swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Pemazyre

International non-proprietary name: pemigatinib

Pharmaceutical form: tablets

Dosage strength(s): 4.5 mg, 9 mg and 13.5 mg

Route(s) of administration: oral

Marketing authorisation holder: Incyte Biosciences International

Marketing authorisation no.: 68143

Decision and decision date: extension of therapeutic indication approved on 24 July 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BP	Blast phase
CCyR	Complete cytogenetic response
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CP	Chronic phase
CR	Complete response
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMD	Extramedullary disease
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HSCT	Haematopoietic stem cell transplantation
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MLN	Myeloid/lymphoid neoplasm
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PDGFR	Platelet-derived growth factor receptor

PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 7 December 2020.

2.2 Indication and dosage

2.2.1 Requested indication

PEMAZYRE is indicated for the treatment of adults with myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement.

2.2.2 Approved indication

PEMAZYRE is indicated as monotherapy for the treatment of adults with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement (see the "Clinical efficacy" section).

The applicant withdrew part of the indication initially claimed for Pemazyre.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dosage of PEMAZYRE is 13.5 mg orally once daily on a continuous basis.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	28 June 2024
Formal objection	19 July 2024
Response to formal objection	31 July 2024
Formal control completed	31 August 2024
List of Questions (LoQ)	23 December 2024
Response to LoQ	13 March 2025
Preliminary decision	19 May 2025

Response to preliminary decision	13 June 2025
Final decision	24 July 2025
Decision	approval

3 Medical context

Myeloid/lymphoid neoplasm with fibroblast growth factor receptor 1 rearrangement (MLN with FGFR1) is a rare subcategory of myeloid/lymphoid neoplasms associated with eosinophilia and rearrangements involving platelet-derived growth factor receptor alpha (PDGFRA), platelet-derived growth factor receptor beta (PDGFRB), fibroblast growth factor receptor 1 (FGFR1), or pericentriolar material 1–Janus kinase 2 (PCM1-JAK2). Although precise incidence estimates are challenging due to the rarity of the disease, available data suggest an incidence of fewer than 1 case per 10 million individuals. The clinical presentation is heterogeneous, with patients presenting in a chronic phase, a blast phase, or with isolated extramedullary disease. The disease course is aggressive, with progression to secondary acute leukaemia commonly occurring within 1 to 2 years of diagnosis. Currently, there are no approved therapies for MLN with FGFR1. Allogeneic haematopoietic stem cell transplantation (HSCT) is the primary treatment approach for eligible patients and has been associated with long-term remission in some cases. A variety of treatments have been used off-label, though these have generally resulted in limited and unsustained complete remissions. As a result, there remains a significant unmet need for effective and durable treatment options for MLN with FGFR1 rearrangement.

4 Nonclinical aspects

The extension of the indication is based upon the results of a phase 2, open label, multicentre, uncontrolled study (INCB 54828-203 / FIGHT-203). The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to posology and method of administration.
The efficacy for the proposed indication will be clinically evaluated.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of the indication.

5 Clinical aspects

5.1 Clinical pharmacology

Updated pemigatinib PopPK and exposure-response analyses in the MLN indication were conducted. The results of these analyses were consistent with the pharmacology of pemigatinib known from the original application.

5.2 Dose finding and dose recommendation

No new dose-finding data were submitted. Of note, the proposed dosing regimen is 13.5 mg once daily on a continuous basis. This differs from the previously approved intermittent dosing for another indication (cholangiocarcinoma), which was 13.5 mg once daily for 14 days followed by a 7-day treatment-free interval. The recommendation for continuous dosing is supported by the clinical outcomes of the FIGHT-203 study, despite the incidence of dose modifications related to adverse events and the inherent challenges in further dose optimisation due to the rarity of the indication.

5.3 Efficacy

Study FIGHT-203 was an open-label, monotherapy study to evaluate the efficacy and safety of pemigatinib in adult patients with MLN with FGFR1 rearrangement. Patients included in the study had to have a documented MLN with 8p11 rearrangement shown to be an FGFR1 activating mutation, and could have relapsed after HSCT or after a disease-modifying therapy, or were not candidates for HSCT or other disease-modifying therapies.
Patients were treated with pemigatinib at 13.5 mg daily intermittently (2 weeks on/1 week off of a 21-day cycle) or 13.5 mg daily on a continuous basis. The dosing regimen was modified from intermittent to continuous during the conduct of the study, which represents a relevant limitation in the interpretation of the results. Pemigatinib was administered until disease progression, the occurrence of unacceptable toxicity, or until patients were able to receive HSCT.
In addition, during the course of this open-label trial, the primary endpoint was changed from overall response rate (ORR) to complete response (CR), introducing an additional important limitation to the reliability of the results.

The median age was 61 years; 56% were women, 62% were White, and 87% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (36%) or 1 (51%). Forty patients had already received at least one line of prior treatment for the treatment of myeloid/lymphoid neoplasms; 5 patients had not received prior treatment. The initial disease presentation category was chronic phase (CP) without extramedullary disease (EMD) for 24 participants (53.3%), CP with EMD for 4 participants (8.9%), blast phase (BP) without EMD for 6 participants (13.3%), BP with EMD for 4 participants (8.9%), EMD only for 4 participants (8.9%), and treated myeloid neoplasm (MN) without bone marrow/peripheral blood involvement or EMD, but with persistent 8p11 translocation and/or FGFR1 rearrangement for 3 participants (6.7%).
At the most recent data cutoff (DCO) of 31 October 2024, the primary endpoint CR by investigator assessment was 68.9%. Among secondary endpoints, the following results were observed: the complete cytogenetic response (CCyR) was 73.3%, the median progression-free survival (PFS) was 73.84 (54.74-NE) months, the PFS rates at 12, 24 and 36 months were 81.0%, 77.1% and 72.6%, respectively, the median overall survival (OS) was not evaluable (NE) (54.74,- NE) months, the OS rates at 12, 24 and 36 months were 79.0%, 71.5% and 68.7% respectively. Of note, the time-to-event endpoints might have been subject to bias from censoring due to discontinuation of study treatment or due to initiation of a new anticancer treatment and should be interpreted with caution given the absence of a control arm. At a previous analysis with DCO of 17 July 2023, the CR was 75% for

patients who began with the continuous dosing regimen and 53.8% for those who began with the intermittent dosing regimen.

