Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Pemigatinib 4.5 mg tablets

Pemigatinib 9 mg tablets

Pemigatinib 13.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- Each 4.5 mg tablet contains 4.5 mg of pemigatinib
- Each 9 mg tablet contains 9 mg of pemigatinib
- Each 13.5 mg tablet contains 13.5 mg of pemigatinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

- 4.5 mg tablet: round (5.8 mm), white to off-white tablet debossed on one side with “I” and “4.5” on the reverse
- 9 mg tablet: oval (10x5 mm), white to off-white tablet debossed on one side with “I” and “9” on the reverse
- 13.5 mg tablets: round (8.5 mm), white to off-white tablet debossed on one side with “I” and “13.5” on the reverse

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Pemigatinib monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that is relapsed or refractory after at least one 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.

FGFR2 fusion positivity status must be known prior to initiation of pemigatinib therapy. Assessment for FGFR2 fusion positivity in tumour specimen should be performed with an appropriate diagnostic test.

Molecular testing for the EAMS programme will be conducted at specific genomic NHS laboratory hubs. . When the HCP wishes to assess the FGFR2 status of an eligible patient they should contact Incyte Bioscience UK Ltd on EAMS@incyte.com for further instructions.::

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 four 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.

Serum calcium and phosphate levels should be obtained at baseline prior to initiation of treatment with pemigatinib. 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 hypocalcaemia, soft tissue mineralization, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias (see section 4.4 of the Treatment Protocol for HCP).

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

Dose adjustment due to drug interaction

Concomitant use of pemigatinib with strong CYP3A4 inhibitors
If co-administration with a strong CYP3A4 inhibitor (e.g., grapefruit/grapefruit juice, itraconazole, ketoconazole, ritonavir) is necessary, the dose of patients who are taking pemigatinib 13.5 mg once daily should be reduced to 9 mg once daily and the dose of patients who are taking pemigatinib 9 mg once daily should be reduced to 4.5 mg once daily (see sections 4.4 and 4.5 of the Treatment Protocol for HCP). Where possible, concurrent use of strong CYP3A4 inhibitors should be avoided during treatment with pemigatinib.

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 once daily for 14 days followed by 7 days off therapy	9 mg once daily for 14 days on, followed by 7 days off therapy	4.5 mg once daily for 14 days on, followed by 7 days off therapy

Pemigatinib should be permanently discontinued if a patient is unable to tolerate a 4.5 mg dose once daily.

Dosage modifications for hyperphosphataemia are provided in Table 2.

Table 2. Dose modifications for hyperphosphataemia

Adverse reaction	**Pemigatinib dose modification**
>5.5 mg/dL to ≤7 mg/dL	• Continue pemigatinib at current dose
>7 mg/dL to ≤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 two weeks of starting a phosphate lowering therapy. Pemigatinib 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 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 one week. Pemigatinib 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.

Dosage modifications for serous retinal detachment are provided in Table 3. Ophthalmic examination including optical coherence tomography (OCT) is required prior to initiation of therapy and at regular intervals thereafter (see section 4.4 of the Treatment Protocol for HCP).

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 of the Treatment Protocol for HCP
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 two 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 two dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of pemigatinib should be considered, based on clinical status.

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

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 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 section 5.2 of the Treatment Protocol for HCP).

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 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 section 5.2 of the Treatment Protocol for HCP).

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

Method of administration

Pemigatinib 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 any of the excipients listed in section 6.1.
Concomitant use of St John's Wort (see section 4.5 of the Treatment Protocol for HCP).

4.4 Special warnings and precautions for use

Hyperphosphataemia

Hyperphosphataemia is a pharmacodynamic effect expected with pemigatinib administration (see section 5.1 of the Treatment Protocol for HCP). Prolonged hyperphosphatemia 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 of the Treatment Protocol for HCP).

Clinical presentation of soft tissue /intravascular mineralization may vary and monitoring should be clinical in the first instance with any signs and symptoms associated with possible soft tissue mineralization followed up with more specific radiological examination such as X-Ray, MRI, or CT scan.

Soft tissue/ intravascular mineralization can be seen on radiological examinations and any new findings on CT/MRI would be reported by the radiologist. In some cases, biopsy may be performed to confirm or exclude ectopic calcification. Any new ophthalmologic evidence of mineralization would be routinely reported.

