Date: 10 September 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Pemazyre

International non-proprietary name: pemigatinib

Pharmaceutical form: tablets

Dosage strengths: 13.5 mg, 9 mg and 4.5 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Incyte Biosciences International

Marketing Authorisation No.: 68143

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 13.07.2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

2L	Second line
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CCA	Cholangiocarcinoma
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
iCCA	intrahepatic Cholangiocarcinoma
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LDPE	Low density polyethylene
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance pemigatinib of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 7 December 2020.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

PEMAZYRE is indicated as monotherapy 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.

2.2.2 Approved 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 has progressed after at least one line of systemic therapy (see "Clinical efficacy").

2.2.3 Requested Dosage

Confirm the presence of an FGFR2 fusion or rearrangement prior to initiation of treatment with PEMAZYRE.
The recommended dosage of PEMAZYRE is 13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	25 January 2021
Formal control completed	8 February 2021
Predecision	14 April 2021
Answers to Predecision	12 May 2021
Second Predecision	3 June 2021
Answers to second Predecision:	21 June 2021 and 28 June 2021
Final Decision	13 July 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical Context

Cholangiocarcinomas (CCA) are a diverse group of malignancies arising from the biliary epithelium and are classically sub-divided into three groups depending on the anatomical site of origin: intrahepatic CCA (iCCA), perihilar CCA (pCCA) and distal CCA (dCCA).
Most patients (> 65%) are diagnosed with non-resectable disease, and there is a high relapse rate in the minority of patients who undergo potentially curative surgery. The five-year survival rate is approximately 5% to 15% when considering all patients; estimated five-year survival rate varies with stage: 50% for American Joint Committee on Cancer (AJCC) stage I, 30% for stage II, 10% for stage III, and 0% for stage IV.
Robust (phase III) evidence is available for the use of first-line chemotherapy in patients presenting with advanced disease. Cisplatin and gemcitabine have become the reference regimen; other regimens are considered by individual clinicians based on phase II studies.
The role of second-line therapy FOLFOX is less clear, with very moderate improvements in median overall survival (OS) as compared to best supportive care. Based on these limited options in second-line (2L), there is a clear need for the development of novel (targeted) therapy approaches to improve patient outcome with the lowest toxicity.
Pemigatinib potently inhibits the kinase activity of fibroblast growth factor receptors FGFR1, FGFR2, and FGFR3, which are a reported genetic modification in iCCA and have been identified as an early driver of oncogenic events in iCCA.

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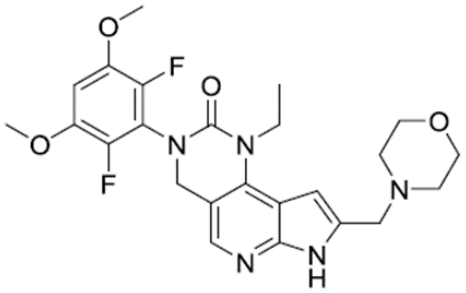
4 Quality Aspects

4.1 Drug Substance

INN: Pemigatinib
Chemical name: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one
Molecular formula: $C_{24}H_{27}F_2N_5O_4$
Molecular mass: 487.5 g/mol
Molecular structure:



Physico-chemical properties: Pemigatinib is a white to off-white solid. There are no chiral centres present for pemigatinib. The compound is classified as a BCS (Biopharmaceutical Classification System) class 2 compound due to its limited in vitro solubility at neutral pH and high permeability.

Synthesis: The drug substance is manufactured by a multi-step chemical synthesis with final crystallisation. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification: The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent quality of pemigatinib.

Stability: The drug substance is packaged in LDPE bags. A stability study was carried out according to the current guideline recommendations. Based on the results of this study, a satisfactory retest period was established.

