SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Pemazyre 9 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pemazyre 9 mg tablets
Each tablet contains 9 mg of pemigatinib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Pemazyre 9 mg tablets
Oval (10 × 5 mm), white to off-white tablet debossed on one side with "I" and "9" on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 have progressed after at least one prior line of systemic therapy.

4.2 Posology and method of administration

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

FGFR 2 fusion positivity status must be known prior to initiation of Pemazyre therapy. Assessment for FGFR 2 fusion positivity in tumor specimen should be performed with an appropriate diagnostic test.

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

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

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

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 level is > 7 mg/dL. The dose of phosphate-lowering therapy should be adjusted until serum phosphate level returns to < 7 mg/dL. Prolonged hyperphosphataemia can cause precipitation of calcium-phosphate crystals that can lead to hypocalcaemia, soft tissue mineralization, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias (see section 4.4).

Discontinuing phosphate-lowering therapy and diet should be considered during Pemazyre treatment breaks or if serum phosphate level falls below normal range. Severe hypophosphataemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and haemolytic anaemia (see section 4.4).

Dose adjustment due to drug interaction

Concomitant use of pemigatinib with strong CYP3A4 inhibitors
Concurrent use of strong CYP3A4 inhibitors, including grapefruit juice, should be avoided during treatment with pemigatinib. If co-administration with a strong CYP3A4 inhibitor is necessary, the dose of patients who are taking 13.5 mg pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily (see sections 4.4 and 4.5).

Management of toxicities

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

Pemigatinib dose reductions levels are summarised 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 on, followed by 7 days off therapy	4.5 mg taken orally once daily for 14 days on, followed by 7 days off therapy

Treatment should be permanently discontinued if patient is unable to tolerate 4.5 mg pemigatinib once daily.

Dose modifications for hyperphosphataemia are provided in table 2.

Table 2: Dose modifications for hyperphosphataemia

Adverse reaction	pemigatinib dose modification
> 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 as needed 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 a phosphate lowering therapy. pemigatinib and phosphate-lowering therapy should be restarted at the same dose when level returns to < 7 mg/dL. • Upon recurrence of serum phosphate at > 7 mg/dL with phosphate-lowering therapy, pemigatinib should be reduced 1 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 1 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 provided in table 3.

Table 3: Dose modifications for serous retinal detachment

Adverse reaction	pemigatinib dose modification
Asymptomatic	• pemigatinib should be continued at current dose. Monitoring should be performed as described in section 4.4.

Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline); limiting instrumental activities of daily living	• pemigatinib should be withheld until resolution. If improved on subsequent examination, pemigatinib should be resumed at the next lower dose level. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered based on clinical status.
Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or > 3 lines decreased vision from baseline up 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 examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status.
Visual acuity worse than 20/200 in affected eye; 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 examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status.

Special populations

Elderly patients
The dose of pemigatinib is the same in elderly patients as younger adult patients (see section 5.1).

Renal impairment
Dose adjustment is not required for patients with mild, moderate renal impairment or End Stage Renal Disease (ESRD) on haemodialysis. For patients with severe renal impairment, the dose of patients who are taking 13.5 mg pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily (see section 5.2).

Hepatic impairment
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 pemigatinib once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg pemigatinib once daily should be reduced to 4.5 mg once daily (see section 5.2).

Paediatric population
The safety and efficacy of Pemazyre in patients less than 18 years of age have not been established. No data are available.

Method of administration

Pemazyre is for oral use. The tablets should be taken at approximately the same time every day. Patients should not crush, chew, split or dissolve the tablets. Pemigatinib may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use with St John's wort (see section 4.5).

4.4 Special warnings and precautions for use

Hyperphosphataemia
Hyperphosphataemia is a pharmacodynamic effect expected with pemigatinib administration (see section 5.1). Prolonged hyperphosphataemia can cause precipitation of calcium-phosphate crystals that can lead to hypocalcaemia, soft tissue mineralization, anaemia, secondary hyperparathyroidism, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias (see section 4.2). Soft tissue mineralization, including cutaneous calcification, calcinosis and non-uraemic calciphylaxis have been observed with pemigatinib treatment.

Recommendations for management of hyperphosphataemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see section 4.2).
Phosphate-lowering therapy was used by 19 % of patients during treatment with pemigatinib (see section 4.8).

Hypophosphataemia
Discontinuing phosphate-lowering therapy and diet should be considered during pemigatinib treatment breaks or if serum phosphate level falls below normal range. Severe hypophosphataemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and haemolytic anaemia (see section 4.2). Hypophosphataemia reactions were ≥ Grade 3 in 14.3 % 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 hyperphosphataemia or hypophosphataemia, 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 (see section 4.8). This can moderately influence the ability to drive and use machines (see section 4.7).

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 (see section 4.2).

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 (see section 4.8). 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 (see section 5.3), 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 (see section 4.6).

