PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

PEMAZYRE (PEMIGATINIB)

4.5 mg, 9 mg and 13.5 mg tablets

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LIST OF ABBREVIATIONS

Abbreviation	Definition
APAC	Asia-Pacific
BUN	blood urea nitrogen
CI	confidence interval
CTCAE	common terminology criteria for adverse events
DOR	duration of response
ECG	electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FGFR	fibroblast growth factor receptor
MAPK	mitogen-activated protein kinases
NA	North America
NCI	National Cancer Institute
OCT2	organic cation transporter 2
ORR	objective response rate
OS	overall survival
PAES	post authorisation efficacy study
PFS	progression-free survival
PPI	proton-pump inhibitor
PSUR	Periodic Safety Update Report
PT	preferred term
QD	once a day
RECIST	response evaluation criteria in solid tumors
RMP	Risk Management Plan
ROW	rest of world
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event

OVERVIEW

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 Pemazyre 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 Pemazyre in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Incyte Biosciences International Sàrl is fully responsible for the accuracy and correctness of the content of the published summary RMP of Pemazyre.

SUMMARY OF RISK MANAGEMENT PLAN FOR PEMAZYRE (PEMIGATINIB)

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

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

This summary of the RMP for Pemazyre should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

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

I THE MEDICINE AND WHAT IT IS USED FOR

Pemazyre is authorised for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. It contains pemigatinib as the active substance and it is given by either 4.5 mg, 9 mg, or 13.5 mg tablets once daily for 2 weeks followed by 1 week off therapy.

Further information about the evaluation of pemigatinib's benefits can be found in pemigatinib's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page on (https://www.ema.europa.eu/en/medicines/human/EPAR/pemazyre).

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
  - Recommendation for opthalmological examinations prior to initiation of therapy and every 2 months for the first 6 months of treatment, every 3 months afterwards, and urgently at any time for visual symptoms are included in the SmPC section 4.4. Dosage modifications for serous retinal detachment events are provided for the prescriber in the SmPC section 4.2
  - Recommendations for management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose

modification when required are provided for the prescriber in the SmPC section 4.2.

– Advise pregnant women of the potential risk to the fetus. Women of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for 1 week after the last dose. These recommendations are included in the SmPC section 4.4 and section 4.6.

Together, these measures constitute routine risk minimisation measures.

In the case of pemigatinib, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks below.

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 pemigatinib is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of pemigatinib 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 pemigatinib. 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 (eg, on the long-term use of the medicine).

Table II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Serous retinal detachment Hyperphosphatemia
Important potential risks	Embryo-Fetal Toxicity Acute kidney injury
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk: Serous retinal detachment	
Evidence for linking the risk to the medicine	Treatment-emergent adverse events of serous retinal detachment have been observed with administration of tyrosine kinase inhibitors and are attributed to disruption of the MAPK signalling cascade (van der Noll et al 2013, Velazquez-Villoria et al 2017). As pemigatinib intervenes with the MAPK pathway, an evaluation of serous retinal detachment events including the PTs listed above was performed. Based on available information, the causal relationship between pemigatinib and the serous retinal detachment is plausible.
Risk factors and risk groups	At this time, the risk factors/groups for pemigatinib are unknown.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • SmPC section 4.8 • Package Leaflet section 2 Additional risk minimisation measures: None

Important Identified Risk: Hyperphosphatemia	
Evidence for linking the risk to the medicine	In rats, pemigatinib was administered on a 2-weeks-on/1-week-off schedule for 2 cycles in the 28-day study and QD continuously in the 3-month study; in monkeys, pemigatinib was administered daily in both studies. One of the most prominent findings following repeat-dose exposure to pemigatinib in both rats and monkeys was hyperphosphatemia. Consistent with the expected pharmacological effect of FGFR inhibition on serum phosphate levels, hyperphosphatemia was one of the most frequently occurring TEAEs in clinical trials.
Risk factors and risk groups	At this time, the risk factors/groups for pemigatinib are unknown.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • SmPC section 4.8 • Package Leaflet section 2 Additional risk minimisation measures: None