Recommendations for management of hyperphosphataemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see section 4.2 of the Treatment Protocol for HCP). Phosphate-lowering therapy was used by 28.5% of patients during treatment with pemigatinib (see section 4.8 of the treatment Protocol for HCP).

Hypophosphataemia

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 haemolytic anaemia (see section 4.2). Hypophosphatemia reactions were Grade ≥3 in 12.3% of participants in the FIGHT-202 study. None of the events of 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 (see section 4.8 of the Treatment Protocol for HCP). This can

moderately influence the ability to drive and use machines (see section 4.8 of the Treatment Protocol for HCP).

Ophthalmological examination, including optical coherence tomography (OCT) should be performed prior to initiation of therapy and every two months for the first six months of treatment, every three months thereafter, and urgently at any time for visual symptoms. For serous retinal detachment reactions, the dose modification guidelines should be followed (see section 4.2 of the Treatment Protocol for HCP).

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 of the Treatment Protocol for HCP). Patients should be treated with ocular demulcents as needed.

Embryo-foetal toxicity

Based on the mechanism of action and findings in an animal reproduction study (see section 5.3 of the Treatment Protocol for HCP), pemigatinib can cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus. Female patients require a negative pregnancy test prior to initiation of treatment with pemigatinib.

Women of childbearing potential should be advised to use effective contraception during treatment with pemigatinib and for one 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 one week after the last dose (see section 4.6 of the Treatment Protocol for HCP).

Increased serum creatinine

Pemigatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine (see section 4.8 of the Treatment Protocol for HCP). Alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed.

Combination with strong CYP3A4 inhibitors

Concomitant use of pemigatinib with strong CYP3A4 inhibitors should be avoided (see sections 4.2 and 4.5 of the Treatment Protocol for HCP). Patients should be advised to avoid eating grapefruit or drinking grapefruit juice while using this medication.

Combination with strong or moderate CYP3A4 inducers

Concomitant use of pemigatinib with strong or moderate CYP3A4 inducers is not recommended (see sections 4.5 of the Treatment Protocol for HCP).

CNS metastasis
Untreated or progressing brain/CNS metastasis were not allowed in the study, so efficacy in this population has not been evaluated., The blood-brain barrier penetration of pemigatinib is expected to be low (see section 5.3 of the Treatment Protocol for HCP).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other agents 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 pemigatinib 13.5 mg once daily should have their dose reduced to 9 mg once daily and patients who are taking pemigatinib 9 mg once daily should have their dose reduced to 4.5 mg once daily (see section 4.2 of the Treatment Protocol for HCP). Where possible, concurrent use of strong CYP3A4 inhibitors (e.g., grapefruit/grapefruit juice, 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 of the Treatment Protocol for HCP). Concomitant use of pemigatinib with St John's wort is contraindicated (see section 4.3 of the Treatment Protocol for HCP).

Physiologically-based pharmacokinetic (PBPK) modelling showed that co-administration of a moderate CYP3A4 inducer (e.g., bosentan, efavirenz, etravirine, phenobarbital, primidone) decreased the pemigatinib AUC geometric mean by more than 50 %, which may decrease the efficacy of pemigatinib. Where possible, concurrent use of moderate CYP3A4 inducers should be avoided during treatment with pemigatinib. If needed, moderate enzyme inducers (e.g., efavirenz) should be used under close surveillance.

Effects of pemigatinib on other agents

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 narrow therapeutic index.

Effect of Pemigatinib on Transporters
Pemigatinib is an inhibitor of P-gp, OCT2, and MATE1. 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

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. Women of childbearing potential and males with female partners of childbearing potential should use an effective method of contraception during treatment with pemigatinib and for one 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 animal have shown reproductive toxicity (see section 5.3 of the Treatment Protocol for HCP). Pemigatinib is not recommended

during pregnancy and in women of childbearing potential not using contraception. A negative pregnancy test should be obtained prior to the initiation of treatment with pemigatinib.

Breast-feeding

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

Fertility

There are no data on the impact of pemigatinib on human fertility. Dedicated 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 a 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 of the Treatment Protocol for HCP).