5.4 Safety

In the FIGHT-203 study, pemigatinib demonstrated notable toxicity, particularly in terms of the frequency of hyperphosphataemia, gastrointestinal disorders, ocular disorders, anaemia, and the overall severity of treatment-emergent adverse events (TEAEs), with 83% Grade ≥3 TEAEs and 57.4% serious adverse events (SAEs). Nevertheless, the toxicity profile observed is generally consistent with the known safety profile of pemigatinib from pooled analyses across all indications and is considered acceptable in the context of MLN.
Continuous dosing (CD) was the most commonly used regimen in the FIGHT-203 study. When comparing pooled data from continuous versus intermittent dosing, certain TEAEs occurred more frequently in the CD setting than in the intermittent regimen. These included hyperphosphataemia, stomatitis, palmar-plantar erythrodysaesthesia (hand-foot syndrome), and paronychia.

5.5 Final clinical benefit risk assessment

The assessment of the FIGHT-203 study presented some limitations, primarily its single-arm design, which is acceptable given the rarity of MLN, and protocol changes during the study, including changes to the primary endpoint and dosing schedule. Nevertheless, at the most recent DCO, pemigatinib demonstrated a high CR rate and CCyR, supported by favourable PFS and OS outcomes. Efficacy results favoured the continuous dosing regimen over the intermittent dosing regimen.
The safety profile observed in FIGHT-203 was consistent with the established safety profile of pemigatinib and is considered acceptable in the relapsed/refractory MLN setting. Although some adverse events were more frequent with continuous dosing than with intermittent dosing, and uncertainties remain regarding the optimal dosing strategy, continuous dosing was the most commonly used regimen in the study.
Of note, as only five treatment-naïve patients were included in FIGHT-203, the evidence is not sufficient to support a valid evaluation of the efficacy and safety of pemigatinib in the first-line treatment of MLN.
Overall, considering the submitted evidence, the poor prognosis of MLN and the absence of approved treatment options, the benefit-risk is positive for the use of pemigatinib for the treatment of adult patients with relapsed/refractory MLN with FGFR1 rearrangement.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Pemazyre tablets was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

Information for Healthcare Professionals

▼ This medicinal product is subject to additional monitoring which will enable quick identification of new safety information. Healthcare professionals are required to report any suspected new or serious side effects. See the “Undesirable effects” section for the terms and conditions for reporting side effects.

PEMAZYRE has a temporarily authorised indication (see the “Properties/Effects” section).

PEMAZYRE

Composition

Active Substances

Pemigatinib

Excipients

Microcrystalline cellulose (E 460), sodium starch glycolate (type A), magnesium stearate (E 572)
Each 4.5 mg, 9 mg and 13.5 mg tablet contains 0.176 mg, 0.352 mg and 0.528 mg of sodium, respectively.

Pharmaceutical form and active substance quantity per unit

4.5 mg, 9 mg and 13.5 mg tablets
4.5 mg: round tablet (5.8 mm), white to off-white, debossed on one side with “I” and “4.5” on the reverse.
9 mg: oval tablet (10 x 5 mm), white to off-white, debossed on one side with “I” and “9” on the reverse.
13.5 mg: round tablet (8.5 mm), white to off-white, debossed on one side with “I” and “13.5” on the reverse.

Indications/Uses

Temporarily authorised indication
PEMAZYRE is indicated as monotherapy for the treatment of adults with locally advanced, unresectable or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement, that have progressed after at least one line of systemic therapy (see the “Clinical efficacy” section).
This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

Indication with non-limited authorization

PEMAZYRE is indicated as monotherapy for the treatment of adults with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement (see the “Clinical efficacy” section).

Dosage/Administration

Treatment for cholangiocarcinoma should be initiated by a physician experienced in the diagnosis and treatment of patients with bililary tract cancer.
Treatment for myeloid/lymphoid neoplasms (MLNs) should be initiated by a physician experienced in the diagnosis and treatment of patients with MLNs.

For treatment of cholangiocarcinoma, FGFR2 fusion positivity status must be confirmed prior to initiation of PEMAZYRE therapy. FGFR2 fusion positivity in the tumor specimen should be performed with a validated diagnostic test.
For treatment of myeloid/lymphoid neoplasms, FGFR1 rearrangement positivity status must be confirmed prior to initiation of Pemazyre therapy. Assessment for FGFR1 rearrangement positivity should be performed with a validated diagnostic test (see the “Clinical efficacy” section).

Usual dosage

The recommended dose for the treatment of cholangiocarcinoma is 13.5 mg of pemigatinib taken once daily for 14 days followed by 7 days off therapy.
The recommended dose for the treatment of myeloid/lymphoid neoplasms is 13.5 mg pemigatinib taken orally once daily on a continuous basis.

If a dose of pemigatinib is missed by 4 hours or more or if vomiting occurs after a dose, an additional dose should not be administered and dosing should be resumed with the next scheduled dose.

In all patients, a low phosphate diet should be initiated when serum phosphate level is > 5.5 mg/dl and adding a phosphate-lowering therapy should be considered when the level is > 7 mg/dl. The dose of phosphate-lowering therapy should be adjusted until serum phosphate level returns to < 7 mg/dl. Prolonged hyperphosphatemia can cause precipitation of calcium phosphate crystals that can lead to hypocalcemia, soft tissue mineralization, muscle cramps, seizure activity, QT prolongation and arrhythmias (see the “Warnings and precautions” section).
Discontinuing phosphate-lowering therapy and diet should be considered during PEMAZYRE treatment breaks or if the serum phosphate levels falls below normal range. Severe hypophosphatemia may present with confusion, seizures, focal neurological findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis and hemolytic anemia (see the “Warnings and precautions” section).

Duration of treatment

For the treatment of cholangiocarcinoma, treatment with PEMAZYRE should be continued as long as the patient does not have evidence of disease progression or unacceptable toxicity.
For the treatment of myeloid/lymphoid neoplasms, treatment with PEMAZYRE should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity, or until the patient is receiving allogeneic hematopoietic stem cell transplantation (ASCT).

