mitogen activated protein kinase; PL=package leaflet; SmPC=summary of product characteristics.

Potential risk: Embryo-foetal toxicity/teratogenicity	
Evidence for linking the risk to the medicine	Teratogenicity seems directly linked to the mechanism of futibatinib action since FGFR signalling axis is fundamental for embryonic development (Turner, 2010). The nonclinical development programme showed reproductive toxicity associated with futibatinib in the rat, where visceral and skeletal abnormalities were observed. The clinical relevance of these findings is unclear since there is no experience with the use of futibatinib during pregnancy. However, embryotoxicity/teratogenicity was reported in association with many tyrosine kinase inhibitors (Abruzzese, 2014), including FGFR inhibitors (e.g. erdafitinib).

Potential risk: Embryo-foetal toxicity/teratogenicity	
Risk factors and risk groups	Any women of childbearing potential who receives futibatinib or whose partner receives futibatinib are at risk of embryo-foetal toxicity associated with futibatinib.
Risk minimisation measures	**Routine Risk Minimisation Measures:** – SmPC sections 4.4, 4.6, and 5.3 – PL section 2 Recommendations for pregnancy testing prior treatment initiation is included in the SmPC section 4.4. Recommendation on the use of effective contraception during treatment and for at least 1 week after the last dose is included in the SmPC sections 4.4 and 4.6 and PL section 2. Subject to restricted medical prescription **Additional Risk Minimisation Measures:** None

References: Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P. Tyrosine kinase inhibitors and pregnancy. J Cereb Blood Flow Metab 2014, 6(1): e2014028.
Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer 2010, 10(2): 116-29.
Abbreviations: FGFR=fibroblast growth factor receptor; PL=package leaflet; SmPC=summary of product characteristics.

II.C Post-authorisation development plan

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

The following study is specific obligation of Lytgobi:

Study TAS-120-205

Purpose of the study:

- Primary objective:
  - To assess the efficacy of futibatinib administered at 20 mg and 16 mg once daily (QD) to verify and describe the clinical benefit
- Secondary objective(s):
  - To evaluate further efficacy parameters of futibatinib administered at 20 mg and 16 mg QD
  - To evaluate the safety and tolerability of futibatinib administered at 20 mg and 16 mg QD
  - To evaluate Patient Reported Outcomes

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

There are no studies required for Lytgobi.