Summary Report of Benefit-Risk Assessment

PEMAZYRE TABLETS 4.5 MG, 9 MG AND 13.5 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Pemigatinib
Product Registrant	Specialised Therapeutics Asia Pte Ltd
Product Registration Number	SIN17042P, SIN17043P, SIN17044P
Application Route	Abridged evaluation
Date of Approval	9 July 2024

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A INTRODUCTION

Pemazyre Tablets 4.5 mg, 9 mg and 13.5 mg are indicated for the treatment adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after at least one prior line of systemic therapy.

Pemazyre contains pemigatinib, a small molecule kinase inhibitor of FGFR1, 2 and 3. It inhibits FGFR 1-3 phosphorylation and signalling and decreases cell viability in cancer cell lines with activating FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements that resulted in constitutive activation of FGFR signalling.

Pemazyre is available as tablets containing 4.5 mg, 9 mg and 13.5 mg of pemigatinib. Other ingredients in the tablet core are magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, pemigatinib, is manufactured at Carbogen Amcis AG, Bubendorf, Switzerland. The drug product, Pemazyre, is manufactured at Lonza Tampa LLC, Florida, United States.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits have been considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is low density polyethylene (LDPE) liner in double LDPE bags. The LDPE bags are stored in high-density polyethylene (HDPE) drum and lid. The stability data presented was adequate to support the storage of the drug substance at 25^{o}C with a re-test period of 36 months.

Drug product:

The tablets are manufactured using a direct compression approach which is considered a standard manufacturing process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30^{o}C. The container closure system is an Aclar/PVC film with paper/ heat sealable aluminum foil lid (Aclar/PVC-Alu/paper) containing 14 tablets/blister.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy data of pemigatinib in the treatment of CCA was based on one pivotal study FIGHT-202. Study FIGHT-202 was a Phase 2, multicentre, open-label, single-arm study conducted in patients with locally advanced/metastatic or surgically unresectable cholangiocarcinoma (CCA) who had progressed on at least 1 line of prior systemic therapy.

Participants were assigned to 1 of 3 cohorts based on tumour FGF/FGFR status. Cohort A included patients with FGFR2 rearrangement or fusions, and is the cohort of interest for this application. Pemigatinib was administered in 21-day cycles at a dosage of 13.5 mg once daily for 14 days, followed by 7 days off therapy, until disease progression or unacceptable toxicity. Given the absence of a current standard-of-care treatment for this rare disease, a single-arm study design was considered acceptable for demonstrating efficacy.

The primary endpoint of the study was the objective response rate (ORR), defined as a complete response (CR) or partial response (PR), as determined by an independent review committee (IRC) based on RECIST v1.1. Objective assessment of tumour status using radiologic imaging was performed every 2 cycles (6 weeks) through Cycle 4 and every 3 cycles (9 weeks) thereafter starting with Cycle 7. Based on historical ORR data from published literature in CCA patients, the study was predetermined to be considered positive if the lower limit of the 95% CI for ORR exceeded 15%.

Duration of response (DOR) was the key secondary endpoint. Other secondary endpoints included progression-free survival (PFS) and overall survival (OS).

The efficacy population in Cohort A consisted of 108 patients, 107 of whom had 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. The median age of the patients was 55.5 years (range: 26 to 77 years), with 23.1% being 65 years or older. Additionally, 61.1% were female, 73.1% were Caucasian, and 11.1% were Asian. All patients had received at least 1 prior line of systemic therapy, with 27.8% having 2 prior lines of therapy, and 12.0% having 3 or more prior lines of therapy. Furthermore, 95% of patients had received prior platinum-based therapy, including 78% with prior gemcitabine/cisplatin.

At the initial data cut-off on 22 March 2019, the ORR in Cohort A was 35.5% (95% CI: 26.50, 45.35) based on IRC-assessed, confirmed tumour responses. Of these patients, 2.8% had CR and 32.7% had PR. Updated data as of 7 April 2020 showed an ORR of 37.0% (95% CI: 27.94, 46.86), with 3.7% having CR and 33.3% with PR. Efficacy was maintained with an ORR of

37.0% (95% CI: 27.94, 48.86), with 2.8% having CR and 34.3% with PR, as of the final data cut-off on 8 July 2021.