Dosage adjustments as a result of interactions/adverse reactions

Dose modifications or interruption of dosing should be considered for the management of toxicity.

The pemigatinib dose reduction levels are summarized in Table 1.

Table 1: Recommended pemigatinib dose reduction levels

Dose	Dose reduction levels		
	First	**Second**	**Third**
Cholangiocarcinoma:13.5 mg taken orally once daily for 14 days, followed by 7 days off therapy	9 mg taken orally once daily for 14 days, followed by 7 days off therapy	4.5 mg taken orally once daily for 14 days, followed by 7 days off therapy	Permanently discontinue PEMAZYRE
Myeloid/lymphoid neoplasms: 13.5 mg taken orally once daily on a continuous basis	9 mg taken orally once daily on a continuous basis	4.5 mg taken orally once daily on a continuous basis	4.5 mg taken orally once daily for 14 days followed by 7 days off therapy*

*Treatment with pemigatinib should be permanently discontinued if the patient cannot tolerate 4.5 mg of pemigatinib once daily for 14 days followed by 7 days off therapy.

Dose modifications in case of hyperphosphatemia are shown in Table 2.

Table 2: Dose modifications in case of hyperphosphatemia

Adverse reaction	Pemigatinib dose adjustment
> 5.5 mg/dl - ≤ 7 mg/dl	• Pemigatinib should be continued at current dose.
> 7 mg/dl - ≤ 10 mg/dl	• Pemigatinib should be continued at current dose, phosphate-lowering therapy should be initiated, serum phosphate should be monitored weekly, dose of phosphate-lowering therapy should be adjusted if necessary until level returns to < 7 mg/dl. • Pemigatinib should be withheld if levels do not return to < 7 mg/dl within 2 weeks of starting phosphate-lowering therapy. Pemigatinib and phosphate-lowering therapy should be restarted at the same dose when levels return to < 7 mg/dl. • Upon recurrence of serum phosphate at > 7 mg/dl with phosphate-lowering therapy, pemigatinib should be reduced one dose level.

> 10 mg/dl	• Pemigatinib should be continued at current dose, phosphate-lowering therapy should be initiated, serum phosphate should be monitored weekly and dose of phosphate-lowering therapy should be adjusted as needed until level returns to < 7 mg/dl. • Pemigatinib should be withheld if levels continue > 10 mg/dl for 1 week. Pemigatinib and phosphate-lowering therapy should be restarted one dose level lower when serum phosphate is < 7 mg/dl. • If there is recurrence of serum phosphate > 10 mg/dl following 2 dose reductions, pemigatinib should be permanently discontinued.

Dose modifications for serous retinal detachment are presented in Table 3.

Table 3: Dose modifications for serous retinal detachment

Adverse reaction	Pemigatinib dose adjustment
Asymptomatic	• Pemigatinib should be continued at current dose. Monitoring should be performed as described in the "Warnings and precautions" section.
Moderate decrease in visual acuity (best corrected visual acuity of 20/40 or better or decrease in vision ≤ 3 lines from baseline); limiting instrumental activities of daily living	• Pemigatinib should be withheld until resolution. If improved on a subsequent examination, pemigatinib should be resumed at the next lower dose level. • If it recurs, symptoms persist or the examination does not improve, permanent discontinuation of pemigatinib should be considered based on clinical status.
Marked decrease in visual acuity (best corrected visual acuity less than 20/40 or decrease of > 3 lines from baseline to 20/200); limiting activities of daily living	• Pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or the examination does not improve, permanent discontinuation of pemigatinib should be considered.
Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	• Pemigatinib should be withheld until resolution. If improved on a subsequent examination, pemigatinib may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or the examination does not improve, permanent discontinuation of pemigatinib should be considered.

Dose adjustments for other adverse reactions are shown in Table 4.

Table 4 Dose adjustments for other adverse reactions

Adverse reaction	Pemigatinib dose adjustment
Grade 3 adverse reaction	• Pemigatinib should be withheld until reduction to Grade 1 or resolution of the adverse reaction. • If there is an improvement, pemigatinib should be resumed at the lower dose if the adverse reaction resolves within 2 weeks. • Permanent discontinuation of pemigatinib should be considered if the adverse reaction does not resolve within 2 weeks. • In case of Grade 3 recurrence after 2 dose reductions, permanent discontinuation of pemigatinib should be considered.
Grade 4 adverse reaction	• Permanent discontinuation of pemigatinib should be considered.

Concomitant use of pemigatinib and strong CYP3A4 inhibitors

The concomitant administration of strong CYP3A4 inhibitors, including grapefruit juice, should be avoided during treatment with pemigatinib. If concomitant administration with a strong CYP3A4 inhibitor is necessary, the dose of patients taking 13.5 mg of pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients taking 9 mg of pemigatinib once daily should be reduced to 4.5 mg once daily (see the “Warnings and Precautions” and “Interactions” sections).

Patients with impaired hepatic function

Dose adjustment is not required for patients with mild or moderate hepatic impairment. For patients with severe hepatic impairment, the dose of patients who are taking 13.5 mg of pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg of pemigatinib once daily should be reduced to 4.5 mg once daily according to the schedule (intermittent or continuous) designated for the indication (see the “Pharmacokinetics” section).

Patients with impaired renal function

Dose adjustment is not required for patients with mild or moderate renal impairment or end-stage renal disease (ESRD) on hemodialysis. For patients with severe renal impairment, the dose of patients who are taking 13.5 mg of pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg of pemigatinib once daily should be reduced to 4.5 mg once daily according to the schedule (intermittent or continuous) designated for the indication (see the “Pharmacokinetics” section).

Elderly patients

The dose of pemigatinib is the same in elderly patients as younger adult patients (see the “Properties/Effects” section).

Children and adolescents

The safety and efficacy of PEMAZYRE in patients less than 18 years have not yet been established. No data are available.