4.2 Drug Product

Description and composition: Pemigatinib drug product is supplied as immediate-release uncoated tablets for oral administration in three strengths:
4.5 mg tablet: round shaped (5.8 mm diameter) white to off-white tablet, debossed with "I" on one side and with "4.5" on the other side.
9 mg tablet: oval shaped (10 mm by 5 mm) white to off-white tablet, debossed with "I" on one side and with "9" on the other side.
13.5 mg tablet: round shaped (8.5 mm diameter) white to off-white tablet, debossed with "I" on one side and with "13.5" on the other side.
The tablets contain the pharmaceutical excipients microcrystalline cellulose, sodium starch glycolate (Type A) and magnesium stearate.
Pharmaceutical development: A formulation was developed that is qualitatively and quantitatively proportional across the three proposed commercial dosage strengths. The development reflected the principles and concepts of pharmaceutical development as outlined in ICH Q8 (R2).

Manufacture: The manufacturing process is identical for all three tablet strengths and uses conventional pharmaceutical processes such as blending and tableting. The manufacturing process is

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described narratively and in sufficient detail, taking into account pharmaceutical development data. Information on batch manufacturing formulas and in-process controls is included.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and at shelf-life are established. The specifications are based on the requirements of the European Pharmacopoeia for tablets and on the recommendations of the relevant pharmaceutical guidelines.

Container Closure System: Pemigatinib drug product tablets are packaged in blister cards suitable for pharmaceutical use. Each blister card contains 14 pemigatinib tablets in individually sealed blisters (2 rows of 7 tablets each).

Stability: Drug product stability studies were conducted with three primary stability batches according to the recommendations of the relevant ICH guidelines. Based on these studies, a shelf-life was established. The storage recommendation is “Store at room temperature (15 – 25°C)”.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Pemazyre (pemigatinib), the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the CHMP assessment report (approval 25.02.2021) and the US FDA Multi-Disciplinary Review and Evaluation (02.04.2018) provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Pemazyre in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised.
Significant nonclinical findings were observed in the repeat-dose toxicity studies (soft tissue mineralisation, ophthalmic findings, and nephrotoxicity). These effects are likely to occur in humans as no safety margins exist and the effects are adequately mentioned in the Nonclinical Specifications in the RMP.
No effects on reproductive organs have been observed in the repeat-dose toxicity studies with pemigatinib. Nevertheless, according to the published literature, fibroblast growth factors (FGFs) and fibroblast growth factor receptors (FGFRs) are present in both female and male reproductive tissues of several species, including humans, where they help regulate reproductive function. Based on the pharmacology of pemigatinib, impairment of male and female fertility cannot be excluded.
It is unknown whether pemigatinib is excreted into human breast milk. Since FGF signalling is involved in several physiological developmental processes, a risk to the suckling child cannot be excluded. The recommendation to discontinue breast-feeding during treatment and for one week following completion of therapy is considered appropriate.
Since this product is only intended for the treatment of adults, the lack of juvenile toxicity studies in animals is acceptable. Furthermore, pemigatinib was granted a full paediatric waiver for development for the treatment of either cholangiocarcinoma or urothelial carcinoma (EMA decision P/0386/2018).
All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data in this application has been carried out in reliance on previous regulatory decisions by the EMA and the FDA. The available assessment report and corresponding product information from EMA and FDA were used as a basis for the clinical and clinical pharmacology evaluation.
For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see section 8.1 of this report.

Available efficacy data for pemigatinib in adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement appear to be clinically meaningful. Due to the limited size of the efficacy database, including uncertainties related to the single-arm nature of the submitted pivotal study FIGHT-202, the presently available efficacy data for pemigatinib are not considered sufficient for regular approval. In addition, concerns exist regarding the potential long-term toxicity of pemigatinib. Therefore, a temporary approval was granted. In order to further confirm the currently available results, the applicant will submit updated efficacy and safety data from study FIGHT-202 and the confirmatory phase 3 study FIGHT-302.

6.2 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 is authorized for a limited period of time (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

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 “Clinical efficacy”).

Dosage/Administration

Treatment should be initiated by a physician experienced in the diagnosis and treatment of patients with bililary tract cancer.
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.