As of 8 July 2021, the median DOR among 40 patients in Cohort A with confirmed tumour responses was 9.13 months (95% CI: 6.01, 14.49). The median PFS based on IRC assessment was 7.03 months (95% CI: 6.08, 10.48) and the median OS was 17.48 months (95% CI: 14.36, 22.93).

Table of summary of efficacy results

Endpoint	Cohort A (N=107) (initial data cut-off 22 March 2019)	Cohort A (N=108) (8 July 2021 cut-off)
ORR, n (%)	38 (35.5)	40 (37.0)
95% CI	26.50, 45.35	27.94, 46.86
CR, n (%)	3 (2.8)	3 (2.8)
PR, n (%)	35 (32.7)	37 (34.3)
Median DOR (months) (95% CI)	7.49 (5.65, 14.49)	9.13 (6.01, 14.49)
Median PFS (months) (95% CI)	6.93 (6.18, 9.59)	7.03 (6.08, 10.48)
Median OS (months) (95% CI)	21.06 (14.82, NE)	17.48 (14.36, 22.93)

ORR: Overall response rate; CR: Complete response; PR: Partial response; DOR: Duration of response; PFS: Progression-free survival; OS: Overall survival; NE: Not evaluable

Overall, while the efficacy of pemigatinib based on the primary endpoint ORR was modest, the result was numerically higher than that reported for current chemotherapy in the second-line setting (ORR of 5% and median PFS of 4 months for FOLFOX). The ORR was considered clinically meaningful in the context of a rare, life-threatening disease with no approved treatment options. An ongoing Phase 3 study INCB-54828-302 comparing the efficacy of pemigatinib vs gemcitabine plus cisplatin in the first-line setting is required to be submitted to confirm the clinical benefit of pemigatinib.

D ASSESSMENT OF CLINICAL SAFETY

The overall safety population comprised 147 patients enrolled in Study FIGHT-202 for a median duration of exposure of 181 days (as of 8 July 2021 data cut-off).

Summary of safety (FIGHT-202)

Category, n (%)	Cohort A (n=108)	All patients (n=147)
TEAEs		
All	108 (100.0)	147 (100.0)
Related	102 (94.4)	135 (91.8)
≥ Grade 3 TEAE	72 (66.7)	101 (68.7)
SAE	46 (42.6)	68 (46.3)

TEAE leading to treatment discontinuation	7 (6.5)	15 (10.2)
Fatal TEAE	3 (2.8)	6 (4.1)

The most frequently reported treatment-emergent adverse events (TEAEs) in patients from Cohort A were alopecia (59.3%), hyperphosphataemia (55.6%), diarrhoea (53.7%), fatigue (46.3%), nausea (42.6%), stomatitis and constipation (42.6% each). Other common TEAEs (>30%) included dysgeusia (41.7%), dry mouth (38.9%), dry eye (35.2%), arthralgia (34.3%), and vomiting (33.3%).

The most commonly reported ≥ Grade 3 TEAEs (>5%) in patients from Cohort A were hypophosphataemia (14.8%), stomatitis (9.3%), arthralgia (6.5%), palmar-plantar erythrodysaesthesia syndrome (6.5%) and abdominal pain (5.6%).

Serious adverse events (SAEs) were reported in 42.6% of patients which included abdominal pain (3.7%), pyrexia (4.6%) and cholangitis (4.6%). TEAEs leading to pemigatinib discontinuation occurred in 6.5% of patients, and 3 patients (2.8%) had fatal TEAEs; failure to thrive in 2 patients and bile duct obstruction in one patient. These events were not considered related to pemigatinib by the investigator.