Method of administration

PEMAZYRE is for oral use. The tablets should be taken at approximately the same time each day. Patients should not crush, chew, break or dissolve the tablets. Pemigatinib can be taken with or without food.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in the “Composition” section. Concomitant use with St. John's wort (see the “Interactions” section).

Warnings and precautions

Hyperphosphatemia

Hyperphosphatemia is a pharmacodynamic effect expected with pemigatinib administration (see the "Properties/Effects" section). Prolonged hyperphosphatemia can cause precipitation of calcium phosphate crystals that can lead to hypocalcemia, soft tissue mineralization, anemia, secondary hyperparathyroidism, muscle cramps, seizure activity, QT interval prolongation and arrhythmias (see the "Dosage/Administration" section). Soft tissue mineralization, including cutaneous calcification, calcinosis and non-uraemic calciphylaxis have been observed with pemigatinib treatment.

Recommendations for the management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see the "Dosage/Administration" section). A phosphate-lowering therapy was used by 19% of patients with cholangiocarcinoma and by 34 % of patients with MLNs during treatment with pemigatinib (see the "Undesirable effects" section).

Hypophosphatemia

Discontinuing phosphate-lowering therapy and diet should be considered during pemigatinib treatment breaks or if serum phosphate level falls below normal range. Severe hypophosphatemia may present with confusion, seizures, focal neurological findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis and hemolytic anemia (see the "Dosage/Administration" and "Undesirable effects" sections).

For patients presenting with hyperphosphatemia or hypophosphatemia, additional surveillance close monitoring and follow-up is recommended regarding dysregulation of bone mineralization.

Serous retinal detachment

Pemigatinib can cause serous retinal detachment reactions, which may present with symptoms such as blurred vision, visual floaters or photopsia (see the "Undesirable effects" section). This can moderately influence the ability to drive and use machines (see the "Effects on ability to drive and use machines" section).

Ophthalmologic examination, including optical coherence tomography (OCT), should be performed 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. For serous retinal detachment reactions, dose modification guidelines should be followed (see the "Dosage/Administration" section).

During the initial conduct of the clinical studies, there was no routine monitoring including OCT to detect asymptomatic serous retinal detachment; therefore, the incidence of asymptomatic serous retinal detachment with pemigatinib is unknown.

Careful consideration should be taken with patients that have clinically significant medical eye disorders, such as retinal disorders, including but not limited to central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment.

Dry eye

Pemigatinib may cause dry eye (see the “Undesirable effects” section). Patients should use ocular demulcents in order to prevent or treat dry eye as needed.

Blood creatinine increase

Pemigatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine; this may occur due to inhibition of renal transporters OCT2 and MATE1 and may not affect glomerular function. For patients with cholangiocarcinoma, serum creatinine increased (mean increase of 0.2 mg/dl) within the first cycle of treatment and reached steady-state by Day 8, then decreased during the 7 days off therapy (see the “Undesirable effects” section). For patients with MLNs, mean creatinine levels were elevated approximately 0.02 to 0.26 mg/dL above baseline at each cycle through Cycle 35. Alternative markers of renal function should be considered if persistent serum creatinine elevation are observed.

CNS metastases

Since untreated or progressive brain/CNS metastases were not allowed in the studies, efficacy in this population has not been evaluated and no dose recommendations can be made; however, the blood-brain barrier penetration of pemigatinib is expected to be low (see the “Preclinical data” section).

Embryo-fetal toxicity

Based on the mechanism of action and findings in an animal reproduction study (see the “Preclinical data” section), pemigatinib can cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus (see the “Pregnancy, Lactation” section).

Contraception

PEMAZYRE can cause foetal harm when administered to a pregnant woman, and women of childbearing potential should therefore be advised not to become pregnant and men should be advised not to father a child during treatment. An effective method of contraception must be used during treatment with PEMAZYRE and for 1 week following completion of therapy (see the “Pregnancy, Lactation” section).

Pregnancy test

A pregnancy test must be performed before treatment initiation to exclude pregnancy.

Combination with proton pump inhibitors
Concomitant use of pemigatinib and proton pump inhibitors should be avoided (see the “Interactions” section).

Combination with strong CYP3A4 inhibitors
Concomitant use of pemigatinib and strong CYP3A4 inhibitors requires dose adjustment (see the “Dosage/Administration” and “Interactions” sections).

Combination with strong or moderate CYP3A4 inducers
Concomitant use of pemigatinib and strong or moderate CYP3A4 inducers is not recommended (see the “Interactions” section).

Sodium
This medicinal product contains less than 1 mmol (23 mg) of sodium per tablet, i.e. it is essentially “sodium-free”.

Interactions

Strong CYP3A4 inhibitors
Concomitant administration of pemigatinib and strong CYP3A4 inhibitors should be avoided and requires a dose adjustment (see the “Dosage/Administration” section). Patients should be advised to avoid eating grapefruit or drinking grapefruit juice while taking pemigatinib.
A strong CYP3A4 inhibitor (itraconazole 200 mg once daily) increased pemigatinib AUC geometric mean by 88% (90% CI of 75%, 103%), which may increase the incidence and severity of adverse reactions with pemigatinib. Patients who are taking 13.5 mg pemigatinib once daily should have their dose reduced to 9 mg once daily and patients who are taking 9 mg pemigatinib once daily should have their dose reduced to 4.5 mg once daily (see the “Dosage/Administration” section).

CYP3A4 inducers
A strong CYP3A4 inducer (rifampin 600 mg once daily) decreased pemigatinib AUC geometric mean by 85% (90% CI of 84%, 86%), which may decrease the efficacy of pemigatinib. Concomitant use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) should be avoided during treatment with pemigatinib (see the “Warnings and precautions” section). Concomitant use of pemigatinib and St John's wort is contraindicated (see the “Contraindications” section). If needed, other enzyme inducers (e.g. efavirenz) should be used under close surveillance.

Proton pump inhibitors

Pemigatinib geometric mean ratios of pemigatinib (90% CI) for C_{max} and AUC were 65.3% (54.7, 78.0) and 92.1% (88.6, 95.8), respectively when co-administered in healthy subjects with esomeprazole (a proton pump inhibitor) relative to pemigatinib alone. Co-administration of a proton pump inhibitor (esomeprazole) did not result in clinically significant change in pemigatinib exposure.
However, in more than one third of patients given PPIs, a significant reduction of the exposure of pemigatinib was observed. PPIs should be avoided in patients receiving pemigatinib (see the "Warnings and precautions" section).