4.8 Undesirable effects

Summary of the safety profile

The safety of pemigatinib was evaluated in 146 patients who received at least one dose of pemigatinib in the pivotal FIGHT-202 study. Participants received pemigatinib on a 14 days on followed by 7 days off schedule at a starting dose of 13.5 mg daily. The median duration of exposure, including scheduled dose holds, was 181.0 days (range: 7–730 days).

The most common adverse reactions were hyperphosphataemia (60.5%), alopecia (49.7%), diarrhoea (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%), hypophosphataemia (23.1%), dry skin (21.8%), and palmar-plantar erythrodysaesthesia syndrome (16.3 %).

Serious TEAEs occurred in 45% of patients in FIGHT-202. The most frequently reported serious TEAEs were abdominal pain and pyrexia (4.8% each) and cholangitis and pleural effusion (3.4% each). Six participants (4.1%) had serious TEAEs with a fatal outcome as of the data cut-off date (22 MAR 2019): failure to thrive in 2 participants and bile duct obstruction, cholangitis, sepsis, and pleural effusion in a single participant each.

Tabulated list of adverse reactions

Adverse reactions are presented in table 4. Frequency categories are very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Adverse reactions observed in FIGHT-202 study – frequency reported by incidence of treatment emergent events

System organ class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Very common	Hyponatraemia, Hyperphosphatemia[a], Hypophosphatemia[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
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 Hyperphosphatemia and Blood phosphorous increased
[b] Includes Hypophosphatemia 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 usually develops within the first 14 days and was reported in 59.4% of all patients treated with pemigatinib across all cancers (All Cancer Population; N=466). Hyperphosphataemia events of Grade ≥3 severity occurred in four participants, and serious events of hyperphosphataemia occurred in two participants in the All Cancer Population. All but one of these events, which occurred in five unique participants, had resolved as of the data cut-off date. Hyperphosphataemia led to dose interruption in 3.6% and dose reduction in 0.9% of patients (All Cancer Population).

Hypophosphataemia
The incidence of hypophosphataemia was 14.4% in the All Cancer Population (N=466). Hypophosphataemia was the second most common Grade ≥3 TEAE among participants in the All Cancer Population (6.2%). No TEAEs of hypophosphatemia were serious or led to discontinuation of pemigatinib, and no event led to dose reduction. A total of three participants interrupted pemigatinib due to a TEAE of hypophosphataemia and two of the three events had resolved as of the data cut-off date.

Serous retinal detachment
Serous retinal detachment occurred in 7.5% of all patients treated with pemigatinib (All Cancer Population; N=466). Reactions were generally Grade 1 or 2 in severity; Grade ≥3 events included detachment of retinal pigment epithelium in 1 participant (0.2%) and retinal detachment in 2 participants (0.4%). Serous retinal detachment events that led to discontinuation of pemigatinib in 2 participants (0.4% of the All Cancer Population) were ongoing at the time of the data cut-off date (22 MAR 2019). Recommendations for management of serous retinal detachment are provided in sections 4.2 and 4.4 of the Treatment Protocol for HCP.

Other ocular disorders
The most frequently occurring eye disorder, other than serous retinal detachment, was dry eye (19.5% in the All Cancer Population). This was generally Grade 1 or 2 in severity. A total of seven participants (1.5%) in the All Cancer Population had one or more ocular TEAEs, other than serous retinal detachment, of Grade ≥3 severity. These events included dry eye and punctate keratitis in two participants each and corneal thinning, eyelid disorder, eye pain, growth of eyelashes, keratitis, retinal artery occlusion, ulcerative keratitis, and vision blurred in one participant each. Most of these events had resolved or were improving at the time of the data cut-off dates.

Nail disorders
Nail toxicity events, most frequently reported as events of nail discoloration, onychomadesis, and onycholysis, occurred in 35% of the All Cancer Population (N=466), and the time-to-first event was approximately 6.47 months. Events were generally Grade 1 or 2 in severity, and no nail toxicity event was serious or led to pemigatinib discontinuation. Twelve patients (2.6%) had a Grade ≥3 TEAE of nail toxicity (All Cancer Population). Nail toxicity events leading to pemigatinib dose interruption or dose reduction occurred in 4.7% and 3.2% of patients in the All Cancer Population, respectively.

Increased serum creatinine

Pemigatinib may increase serum creatinine due to inhibition of renal transporters OCT2 and MATE1 and may not affect glomerular function. Within the first 21-day cycle of pemigatinib dosing, 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.

