Pemigatinib (Pemazyre®) for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement

General information

Drug description [1]	Indication [2]
Pemigatinib is a selective, potent, oral competitive inhibitor of FGFR1, FGFR2, and FGFR3.	Pemigatinib monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.

Current treatment

- Surgery is currently the only curative treatment for cholangiocarcinoma; however, surgery is an option for only around 35% of patients and, of those who undergo potentially curative resection, approximately 35% subsequently relapse within 2 years [1].
- The ESMO guidelines recommend the following drugs for palliative chemotherapy:
  - Gemcitabine/cisplatin is the reference chemotherapy regimen for good performance status (PS) 0-1 patients.
  - Gemcitabine monotherapy may be considered for PS 2 patients.
  - There is no established second-line chemotherapy regimen.
  - There is no established evidence to support the use of targeted therapies.
- Cancer research UK indicates that the following drugs are used for biliary tract cancer:
  - Gemcitabine and cisplatin combination therapy (most common)
  - Oxaloplatin
  - Gemcitabine
  - Capecitabine
  - Flurouracil
  - Cisplatin [3].

Regulatory status

EMA [2]	FDA [4]
Approval status for this indication: On 28 January 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Pemazyre®. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 26/03/2021 <u>The full indication is:</u> Pemazyre® monotherapy is indicated 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. **Other indications**: none ✓ **Orphan status** ✓ **Medicine received a conditional marketing authorisation[1]** ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 17 April 2020, the FDA granted accelerated approval to Pemazyre®, the first treatment approved for adults with certain types of previously treated, advanced cholangiocarcinoma. **Other indications**: none ✓ **Priority review** ✓ **Breakthrough therapy designation** ✓ **Orphan drug designation**

Costs

14 Pemazyre® tablets 13.5 mg = € 7,732.00 [5]

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

FIGHT-202 trial patients received oral pemigatinib at a starting dose of 13.5 mg once daily (21-day cycle; 2 weeks on, 1 week off); median duration of treatment was 7.2 months in patients with FGFR2 fusions or rearrangements, 1.4 months in patients with other FGF/FGFR alterations, and 1.3 months in patients with no FGF/FGFR alterations [1].
According to this dosing regimen, costs for one 21-day cycle of pemigatinib treatment → € 7,732.00.

Special warnings and precautions for use [6]

- Hyperphosphatemia
  - Hyperphosphatemia is a pharmacodynamic effect expected with pemigatinib administration. 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.
  - Soft tissue mineralization, including cutaneous calcification and calcinosis, have been observed with pemigatinib treatment.
  - Recommendations for management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required. Phosphate-lowering therapy was used by 28.5 % of patients during treatment with pemigatinib.
- 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 neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and hemolytic anemia.
  - Hypophosphatemia reactions were ≥ Grade 3 in 12.3% of participants. None of the events were serious, led to discontinuation or to dose reduction. Dose interruption occurred in 1.4 % of participants.
  - For patients presenting with hyperphosphatemia or hypophosphatemia, additional 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. This can moderately influence the ability to drive and use machines.
  - Ophthalmological 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, the dose modification guidelines should be followed.
  - 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 can cause dry eye. Patients should use ocular demulcents, in order to prevent or treat dry eye, as needed.
- Embryo-foetal toxicity
  - Based on the mechanism of action and findings in an animal reproduction study, pemigatinib can cause foetal harm when administered to a pregnant woman.
  - Pregnant women should be advised of the potential risk to the foetus. Women of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for 1 week after the last dose.
  - Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for at least 1 week after the last dose.
- 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, and then decreased during the 7 days off therapy.
  - Alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed.
- Combination with proton pump inhibitors
  - Concomitant use of pemigatinib with proton pump inhibitors should be avoided.
- Combination with strong CYP3A4 inhibitors
  - Concomitant use of pemigatinib with strong CYP3A4 inhibitors requires dose adjustment.
- Combination with strong or moderate CYP3A4 inducers

- Concomitant use of pemigatinib with strong or moderate CYP3A4 inducers is not recommended.

❖ CNS metastasis
- Since untreated or progressing brain/CNS metastasis 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.

❖ Contraception
- Based on findings in an animal study and its mechanism of action, Pemazyre® can cause fetal harm when administered to a pregnant woman. Women of childbearing age being treated with Pemazyre® should be advised not to become pregnant and men being treated with Pemazyre® should be advised not to father a child during treatment. An effective method of contraception should be used in women of 7 childbearing potential and in men with women partners of childbearing potential during treatment with Pemazyre® and for 1 week following completion of therapy.