H2-receptor antagonists
Co-administration of ranitidine did not result in a clinically important change in pemigatinib exposure.

Effect of pemigatinib on CYP2B6 substrates
In vitro studies indicate that pemigatinib induces CYP2B6. Co-administration of pemigatinib with CYP2B6 substrates (e.g. cyclophosphamide, ifosfamide, methadone, efavirenz) may decrease their exposure. Close clinical surveillance is recommended when pemigatinib is administered with these medicinal products.

Effect of pemigatinib on P-gp substrates
In vitro, pemigatinib is an inhibitor of P-gp. Co-administration of pemigatinib with P-gp substrates (e.g. digoxin, dabigatran, colchicine) may increase their exposure and thus their toxicity. Pemigatinib administration should be separated by at least 6 hours before or after administration of P-gp substrates with a narrow therapeutic index.

CYP Substrates
Pemigatinib at clinically relevant concentrations is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 or an inducer of CYP1A2 and CYP3A4.

Transporters
Pemigatinib is a substrate of P-gp and BCRP. P-gp or BCRP inhibitors are not expected to affect pemigatinib exposure at clinically relevant concentrations.

In vitro, pemigatinib is an inhibitor of OATP1B3, OCT2, and MATE1. OCT2 inhibition may increase serum creatinine.

Pregnancy, Lactation

Contraception in men and women of childbearing potential

Based on findings in an animal study and regarding its mechanism of action, pemigatinib can cause foetal harm when administered to a pregnant woman. Women of childbearing potential treated with pemigatinib should be advised not to become pregnant and men treated with pemigatinib should be advised not to father a child during treatment. An effective method of contraception must be used in women of childbearing potential and in men with women partners of childbearing potential, during treatment with pemigatinib and for 1 week following completion of therapy. Since the effect of pemigatinib on the metabolism and efficacy of systemic contraceptives has not been investigated, barrier methods should be applied as a second form of contraception to avoid pregnancy.

Pregnancy

There are no available data from the use of pemigatinib in pregnant women. Studies in animal have shown reproductive toxicity (see the “Preclinical data” section). PEMAZYRE should not be used during pregnancy unless the clinical condition of the women requires treatment with pemigatinib. A pregnancy test must be performed prior to initiation of treatment to exclude pregnancy.

Breast-feeding

It is unknown whether pemigatinib or its metabolites are excreted in breast milk. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment with PEMAZYRE and for 1 week following completion of therapy.

Fertility

There are no data on the impact of pemigatinib on human fertility. Animal fertility studies have not been conducted with pemigatinib. In repeat-dose toxicity studies, oral administration of pemigatinib resulted in no dose-related adverse effects on the male or female reproductive organs. Based on the pharmacology of pemigatinib, impairement of male and female fertilty cannot be excluded.

Effect on the ability to drive and use machines

Pemigatinib has moderate influence on the ability to drive and use machines. Adverse reactions such as fatigue and visual disturbances have been associated with pemigatinib. Therefore, caution should be recommended when driving or operating machines (see the “Warnings and Precautions” section).

Undesirable effects

Safety profile summary

The safety of Pemazyre was evaluated in 679 patients with advanced malignancies who received Pemazyre at a starting dose of 13.5 mg, including 147 patients with previously treated, advanced, or metastatic cholangiocarcinoma in Study FIGHT-202 and 47 patients with myeloid/lymphoid

neoplasms with FGFR1 rearrangement in Study FIGHT-203 The median duration of treatment in that overall clinical trial population was 113 days.
The most common adverse reactions identified in those patients who received at least one dose of pemigatinib were hyperphosphatemia (67.0%), diarrhea (44.0%), alopecia (43.3%), nail toxicity (42.7%), stomatitis (42.0%), constipation (34.6%), dry mouth (33.7%), fatigue (32.5%), decreased appetite (30.6 %), nausea (29.7%), dysgeusia (29.3%), abdominal pain (25.9%), dry eye (23.4%), arthralgia (20.0%), dry skin (19.4%), anaemia (18.1%), palmar-plantar erythrodysesthesia syndrome (16.2%) and blood creatinine increased (15.9 %).

The most common serious adverse reactions were acute kidney injury (2.9%), abdominal pain (2.5%), hyponatremia (1.8%), fatigue (1.2%), anaemia (1.2%), constipation (1.0%) and blood creatinine increased (1.0%). One serious adverse reaction of diarrhoea, one serious adverse reaction of detachment of retinal pigment epithelium, one serious adverse reaction of alopecia, one serious adverse reaction of cutaneous calcification, one serious adverse reaction of syncope, one serious adverse reaction of transaminases increased and one serious adverse reaction of fatigue (0.1 % each) led to pemigatinib dose reduction. Five serious adverse reactions of hyponatraemia (0.7%), two serious adverse reactions of nausea (0.3%), two serious adverse reactions of abdominal pain (0.3%), one serious adverse reaction of blood creatinine increased, one serious adverse reaction of stomatitis, one serious adverse reaction of acute kidney injury, and one serious adverse reaction of hyperphosphataemia and one serious adverse reaction of decreased appetite (0.1% each) led to dose interruption. The following serious adverse reactions led to treatment discontinuation: hyponatraemia (0.3%), blood creatinine increased (0.3 %), acute kidney injury (0.3%), blood alkaline phosphatase increased (0.1%) and chorioretinopathy (0.1%).

Eye disorders serious adverse reactions were chorioretinopathy, detachment of retinal pigment epithelium, retinal detachment, non-arteritic ischemic optic ischemic neuropathy and retinal artery occlusion (0.1% each).

Table of adverse reactions
The adverse reactions observed are presented below. Frequency categories are “very common” (≥ 1/10), “common” (≥ 1/100 to < 1/10) and “uncommon” (≥ 1/1,000 to < 1/100). Within each frequency grouping, the adverse reactions are presented in order of decreasing frequency.