Hyponatraemia
Hyponatraemia occurred in 10.3% of the All Cancer Population (N=466). Serious TEAEs of hyponatraemia occurred in 1.9% of the All Cancer Population. The incidence of grade 3 or higher hyponatremia in the All Cancer Population was 5.9% (n=32).

Fractures
In the All Cancer Population, 2.1% of subjects reported a fracture. The events were Grades 1-3 and none were considered related to study drug. Events included vertebral, rib and lower limb fractures. .

Special Populations – Demographic Characteristics

Sex
The overall incidence of TEAEs was generally similar for men and women in the All Cancer Population (n=466). The most frequently occurring TEAEs occurred in higher proportions of women than men: hyperphosphatemia (63% vs. 48%), alopecia (54.5% vs 33.5%), nausea (38% vs 24.5%), and vomiting (28% vs 16%). For ≥ Grade 3 TEAEs, the most frequently occurring events, including hypophosphatemia, hyponatremia, arthralgia, and palmar-plantar erythrodysaesthesia syndrome, were similar for the 2 sex subgroups.

ECOG Performance Status
The incidences of ≥ Grade 3 TEAEs, serious TEAEs, and serious TEAEs with a fatal outcome increased with worsening baseline ECOG performance status. The limited number of participants in the worst performance status subgroup (ECOG PS 2) precluded meaningful comparisons of events.

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 as instructed (see Additional Information).

4.9 Overdose

There is no information on overdosage of pemigatinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pemigatinib is a small molecule kinase inhibitor of FGFR1, 2 and 3. Pemigatinib inhibited FGFR 1-3 phosphorylation and signalling and decreased cell viability in cell lines expressing FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements.

Pharmacodynamic effects

Serum phosphate
Pemigatinib increased serum phosphate level as a consequence of FGFR inhibition. Pemigatinib at the proposed dose was associated with mean increases in blood phosphorus levels of 2 to 3 mg/dL (to ~6 mg/dL), which returned to baseline or below baseline after each 1-week dose holiday in participants on intermittent therapy and which remained steady with a downward trend over time in participants on continuous therapy.

Results of QTc analysis

Pemigatinib did not exhibit a large effect (ie, > 20 ms) on the QTc interval. There is no significant relationship between pemigatinib plasma concentration and change in QTcF. Pemigatinib at doses up to 20 mg QD did not have a relevant effect on cardiac conduction (ie, the PR and QRS intervals).

Clinical studies

FIGHT-202 was a multicentre, open-label, single-arm study to evaluate the efficacy and safety of pemigatinib in previously treated patients with locally advanced unresectable or metastatic cholangiocarcinoma. The efficacy population consists of 107 patients (105 patients with intrahepatic disease) that had progressed after at least one prior therapy and who had FGFR2 fusion or rearrangement, as determined by the test performed at a central laboratory.

Patients received pemigatinib in 21-days cycles consisting of 13.5 mg once daily oral dosing for 14 days, followed by 7 days off therapy. Pemigatinib 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 to 77 years), 31.5 % were ≥65 years, 60.7 % were female, and 73.8 % were Caucasian. 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 one prior line of systemic therapy, 27.1 % had two prior lines of therapy, and 12.1 % had three or more prior lines of therapy. A total of 94% of patients had received prior platinum-based therapy, including 76 % with prior gemcitabine/cisplatin.

In tumour samples from participants in Cohort A (N=107), FGFR2 rearrangements and fusion partners were highly variable, with 56 unique FGFR2 rearrangement or fusion partners identified. The most frequently identified FGFR2 rearrangement or fusion was FGFR2-BICC1 (n = 31).

The median time to response was 2.7 months (range: 0.7–6.9 months). Efficacy results are summarised in Table 5.

Table 5. Efficacy results Cohort A (FGFR2 fusion or rearrangement) from FIGHT-202

Efficacy outcome	**Efficacy evaluable population (N=107)**
ORR (95 % CI)	35.5% (26.5, 45.4)
Complete response (N)	2.8% (3)
Partial response (N)	32.7% (35)
Median duration of response (months) (95 % CI)[a]	9.13 (6.01, 14.49)
Patients with DOR ≥ 6 months %(n)	63% (24)
Patients with DOR ≥ 12 months %(n)	18% (7)
Updated duration of response (30 August 2019) ORR- CR+PR CI= Confidence Interval NE= Not Evaluable 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, 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.