Usual dosage

The recommended dose is 13.5 mg of pemigatinib taken once daily for 14 days followed by 7 days off therapy.

If a dose of pemigatinib is missed by or more 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).
Discontimuing 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

Treatment should be continued as long as the patient does not have evidence of disease progression or unacceptable toxicity.

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
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

Treatment with pemigatinib should be permanently discontinued if the patient cannot tolerate 4.5 mg of pemigatinib once daily.

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

Table 2: Dose adjustments 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 adjustments 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 od decreased vision 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); limitation of 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, patients taking 13.5 mg of pemigatinib once daily should be reduced to 9 mg once daily and 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 (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 taking who are taking 9 mg of pemigatinib once daily should be reduced to 4.5 mg once daily (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 an 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, secondary hyperparathyroidism, muscle cramps, seizure activity, QT interval prolongation and arrhythmias (see the “Dosage/Administration” section). Soft tissue mineralization, including cutaneous calcification and calcinosis 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 28.5% of patients during treatment with pemigatinib (see the “Undesirable effects” section).

Hypophosphatemia

Discontinuating 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 conduct of the clinical study, 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. Within the first cycle, serum creatinine increased (mean increase of 0.2 mg/dl) and reached steady-state by Day 8, then decreased during the 7 days off therapy (see the “Undesirable effects” section). 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 study, 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 should be used during treatment with PEMAZYRE and for 1 week following completion of therapy (see the "Pregnancy, Lactation" section).

Pregnancy test
A pregnancy test should 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 ith 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 fo 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 on 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 should 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 should 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 most common adverse reactions identified in 147 patients participating in the FIGHT-202 study who received at least one dose of pemigatinib were hyperphosphatemia (60.5%) alopecia (49.7%), diarrhea (46.9%), nail toxicity (44.9%), fatigue (43.5%), nausea (41.5%), dysgeusia (40.8%), stomatitis (37.4%), constipation (36,7%), dry mouth (34,0%), dry eye (27,9%), arthralgia (25,9%), hypophosphatemia (23,1%), dry skin (21,8%) and palmar-plantar erythrodysesthesia syndrome (16,3%).

The most common serious adverse reactions were hyponatremia (2.0%) and blood creatinine increased (1.4%). No serious adverse reactions led to pemigatinib dose reduction. One serious adverse reaction of hyponatremia (0.7%) led to dose interruption. One serious adverse reaction of blood creatinine increased (0.7%) led to dose discontinuation.

Eye disorders serious adverse reactions were retinal detachment (0.7%), non-arteritic ischemic optic ischemic neuropathy (0.7%) and retinal artery occlusion (0.7%).

Table of adverse reactions

The adverse reactions observed in the FIGHT-202 study are presented below. Frequency categories are “very common” (≥ 1/10) and “common” (≥ 1/100 to < 1/10). Within each frequency grouping, the adverse reactions are presented in order of decreasing frequency.

Metabolism and nutrition disorders

Very common: Hyperphosphatemia[a] (60.5%), Hypophosphatemia[b] (23.1%), Hyponatremia (10.9%)

Nervous system disorders

Very common: Dysgeusia (40.8%)

Eye disorders

Very common: Dry eye (27.9%)

Common: Trichiasis, Punctate keratitis, Serous retinal detachment[c], Blurred vision

Gastrointestinal disorders

Very common: Diarrhea (46.9%), Nausea (41.5%), Stomatitis (37.4%), Constipation (36.7%), Dry mouth (34%)

Skin and subcutaneous tissue disorders

Very common: Alopecia (49.7%), Nail toxicity[d] (44.9%), Dry skin (21.8%), Palmar-plantar erythrodysesthesia syndrome (16.3%)
Common: Abnormal hair growth

Musculoskeletal and systemic disorders
Very common: Arthralgia (25.9%)

Kidney and urinary tract disorders
Very common: Blood creatinine Increased (11.6%)