Blood and lymphatic system disorders
Very common: Anaemia (18.1%)

Metabolism and nutrition disorders

Very common: Hyperphosphatemia[a] (67.0%), Decreased appetite (30.6 %), Hypophosphatemia[b] (12.7%), Hyponatremia (9.9%)

Nervous system disorders

Very common: Dysgeusia (29.3%)

Common: Syncope

Eye disorders

Very common: Dry eye (23.4%), Serous retinal detachment (10.9%)[c]

Common: Trichiasis, Punctate keratitis, vision blurred

Uncommon: Photopsia

Gastrointestinal disorders

Very common: Diarrhea (44.0%), Nausea (29.7%), Stomatitis (42.0%), Constipation (34.6%), Dry mouth (33.7%), Abdominal pain (25.9 %)

Skin and subcutaneous tissue disorders

Very common: Alopecia (43.3%), Nail toxicity[d] (42.7%), Dry skin (19.4%), Palmar-plantar erythrodysesthesia syndrome (16.2%)

Uncommon: Cutaneous calcification, hair growth abnormal

Musculoskeletal and systemic disorders

Very common: Arthralgia (20.0%)

Renal and urinary disorders

Very common: Blood creatinine Increased (15.9%)

Common: Acute kidney injury

General disorders and administration site conditions

Very common: Fatigue (32.5%), Pain in extremity (14.0%)

Investigations

Common: Blood alkaline phosphatase increased, Transaminases increased

[a] Includes hyperphosphatemia and blood phosphorus increased

[b] Includes hypophosphatemia and blood phosphorus decreased

[c] Includes serous retinal detachment, retinal detachment, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal thickening, subretinal fluid, chorioretinal folds, chorioretinal scar, chorioretinopathy, retinal disorder, retinopathy and maculopathy. See below "Serous retinal detachment"

[d] Includes nail toxicity, nail disorders, nail discoloration, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, fungal paronychia, nail bed bleeding, nail bed tenderness, nail discomfort and paronychia

Description of specific adverse reactions and additional information

Hyperphosphatemia

Hyperphosphatemia was reported in 67% of all patients treated with pemigatinib. Hyperphosphatemia above 7 mg/dl and 10 mg/dl was experienced in 35.1% and 1.0% of patients, respectively. Hyperphosphatemia usually develops within the first 15 days.

Dose interruption and dose reduction occurred in 9.6% of patients and 3.1% of patients, respectively. These results suggest that dietary phosphate restriction and/or administration of phosphate-lowering therapy along with the pemigatinib dose modification when required were effective strategies for managing this on-target effect of pemigatinib.

Recommendations for the management of hyperphosphatemia are provided in the "Dosage/Administration" and "Warnings and precautions" sections.

Hypophosphatemia

During clinical studies of pemigatinib in patients with cholangiocarcinoma, hypophosphataemia reactions were Grade ≥ 3 in 14.3% of participants. None of the events were serious, led to treatment discontinuation or dose reduction. Dosing interruption occurred in 1.4% of participants. During clinical studies of pemigatinib in patients with MLNs, hypophosphataemia reactions were ≥ Grade 3 in 4.3 % of participants. None of the events were serious, led to discontinuation, dose interruption or to dose reduction.

Serous retinal detachment

Serous retinal detachment occurred in 10.9% of all patients treated with pemigatinib. Reactions were generally Grade 1 or 2 (9.5%) in severity; Grade ≥ 3 reactions and serious reactions included retinal detachment, detachment of retinal pigment epithelium and chorioretinopathy in 1 patient (0.1%) each.

Serous retinal detachment events led to dose interruption in 20 patients (2.9 %), to dose reduction in 10 patients (1.5 %), and to discontinuation. in 1 patient (0.1 %)

Recommendations for the management of serous retinal detachment are provided in the "Dosage/Administration" and "Warnings and precautions" sections.

Creatinine increase

For patients with cholangiocarcinoma an increase from baseline in mean creatinine levels of approximately 16 µmol/L occurred on Days 8 and 15 of the 1st cycle. These higher levels generally returned close to baseline by Cycle 2 Day 1. Above-normal creatinine values occurred in 12.9% of patients at baseline, increased to 34.0% on Day 15 of Cycle 1 and were observed in approximately 20% to 30% of participants on Day 1 of subsequent cycles.
The reactions were Grade 1 or 2 with the exception of 2 patients (1.4%) with Grade 3 changes, and resolved without sequelae.
However, normal creatinine values were observed after a one-week treatment suspension period.
For patients with MLNs, mean creatinine levels were elevated approximately 1.4 to 22.8 µmol/L above baseline at each cycle through Cycle 35. The increases from baseline were Grade 1 or 2 with the exception of 1 patient (2.1%) with Grade 3 changes.

The following adverse reactions were reported more frequently with the continuous schedule than the with intermittent schedule:
Hyperphosphataemia (74.2% versus 53.1%).
Stomatitis (50.2% versus 35.8% of patients).
Palmar-plantar erythrodysaesthesia syndrome (24.1% versus 10.3%).
Paronychia (11.7% versus 4.6%).

Reporting suspected adverse reactions after authorization is of great importance. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious side effects via the ElViS online reporting portal (Electronic Vigilance System). You can find information about this on www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Properties/Effects

ATC code:

L01EN02

Mechanism of action

Pemigatinib is a kinase inhibitor of FGFR1, 2 and 3, which inhibits FGFR phosphorylation and signaling and decreases cell viability in cells expressing FGFR genetic alterations, including point mutations, amplifications and fusions or rearrangements. FGFR2 fusions/rearrangements are strong oncogenic drivers and are the most common FGFR alteration occurring, almost exclusively, in 10 to 16% of patients of intrahepatic cholangiocarcinoma (ICC). Myeloid/lymphoid neoplasms with FGFR1 rearrangement is an aggressive hematologic malignancy. The translocation involving the FGFR1 gene located on the chromosome 8p11-12 locus results in the creation of a novel fusion protein between FGFR1 and different partner genes, resulting in the constitutive activation of the FGFR1 tyrosine kinase, thereby promoting oncogenic downstream pathways.