Paediatric population

There are no results of studies with pemigatinib in any subsets of the paediatric population in the treatment of cholangiocarcinoma. See section 4.2 of the Treatment Protocol for HCP for information in paediatric use.

5.2 Pharmacokinetic properties

Pemigatinib exhibits linear pharmacokinetics (PK) in the dose range of 1 to 20 mg. Following oral administration of pemigatinib 13.5 mg once daily, steady - state was reached by four days with a geometric mean accumulation ratio of 1.6. The geometric mean steady-state AUC0-24h 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 PK 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 241 L (35.1%) in patients with cancer based on a population PK analysis.

Biotransformation

Pemigatinib is predominantly metabolised by CYP3A4 in vitro. Following oral administration of a single, radiolabelled, 13.5 mg 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 radiolabelled 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 PK 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 haemodialysis) and End Stage Renal Disease (ESRD) (GFR <30 mL/min and on haemodialysis). Comparing the exposures in subjects with the severe renal impairment to subjects with normal renal function, the geometric mean ratios (90% CI) were 64.6% (44.1%, 94.4%) for C_{max} and 159% (95.4%, 264%) for AUC0 to ∞. Comparing the exposures in the subjects with ESRD before haemodialysis to subjects with normal renal function, the geometric mean ratios (90% CI) was 77.5% (51.2%, 118%) for C_{max} and 76.8% (54.0%, 109%) for AUC0 to ∞. In the comparison of pemigatinib exposures in participants with ESRD after haemodialysis to subjects with normal renal function, the geometric mean ratios (90% CI) were 90.0% (59.3%, 137%) for C_{max} and 91.3% (64.1%, 130%) for AUC0 to ∞. Based on the population PK analysis, mild and moderate renal impairment do not have clinically important effects on the systemic exposure of pemigatinib.

Hepatic impairment

The effect of hepatic impairment on the PK 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. Comparing the exposures in the subjects with moderate hepatic impairment to subjects with normal hepatic function, the geometric mean ratios (90% CI) were 96.7% (59.4%, 157%) for C_{max} and 146% (100%, 212%) for AUC0 to ∞. Comparing the exposures in the subjects with severe hepatic impairment to subjects with normal hepatic impairment, the GMR (90% CI) was 94.2% (68.9%, 129%) for C_{max} and 174% (116%, 261%) for AUC0 to ∞. Based on the population PK analysis, mild and

moderate hepatic impairment do not have clinically important effects on the systemic exposure of pemigatinib.

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 CYP1A2and 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, was not 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.

Developmental toxicity

In rats, administration of pemigatinib at ≥0.3 /kg/day during the period of organogenesis resulted in 100% post-implantation 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.

Blood-brain penetration
In male rats given an IV infusion of pemigatinib for four hours, the average brain homogenate concentration of pemigatinib was 9% of the corresponding total plasma concentration at four hours and the

average cerebral spinal fluid concentration was 13% of the corresponding unbound plasma concentration at four hours, suggesting limited penetration across the blood-brain barrier in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life of pemigatinib is 48 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with child-resistant closure.

Each bottle will contain 14 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. SCIENTIFIC OPINION HOLDER

Incyte Biosciences UK Ltd
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Randalls Way
Leatherhead KT22 7TW
01372 611 240

8. EAMS NUMBER

42338/0002

9. DATE OF SCIENTIFIC OPINION

Additional information

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm patient eligibility within the scheme. Completed form should be sent to EAMS@Incyte.com. Upon receipt of a completed application form, Incyte will assign a unique patient ID and provide information regarding FGFR2 fusion testing. If patient is confirmed to have the FGFR2 fusion, Incyte will arrange safety training and each prescribing physician will also be provided with a physician pack containing all the relevant documents, including the adverse events reporting form, needed to manage patients receiving pemigatinib under EAMS.

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You should also report side effects to Incyte Biosciences UK Ltd by emailing the Incyte Drug Call Centre at eumedinfo@incyte.com or calling 00 800 000 27423. By reporting side effects, you can help provide more information on the safety of this medicine.