General disorders and administration site conditions
Very common: Fatigue (43.5%)

[a] Includes hyperphosphatemia and blood phosphorus increased

[b] Includes hypophosphatemia and blood phosphorus decreased

[c] Includes serous retinal detachment, retinal detachment, detachment of retinal pigment epithelium, retinal thickening, subretinal fluid, chorioretinal folds, chorioretinal scar 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 and paronychia

Description of specific adverse reactions and additional information

Hyperphosphatemia
Hyperphosphatemia was reported in 60.5% of all patients treated with pemigatinib.
Hyperphosphatemia above 7 mg/dl and 10 mg/dl was experienced in 27% and 0% of patients, respectively. Hyperphosphatemia usually develops within the first 15 days.
None of the reactions were ≥ Grade 3 in severity, serious, or led to discontinuation of pemigatinib. Dose interruption occurred in 1.4% of patients and reduction in 0.7% of patients. These results suggest that dietary phosphate restriction and/or administration of phosphate-lowering therapy along with the one-week dose holiday 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
Hypophosphatemia reactions were Grade ≥ 3 in 12.3% of participants. None of the events were serious, led to treatment discontinuation or dose reduction. Dosing interruption occurred in 1.4% of participants.

Serous retinal detachment
Serous retinal detachment occurred in 4.8% of all patients treated with pemigatinib. Reactions were generally Grade 1 or 2 (3.4%) in severity; Grade ≥ 3 reactions and serious reactions included retinal detachment in 1 patient (0.7%). Two adverse reactions of retinal detachment (0.7%) and detachment of retinal pigment epithelium (0.7%) led to dose interruption. None of the reactions led to dose reduction or discontinuation.

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

Creatinine increase
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 lever generally returned close to baseline by Cycle 2 Day 1. Above-normal creatinine values occurred in 13% of patients at baseline, increased to 33.6% 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.

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:

L01EX20

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).

Pharmacodynamics

Serum phosphate
Pemigatinib increased serum phosphate levels as a consequence 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

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 (105 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 56 years (range: 26-77 years), 31.5% were ≥ 65 years, 60.7% were female and 73.8% were Caucasian. Ninety-eight percent (98%) of patients had intrahepatic cholangiocarcinoma. Eighty-six percent (86%) of patients had FGFR2 gene fusions and most often the identified FGFR2 fusion was FGFR2-BICC1 (34%). Fourteen percent (14%) 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 (42.1%) or 1 (53.3%). All patients had at least 1 prior line of systemic therapy, 27.1% had 2 prior lines of therapy and 12.1% had 3 or more prior lines of therapy. Ninety-six percent of patients had received prior platinum-based therapy, including 76% with prior gemcitabine/cisplatin.

The efficacy results are summarized in Table 5.

The median time to response was 2.7 months (range: 0.7 - 6.9 months).

Table 5: Efficacy results (April 7, 2020)

	Cohort A (FGFR2 fusion or rearrangement) Efficacy-evaluable population (N = 108)
ORR (95% CI)	37.0% (27.94; 46.86)
Complete response (N)	3.7% (4)
Partial response (N)	33.3% (36)
Median duration of response (months) (95% CI)[a]	8.08 (5.65; 13.14)
Kaplan-Meier estimates of duration of response (95% CI)	
3 months	100.0 (100.0; 100.0)
6 months	66.0 (48.0; 79.1)
9 months	47.6 (30.2; 63.1)
12 months	37.5 (21.3; 53.7)
Median PFS (months) (95% CI)	7.03 (6.08; 10.48)
Median OS (months) (95% CI)	17.48 (14.42; 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

Elderly patients

In the clinical study on pemigatinib, 31.5% of patients were 65 years and older, and 7.5% of patients were 75 years and 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 $AUC_{(0\text{-}24h)}$ exposures achieved with 13.5 mg of pemigatinib 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 (t½) 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 pharmacology assessments of pemigatinib safety, 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

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

June 2021