Pharmacodynamics

Serum phosphate

Pemigatinib increased serum phosphate levels as a consequence of FGFR inhibition. In pemigatinib clinical studies, phosphate-lowering therapy and dose modifications were permitted to manage hyperphosphatemia (see the “Dosage/Administration”, “Warnings and precautions” and “Undesirable effects” sections).

Clinical efficacy

Cholangiocarcinoma

FIGHT-202 was a multicenter, open-label, single-arm study to evaluate the efficacy and safety of PEMAZYRE in previously treated patients with locally advanced/metastatic or surgically unresectable cholangiocarcinoma. The efficacy population consists of 108 patients (107 patients with intrahepatic disease) who had progressed after at least 1 prior treatment and who had FGFR2 fusion or rearrangement as determined by the test performed at a central laboratory.

Patients received PEMAZYRE in 21-day cycles, consisting of 13.5 mg once daily oral dosing for 14 days followed by 7 days off therapy. PEMAZYRE was administered until disease progression or unacceptable toxicity. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR), as determined by Independent Review Committee (IRC) according to RECIST v1.1.

The median age was 55.5 years (range: 26-77 years), 23.1% were ≥ 65 years, 61.1% were female and 73.1% were Caucasian. Ninety-eight percent (98%) of patients had intrahepatic cholangiocarcinoma. Fiftly-six percent (56%) of patients had FGFR2 gene fusions and most often the identified FGFR2 fusion was FGFR2-BICC1 (29.6%). Five percent (5%) of patients had other FGFR2 rearrangements for which FGFR2 fusion cannot be predicted with certainty. Most (95.4%) patients

had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42.6%) or 1 (52.8%). All patients had at least 1 prior line of systemic therapy, 27.8% had 2 prior lines of therapy and 12.0% had 3 or more prior lines of therapy. Ninety-six percent (96%) of patients had received prior platinum-based therapy, including 78% with prior gemcitabine/cisplatin.

The efficacy results are summarized in Table 5.

The median time to response was 2.69 months (range: 0.7 - 16.6 months).

Table 5: Efficacy results in Patients with Cholangiocarcinoma in FIGHT-202 (July 8, 2021)

	Cohort A (FGFR2 fusion or rearrangement) Efficacy-evaluable population (N = 108)
ORR (95% CI)	37.0% (27.94; 46.86)
Complete response (N)	2.8% (3)
Partial response (N)	34.3% (37)
Median duration of response (months) (95% CI)[a]	9.13 (6.01; 14.49)
Kaplan-Meier estimates of duration of response (95% CI)	
3 months	100.0 (100.0; 100.0)
6 months	67.8 (50.4; 80.3)
9 months	50.5 (33.3; 65.4)
12 months	41.2 (24.8; 56.8)
Median PFS (months) (95% CI)	7.03 (6.08; 10.48)
Median OS (months) (95% CI)	17.48 (14.36; 22.93)

ORR - CR + PR
CI = Confidence Interval
Comments: Data are from the IRC per RECIST v1.1, and complete and partial responses are confirmed.
[a] The 95% CI was calculated using the Brookmeyer and Crowley method

Myeloid/lymphoid neoplasms

FIGHT-203 was a multicenter, open-label, single-arm study to evaluate the efficacy of Pemazyre in patients with MLNs with FGFR1 rearrangement. The efficacy population consists of 45 patients. Inclusion criteria included myeloid/lymphoid neoplasms with 8p11 rearrangement known to lead to FGFR1 activation, based on cytogenetic results and FGFR1-break-apart FISH assay documented locally. Patients had relapsed after allogeneic stem cell transplantation (ASCT) or other disease modifying therapy, or were not current candidates for ASCT or other disease modifying therapies. Patients received Pemazyre 13.5 mg once daily in 21-day cycles, either on an intermittent schedule (once daily for 14 days followed by 7 days off therapy) or on a continuous schedule. Pemazyre was administered until disease progression or unacceptable toxicity or until patients were able to receive ASCT. The major efficacy outcome measure was complete response (CR) per investigator assessment using the protocol-defined response criteria for MLNs with FGFR1 rearrangement. Additional efficacy outcome measures included complete cytogenetic response (CCyR) and duration of complete response (DoCR), as well as overall response rate (ORR).

The median age was 61 years (range: 23-78 years), 56% were female, 62% were white, and 87% had an ECOG performance status of 0 (36 %) or 1 (51 %). Forty patients had at least 1 line of prior therapy for the treatment of MLNs; 5 patients did not have prior therapy. Disease presentation category at baseline was chronic phase (CP) without EMD for 24◦participants (53.3%), CP with EMD for 4 participants (8.9%), BP without EMD for 6◦participants (13.3%), BP with EMD for 4 participants (8.9%), EMD only for 4◦participants (8.9%), and treated MLN without BM/peripheral blood (PB)/EMD involvement but persistent 8p11 translocation and/or FGFR1 rearrangement for 3◦participants (6.7%). Median duration of study follow-up was 62.88 months (range: 29.2-90.2 months).

Efficacy results are summarized in Table 6.

Table 6: Efficacy Results in Patients with Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement in FIGHT-203 (October 30, 2024)

	Pemazyre **Efficacy Evaluable Population (N = 45)**
Complete Response (CR) Rate (95 % CI)[a]	68.9% (53.35, 81.83)

Note: Data are based on Investigator assessment;CI = confidence interval

[a] Based on the exact method for binomial distribution.

Elderly patients

In Study FIGHT-202, 23.1% of patients were 65 years and older, and 4.6% of patients were 75 years and older. In Study FIGHT-203, 40% of patients were 65 years or older, and 4.4 patients were 75 years or older. No difference in efficacy response was detected between these patients and in patients < 65 years of age.

Temporary authorization

Due to incomplete clinical data at the time of review of the marketing authorization application, the medicinal product Pemazyre is authorized for a limited period of time (Art. 9a LPTh). The temporary authorization must be linked to the timely satisfaction of conditions. Once these conditions are met, the temporary authorization may be converted into ordinary authorization.