Important Potential Risk: Embryo/Fetal Toxicity	
Evidence for linking the risk to the medicine	Administration of pemigatinib to time-mated rats was associated with decreased fetal growth and malformations at 0.1 mg/kg per day and total early postimplantation loss at ≥0.3 mg/kg per day. These findings occurred at maternal plasma exposures below the recommended human dose. Based on the findings in an animal study, pemigatinib may cause fetal harm when administered to pregnant women. There are no available data on pemigatinib use in pregnant women to inform the drug-associated risk.
Risk factors and risk groups	At this time, the risk factors/groups for pemigatinib are unknown.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • SmPC section 4.6 • Package Leaflet section 2 Additional risk minimisation measures: None

Important Potential Risk: Acute kidney injury	
Evidence for linking the risk to the medicine	In study INCB 54828-202, serious TEAEs of blood creatinine increased and/or acute kidney injury occurred in 4 participants. The participants all had renal impairment at baseline. One of the serious TEAEs of acute kidney injury was considered related to pemigatinib by the investigator; the other events of blood creatinine increased/acute kidney injury were considered unrelated to pemigatinib by the investigator. None of these events were fatal. Changes in creatinine values appeared to be isolated laboratory findings that were not accompanied by clinical symptoms (eg, concurrent kidney injury) for most participants, a conclusion that is further supported by the absence of discernible trends in BUN. Overall, the frequency, magnitude and pattern (rapid onset followed by rapid reduction post treatment break, without significant long term progression) of the mean increases in creatinine that were observed are typical of blockade of tubular secretion via OCT2. Given the seriousness of acute kidney injury and the potential to impact the benefit-risk of pemigatinib, acute kidney injury is considered an important potential risk.
Risk factors and risk groups	At this time, the risk factors/groups for pemigatinib are unknown.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.4 • SmPC section 4.8 (Blood creatinine increased) Additional risk minimisation measures: None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorisation:

INCB 54828-302: A Phase 3, Open-Label, Randomized, Active-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Versus Gemcitabine Plus Cisplatin Chemotherapy in First-Line Treatment of Participants With Unresectable or Metastatic Cholangiocarcinoma With FGFR2 Rearrangement (FIGHT-302).

Rationale and study objectives:

To confirm efficacy and further characterize safety, a study in the first-line treatment of participants with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement is ongoing.

Primary and Secondary Objective

- Evaluate the efficacy of pemigatinib versus gemcitabine plus cisplatin in the first-line treatment of participants with cholangiocarcinoma with FGFR2 rearrangement.

Study design:

This is a Phase 3, open-label, randomized, active-controlled study of pemigatinib versus gemcitabine plus cisplatin chemotherapy as first-line treatment in participants with unresectable and/or metastatic cholangiocarcinoma with FGFR2 rearrangement. The study will enroll approximately 432 participants in a 1:1 randomization ratio stratified by geographic region (Western [NA and EU] vs APAC vs ROW) and by tumor burden (locally advanced vs distant metastasis) into the following 2 treatment groups:

- Treatment Group A: Pemigatinib (13.5 mg QD) administered as continuous therapy schedule (a cycle is 3 weeks).
- Treatment Group B: Gemcitabine (1000 mg/m2) plus cisplatin (25 mg/m2) administered as intravenous infusion on Days 1 and 8 of every 3-week cycle for up to 8 cycles.

Participants will be required to have documented FGFR2 rearrangement either through a local and/or central (FMI) genomics laboratory to confirm eligibility.

Study objectives and endpoints include the safety and tolerability of pemigatinib and the occurrence of TEAEs and treatment-related AEs according to NCI CTCAE v5.0, physical findings, and vital sign, laboratory, and ECG changes.

Participants will undergo regular safety assessments during treatment, as well as regular efficacy assessments. Participants will be allowed to continue administration in 3-week cycles until disease progression per RECIST v1.1 as assessed by an ICR or unacceptable toxicity is reported. Participants who progress on gemcitabine plus cisplatin may be considered for crossover to pemigatinib as second-line treatment. The estimated duration of study participation is up to 35 days for screening, continuous treatment in consecutive 21-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and at least 30-35 days after

the last dose of study treatment for follow-up. It is estimated that an individual will participate for approximately 12 months.