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 (see section 4.8). 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 (see section 4.5).

Combination with strong CYP3A4 inhibitors

Concomitant use of pemigatinib with strong CYP3A4 inhibitors should be avoided (see sections 4.2 and 4.5). Patients should be advised to avoid eating grapefruit or drinking grapefruit juice while taking pemigatinib.

Combination with strong or moderate CYP3A4 inducers

Concomitant use of pemigatinib with strong or moderate CYP3A4 inducers is not recommended (see section 4.5).

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 (see section 5.3).

Contraception
Based on findings in an animal study and its mechanism of action, Pemazyre can cause foetal 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 childbearing potential and in men with women partners of childbearing potential during treatment with Pemazyre and for 1 week following completion of therapy (see section 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on pemigatinib

Strong CYP3A4 inhibitors

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 section 4.2). Where possible, concurrent use of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, ritonavir) should be avoided during treatment with pemigatinib.

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. Concurrent use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) should be avoided during treatment with pemigatinib (see section 4.4). Concomitant use of pemigatinib with St John's wort is contra-indicated (see section 4.3). If needed, other enzyme inducers (e.g. efavirenz) should be used under close surveillance.

Proton pump inhibitors

Pemigatinib geometric mean ratios (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 a clinically important 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 section 4.4).

H2-receptors antagonists

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

Effects of pemigatinib on other medicinal products

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.

4.6 Fertility, pregnancy and lactation

Contraception in men and women/women of childbearing potential

Based on findings in an animal study and its mechanism of action, pemigatinib can cause foetal harm when administered to a pregnant woman. Women of childbearing potential being treated with pemigatinib should be advised not to become pregnant and men being 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 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 animals have shown reproductive toxicity (see section 5.3). Based on animal data and pharmacology of pemigatinib, Pemazyre should not be used during pregnancy unless the clinical condition of the women requires treatment with pemigatinib. A pregnancy test should be performed before treatment initiation to exclude pregnancy.

Breast-feeding

It is unknown whether pemigatinib or its metabolites are excreted in human 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 (see section 5.3). Based on the pharmacology of pemigatinib, impairment of male and female fertility cannot be excluded.

4.7 Effects on 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 section 4.4).

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions were hyperphosphataemia (60.5 %), alopecia (49.7 %), diarrhoea (47.6 %), nail toxicity (44.9 %), fatigue (43.5 %), nausea (41.5 %), stomatitis (38.1 %), constipation (36.7 %), dysgeusia (36.1 %), dry mouth (34.0 %), arthralgia (29.9 %), dry eye (27.9 %), hypophosphataemia (23.8 %), dry skin (21.8 %), and palmar-plantar erythrodysaesthesia syndrome (16.3 %).

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

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

Tabulated list of adverse reactions
Adverse reactions are presented in table 4. 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, undesirable effects are presented in order of decreasing seriousness.

Table 4: Adverse reactions reported in clinical studies

System organ class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Very common	Hyponatraemia, Hyperphosphataemia[a], Hypophosphataemia[b]
Nervous system disorders	Very common	Dysgeusia
Eye disorders	Very common	Dry eye
	Common	Serous retinal detachment[c], Punctate keratitis, Vision blurred, Trichiasis
Gastrointestinal disorders	Very common	Nausea, Stomatitis, Diarrhoea, Constipation, Dry mouth
Skin and subcutaneous tissue disorders	Very common	Palmar-plantar erythrodysaesthesia syndrome, Nail toxicity[d], Alopecia, Dry skin
	Common	Hair growth abnormal
	Uncommon	Cutaneous calcification
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
General disorders and administration site conditions	Very common	Fatigue
Investigations	Very common	Blood creatinine increased

[a] Includes Hyperphosphataemia and Blood phosphorous increased. See below "*Hyperphosphataemia*".
[b] Includes Hypophosphataemia and Blood phosphorous decreased
[c] Includes Serous retinal detachment, Retinal detachment, Detachment of retinal pigmented epithelium, Retinal thickening, Subretinal fluid, Chorioretinal folds, Chorioretinal scar, and Maculopathy. See below "*Serous retinal detachment*".
[d] Includes Nail toxicity, Nail disorder, Nail discolouration, Nail dystrophy, Nail hypertrophy, Nail ridging, Nail infection, Onychalgia, Onychoclasis, Onycholysis, Onychomadesis, Onychomycosis and Paronychia

Description of selected adverse reactions

Hyperphosphataemia
Hyperphosphataemia was reported in 60.5 % of all patients treated with pemigatinib. Hyperphosphataemia above 7 mg/dL and 10 mg/dL was experienced by 27.2 % and 0.7 % of patients, respectively. Hyperphosphataemia 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 % 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 1-week dose holiday were effective strategies for managing this on-target effect of pemigatinib.