Pharmacokinetics

Absorption

The median time to maximum plasma concentration (t_{max}) was 1.13 (0.5 - 6) hours. The geometric mean (CV%) of C_{max} and $AUC_{(0-24h)}$ exposures achieved with 13.5 mg of pemigatinib once daily were at the steady-state of 236 nM (56% CV) and 2620 nM h (54% CV), respectively.
Pemigatinib steady-state concentrations increased proportionally over the dosing range from 1 to 20 mg (0.07 to 1.5 times the recommended dose). The steady-state was reached within 4 days after repeated once daily administration. With repeated once-daily doses, pemigatinib accumulated with a median accumulation ratio of 1.63 (range of 0.63 to 3.28).

No clinically significant differences with pemigatinib pharmacokinetics were observed following administration of a high-fat and high-calorie meal (800 calories to 1,000 calories, with approximately 50% of total caloric content of the meal was fat) in patients with cancer.

Distribution

Pemigatinib is 90.6% bound to human plasma proteins, predominantly to albumin. The estimated apparent volume of distribution was 235 l (60.8%) after an oral dose of 13.5 mg in cancer patients.

Metabolism

Pemigatinib is predominantly metabolized by CYP3A4 *in vitro.* Following oral administration of a single 13.5 mg radiolabeled pemigatinib dose, unchanged pemigatinib was the major drug-related moeity in plasma, and no metabolites > 10% of total circulating radioactivity were observed.

Elimination

Following oral administration of pemigatinib 13.5 mg once daily in patients with cancer, the geometric mean elimination half-life (t1⁄2) was 15.4 (51.6% CV) hours and the geometric mean apparent clearance (CL/F) was 10.6 l/h (54% CV).

Excretion

Following a single oral dose of radiolabeled pemigatinib, 82.4% of the dose was recovered in the feces (1.4% as unchanged) and 12.6% in urine (1% as unchanged).

Hepatic function disorders

The effect of hepatic impairment on the pharmacokinetics of pemigatinib was evaluated in a hepatic impairment study in subjects with normal hepatic function, moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment. In subjects with moderate hepatic impairment, the geometric mean ratios (90% CI) compared to normal controls were 96.7% (59.4%; 157%) for C_{max} and 146% (100%; 212%) for $AUC_{0-\infty}$. In subjects with severe hepatic impairment, the GMR (90% CI)

was 94.2% (68.9%; 129%) for C_{max} and 174% (116%; 261%) for $AUC_{0-\infty}$. Based on these results, no dose adjustment is recommended for patients with mild and moderate hepatic impairment. However, pemigatinib dose should be reduced for patients with severe hepatic impairment (see the "Dosage/Administration" section).

Renal function disorders

The effect of renal impairment on the pharmacokinetics of pemigatinib was evaluated in a renal impairment study in subjects with normal renal function (GFR ≥ 90 ml/min), severe renal function (GFR < 30 ml/min and not on hemodialysis) and end-stage renal disease (ESRD) (GFR < 30 ml/min and on hemodialysis). In subjects with the severe renal impairment, the geometric mean ratios (90% CI) compared to normal controls were 64.6% (44.1%; 94.4%) for C_{max} and 159% (95.4%; 264%) for $AUC_{0-\infty}$. In the subjects with ESRD before hemodialysis, the geometric mean ratios (90% CI) were 77.5% (51.2%; 118%) for C_{max} and 76.8% (54.0%; 109%) for $AUC_{0-\infty}$. Besides, in participants with ESRD after hemodialysis, the geometric mean ratios (90% CI) were 90.0% (59.3%; 137%) for C_{max} and 91.3% (64.1%; 130%) for $AUC_{0-\infty}$. Based on these results, pemigatinib dose should be reduced for patients with severe renal impairment (see the "Dosage/Administration" section).

Preclinical data

Safety Pharmacology

In vitro, pemigatinib demonstrated hERG IC50 inhibition >8 μM (the highest possible solubility-based concentration), which is > 360 times greater than the unbound steady-state clinical C_{max} at the 13.5 mg dose. *In vivo*, there were no negative findings in safety pharmacology assessments of pemigatinib, including *in vivo* studies of respiratory and central nervous system function in rats and a cardiovascular study in monkeys.

Systemic toxicity

The most prominent findings following repeat dose administration of pemigatinib in both rats and monkeys were attributed to the expected pharmacology of pemigatinib (FGFR1, FGFR2 and FGFR3 inhibition), including hyperphosphatemia, physeal dysplasia and soft tissue mineralization; some of these findings were observed at exposures (AUC) lower than therapeutic. Mineralization was observed in numerous tissues, including kidneys, stomach, arteries, ovaries (monkey only) and eyes (cornea, rat only). Soft tissue mineralization was not reversible, whereas the physeal and cartilage findings were reversible. In addition, changes of the bone marrow (rat) and kidney lesions were observed.

Genotoxicity

Pemigatinib was not mutagenic in a bacterial mutagenicity assay, nor clastogenic in an *in vitro* chromosome aberration test, and did not result in induction of bone marrow micronuclei in an *in vivo* micronucleus assay in rat.

Carcinogenicity

Carcinogenicity studies with pemigatinib have not been conducted.

Developmental toxicity

In rats, administration of pemigatinib at ≥ 0.3 mg/kg/day during the period of organogenesis resulted in a 100% postimplantation loss. At 0.1 mg/kg/day, an increase in foetal skeletal malformations and major blood vessels variations, reduced ossification and decreased fetal body weight were observed. Exposure at that dose is approximately 20% of the clinical exposure at the maximum recommended human dose of 13.5 mg based on AUC.

Special Notes

Incompatibilities

Not applicable.

Stability

This medicinal product should not be used beyond the date appearing after the word <EXP> on the container.

Special comments regarding storage

Store at room temperature (15-25°C).
Keep out of reach of children.

Authorization number

68143 (Swissmedic)

Presentation

4.5 mg tablets: 14 or 28 (blister). [A]
9 mg tablets: 14 or 28 (blister). [A]
13.5 mg tablets: 14 or 28 (blister). [A]

Authorization holder

Incyte Biosciences International Sàrl, Morges

Update of the information

May 2025