The proposed PAES will provide a more robust characterization of the safety profile of pemigatinib in special populations (demographic covariates, including age, gender, and race). In the confirmatory INCB 54828-302 study, creatinine levels and BUN are monitored throughout the study as part of routine safety assessments and alternative markers of renal function can be performed if persistent elevations in serum creatinine are observed. An ad-hoc efficacy analysis from the INCB 54828-302 study will be performed on those participants taking PPIs versus those without PPIs, to assess if there is any impact on survival due to reduced bioavailability of pemigatinib secondary to increased stomach pH caused by PPI use. In this confirmatory study, pharmacokinetic samples will be obtained for participants randomized to the pemigatinib treatment group.

The PAES will also provide more robust laboratory and adverse event data, as well as additional long term safety data.

Study population:

Male and female participants at least 18 years of age who have unresectable and/or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement

Milestones:

First site active - 13 DEC 2018
First patient enrolled - 03 JUN 2019
Last patient in - June 2024
Last patient out - June 2026
Final study report – December 2026

INCB 54828-202: A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy (FIGHT-202)

Rationale and study objectives:

To evaluate the efficacy, safety, and tolerability of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocations, FGF/FGFR alterations and without FGF/FGFR alterations.

Primary Objective:

- The primary objective of this study is to evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with fibroblast growth factor receptor (FGFR) 2 translocation who have failed at least 1 previous treatment.

Secondary Objectives:

- To evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with different molecular subgroups.

- To evaluate the safety of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma.
- To identify and evaluate covariates that may influence the pharmacokinetics of INCB054828 in this subject population through population pharmacokinetic analysis. Additionally, exposure-response analyses for key efficacy and safety parameters will also be considered if sufficient data are available.

Study design:

This is an open-label, monotherapy study of INCB054828 in subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocations, with other FGF/FGFR alterations, or who are negative for FGF/FGFR alterations. The study will enroll approximately 100 subjects into Cohort A (FGFR2 translocations), 20 subjects into Cohort B (other FGF/FGFR alterations), and 20 subjects into Cohort C (US only; negative for FGF/FGFR alterations). Subjects will receive a once daily (QD) dose of INCB054828 at 13.5 mg on a 2-week-on therapy and 1-week-off therapy schedule.

Subject eligibility can be based on local genomic testing results, if available. Confirmatory testing through the central genomics laboratory will be performed on all subjects.

Genomic testing results will allow subjects to be assigned to a cohort:

- Cohort A: FGFR2 translocations with a documented fusion partner in central laboratory report
- Cohort B: other FGF/FGFR alterations
- Cohort C (US only): negative for FGF/FGFR alterations

Subjects enrolled based on a local sequencing report will be assigned to a cohort based on the local results. However, final cohort assignment for statistical analysis of primary and secondary endpoints will be done based on the central genomics testing results. Treatment will start on Day 1. Subjects will undergo regular safety assessments during treatment as well as regular efficacy assessments. Subjects will be allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

Study population:

Subjects with advanced/metastatic or surgically unresectable cholangiocarcinoma with FGFR2 translocations, with other FGF/FGFR alterations, or who are negative for any FGF/FGFR alterations, who failed at least 1 previous treatment.

Milestones:

Final study report submission: December 2021 (Completed)

INCB 54828-202 Clinical Study Report Overall Conclusion:

This study achieved the predetermined threshold for a positive study outcome (lower limit of the 95% CI for ORR > 15%), with an ORR of 37.0% (95% CI: 27.94, 46.86). Tumor responses were durable, with a median DOR of 9.13 months (95% CI: 6.01, 14.49), median PFS of 7.03 months (95% CI: 6.08, 10.48), and median OS of 17.48 months (95% CI: 14.36, 22.93). The safety

profile of pemigatinib 13.5 mg QD on a 2-weeks-on/1-week-off schedule is tolerable. The benefit/risk ratio for pemigatinib therapy with longer follow up (up to 19.9 months) continued to be favorable. Pemigatinib provides a novel, targeted, therapeutic approach for cholangiocarcinoma with FGFR2 rearrangements or fusions.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for pemigatinib.

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