❖ Pregnancy test
- A pregnancy test should be performed before treatment initiation to exclude pregnancy.

Study characteristics [1, 7, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
FIGHT-202 NCT02924376	146[2]	oral pemigatinib at a starting dose of 13.5 mg once daily (21-day cycle; 2 weeks on, 1 week off)	-	the proportion of patients with FGFR2 fusions or rearrangements who achieved an objective response[3], assessed by independent central review	multicentre, open-label, single-arm, multicohort, phase 2 study	FGFR2	Incyte Corporation	[1]

Efficacy (I vs. C)

Objective response (centrally confirmed): 35.5% (95% CI, 26.5–45.4) of patients with FGFR2 fusions or rearrangements
Confirmed CRs and PRs: 2.8% and 32.7%
Disease control achieved by: 82% (95% CI, 74–89]) of 107 patients
Median time to first response: 2.7 months (IQR 1.4–3.9)
Median duration of response among responders: 7.5 months (95% CI 5.7–14.5).
Reductions in centrally assessed best percentage change from baseline in **target lesion size**: 88% of 103 patients with FGFR2 fusions or rearrangements who had post-baseline measurements
Median PFS: 6.9 months (95% CI 6.2–9.6)
OS data were not mature at the data cut-off: 37% of 107 patients had died; **median OS** was 21.1 months (95% CI 14.8 to not estimable)

QoL [9]:
- ❖ Of 107 patients with FGFR2 fusions/rearrangements, 93% were evaluable for QoL, including 36, 48, and 15 with CR/PR, SD, and PD, respectively.
- ❖ From baseline to week 16, QLQ-C30 overall health status was maintained in patients with CR/PR and SD and worsened in patients with PD.
- ❖ Emotional functioning remained stable and similar in pts with CR/PR and SD but worsened in patients with PD.
- ❖ All subgroups showed decline in role and social functioning.
- ❖ Patients with CR/PR and SD experienced decreases in QLQ-BIL21 pain and anxiety; all subgroups showed increases in QLQ-BIL21 treatment side effects.
- ❖ Conclusions: In these patients with advanced cholangiocarcinoma, those with an SD as best overall response had a similar pattern of changes in QoL as those with CR/PR to pemigatinib. Changes in QoL were directionally more favourable in patients with CR/PR or SD than patients with PD.

Safety (I vs. C)

Grade ≥3 AEs: n=93/146 (64%)
SAEs: n=65/146 (45%)
Deaths[4]: n=71/146 (49%)
Discontinuation[5]: n=13/146 (9%)

ESMO-MCBS version 1.1 [10]

[2] 146 patients were enrolled: 107 with FGFR2 fusions or rearrangements, 20 with other FGF/FGFR alterations, 18 with no FGF/FGFR alterations, and one with an undetermined FGF/FGFR alteration.
[3] Best overall response of confirmed complete response or confirmed partial response
[4] The most frequent primary cause of death was disease progression (42% of patients); other primary causes were kidney failure (n=1), respiratory failure (n=1), and brain infarction (n=1); 7 deaths were of unknown causes. Among the 71 patients who died, 6 also had fatal TEAEs. No deaths were deemed by the investigators to be treatment- related.
[5] discontinuation due to AE(s)

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	PFS: 6.9 m	(6.2–9.6)	PFS ≥6 m	3	-	-	-	3
Adapted	-	-	-	-	-	-	-	-	-	-	-

Risk of bias (study level) [11]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
no	no	No, open-label	unclear[6]	yes[7]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DoR=duration of response, EMA=European Medicines Agency, EORTC-QLQ-C30=European Organization Research Treatment of Cancer Quality of Life Questionnaire-C30, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FGFR=fibroblast growth factor receptor, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, m=months, MG=median gain, n=number of patients, OCT=optical coherence tomography, ORR=objective response rate, OS=overall survival, PD=progressive disease, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, PS=performance status, QLQ-BIL21=biliary tract cancer-specific EORTC-QLQ, QoL=quality of life, SAE=serious adverse event, SD=stable disease, ST=standard treatment, TEAEs=treatment-emergent adverse events

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[6] FIGHT-202 trial is currently ongoing; estimated study completion date is June 2021.
[7] Industry-funded

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