Recommendations for management of hyperphosphataemia are provided in sections 4.2 and 4.4.

Serous retinal detachment
Serous retinal detachment occurred in 4.8 % of all patients treated with pemigatinib. Reactions were generally Grade 1 or 2 (4.1 %) in severity; ≥ Grade 3 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 management of serous retinal detachment are provided in sections 4.2 and 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no information on overdose of pemigatinib.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX20

Pemigatinib is a kinase inhibitor of FGFR1, 2 and 3 which inhibits FGFR phosphorylation and signalling 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 10-16 % of intrahepatic cholangiocarcinoma (CCA).

Pharmacodynamic effects

Serum phosphate
Pemigatinib increased serum phosphate level as a consequence of FGFR inhibition. In pemigatinib clinical studies, phosphate-lowering therapy and dose modifications were permitted to manage hyperphosphataemia (see sections 4.2, 4.4 and 4.8).

Clinical studies
FIGHT-202 was a multicentre, 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) that had progressed after at least 1 prior therapy and who had FGFR2 fusion or rearrangement, as determined by the test performed at a central laboratory.

Patients received Pemazyre in 21-days 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 to 77 years), 23.1 % were ≥65 years, 61.1 % were female, and 73.1 % were Caucasian. 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 of patients had received prior platinum-based therapy including 78 % with prior gemcitabine/cisplatin.

Efficacy results are summarised in table 5.

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

Table 5: Efficacy results

	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)

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

Elderly patients
In the clinical study of pemigatinib, 23.1 % of patients were 65 years and older, and 4.6 % of patients were 75 years and older. No difference in efficacy response was detected between these patients and in patients < 65 years of age.

Paediatric population
The Medicines and Healthcare products Regulatory Agency has waived the obligation to submit the results of studies with Pemazyre in all subsets of the paediatric population in the treatment of cholangiocarcinoma. See section 4.2 for information in pediatric use.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The Medicines and Healthcare products Regulatory Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Pemigatinib exhibits linear pharmacokinetics in the dose range of 1 to 20 mg. Following oral administration of Pemazyre 13.5 mg once daily, steady-state was reached by 4 days with a geometric mean accumulation ratio of 1.6. The geometric mean steady-state $AUC_{0\text{-}24h}$ was 2620 nM·h (54 % CV) and C_{max} was 236 nM (56 % CV) for 13.5 mg once daily.

Absorption
Median time to achieve peak plasma concentration (t_{max}) was 1 to 2 hours.

No clinically meaningful 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 from 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 %) in patients with cancer.

Biotransformation

Pemigatinib is predominantly metabolised by CYP3A4 *in vitro*. Following oral administration of a single 13.5 mg radiolabeled pemigatinib dose, unchanged pemigatinib was the major drug-related moiety 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 faeces (1.4 % as unchanged) and 12.6 % in urine (1 % as unchanged).

Renal impairment

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) was 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 section 4.2).

Hepatic impairment

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 section 4.2).

Interactions

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 both 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. Inhibition of OCT2 may increase serum creatinine.

5.3 Preclinical safety data

Systemic toxicity
The most prominent findings following repeat-dose administration of pemigatinib in both rats and monkeys were attributed to the intended pharmacology of pemigatinib (FGFR1, FGFR2, and FGFR3 inhibition), including hyperphosphataemia, 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, while physeal and cartilage findings were reversible. In addition, changes of the bone marrow (rats) and kidney lesions were observed.

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

Carcinogenicity
Carcinogenicity studies with pemigatinib have not been conducted.

Impairment of fertility

No specific animal studies with pemigatinib have been conducted to evaluate the effects of pemigatinib on fertility. In repeated dose toxicity studies, oral administration of pemigatinib did not result in any dose-related adverse effects on male and female reproductive organs.

Developmental toxicity
In rats, administration of pemigatinib at ≥ 0.3 mg/kg/day during the period of organogenesis resulted in 100 % postimplantation loss. At 0.1 mg/kg/day, an increase in foetal skeletal malformations and major blood vessels variations, reduced ossification, and decrease foetal 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.

Safety pharmacology

In vitro, pemigatinib showed an IC50 for hERG inhibition > 8 μM (the highest feasible concentration based on solubility), that is > 360-fold higher than the clinical steady-state unbound C_{max} at the dose of 13.5 mg. *In vivo*, there were no adverse findings in safety pharmacology assessments of pemigatinib, including *in vivo* respiratory and central nervous system function studies in rats and cardiovascular study in monkeys.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E-460)

Sodium starch glycolate (Type A)

Magnesium stearate (E-572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Al blister containing 14 tablets. Carton box containing 14 or 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Incyte Biosciences UK Ltd
First Floor Q1, The Square
Randalls Way, Leatherhead
KT22 7TW, UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 42338/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/01/2026

10 DATE OF REVISION OF THE TEXT

20/01/2026