The adverse events of special interest (AESI) with pemigatinib included hyperphosphataemia and serous retinal detachment. Hyperphosphataemia was the most common TEAE in Study FIGHT-202 (60.5%). None of these TEAEs were ≥ Grade 3 in severity, SAEs, or led to discontinuation of pemigatinib. Dose interruption occurred in 1.4% of patients and dose reduction in 0.7% of patients. Recommendations for management of hyperphosphataemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required.

Serous retinal detachment events occurred in 4.8% of patients in Study FIGHT-202. Events were Grade 1 or 2 in severity and nonserious with the exception of 1 Grade 3 event of retinal detachment which was considered unrelated to pemigatinib by the investigator. No events led to dose reduction or discontinuation of pemigatinib. 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.

Overall, the safety profile of pemigatinib was consistent with its mechanism of action and the TEAEs are generally manageable, with appropriate warnings and dose modification recommendations included in the product labelling to mitigate the known risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

CCA is a rare and aggressive cancer for which there is significant unmet need for effective therapies, especially in the second-line setting, where there are no available treatments. Success with chemotherapies and targeted therapies in the second-line and above setting in molecularly unselected biliary tract cancers has been limited.

The clinical efficacy of pemigatinib was based on one pivotal Phase 2, single-arm, open-label study in patients with FGFR-rearranged CCA who have been previously treated with at least 1 prior therapy. ORR achieved was 37% with a robust duration of response of 9 months, which was numerically higher than that achieved for existing second-line therapy.

The most common adverse reactions occurring with pemigatinib were hyperphosphataemia, alopecia, diarrhoea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphataemia, back pain, and dry skin. Ocular toxicity including serous retinal detachment and hyperphosphataemia are important risks of pemigatinib. To ensure adequate risk mitigation measures, relevant warnings and precautions including recommendations for ophthalmological examination as well as dose modifications are highlighted in the product labelling.

Considering the aggressive nature of the disease and the unmet medical need, the benefits of pemigatinib in the proposed indication outweigh the known safety risks. The registrant is required to submit the final study report of the Phase 3 study INCB-54828-302 as a post-registration condition to further confirm the efficacy and safety of pemigatinib in the treatment of CCA.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk of Pemazyre for the treatment of locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy was deemed favourable and approval of the product registration was granted on 9 July 2024.

APPROVED PACKAGE INSERT AT REGISTRATION

PEMAZYRE® (PEMIGATINIB) TABLETS

1 NAME OF THE MEDICINE

Pemigatinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PEMAZYRE 4.5 mg tablets
Each tablet contains 4.5 mg of pemigatinib.

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

PEMAZYRE 13.5 mg tablets
Each tablet contains 13.5 mg of pemigatinib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablet (immediate release, uncoated).

PEMAZYRE 4.5 mg tablets
Round (5.8 mm), white to off-white tablet debossed on one side with "I" and "4.5" on the reverse.

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

PEMAZYRE 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 THERAPEUTIC INDICATIONS

Pemigatinib is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after at least one prior line of systemic therapy. The decision to approve this indication has been made on the basis of overall response rate (ORR) and duration of response (DOR).

4.2 DOSE 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 PEMAZYRE therapy. Assessment for FGFR2 fusion positivity in tumour specimen should be performed with an appropriate diagnostic test.

Dosage

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

If a dose of PEMAZYRE 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.

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. PEMAZYRE may be taken with or without food.

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 mineralisation, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias (see Section 4.4 Special warnings and precautions for use).

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 Special warnings and precautions for use).

Dose adjustment due to drug interaction

Concomitant use of PEMAZYRE with strong or moderate CYP3A4 inhibitors
If co-administration with a strong or moderate CYP3A4 inhibitor is necessary, the dose of patients who are taking 13.5 mg PEMAZYRE once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg PEMAZYRE once daily should be reduced to 4.5 mg once daily. Grapefruit juice should be avoided during treatment with pemigatinib. Refer Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions.

Management of toxicities

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

PEMAZYRE dose reductions levels are summarised in Table 1.

Table 1: Recommended PEMAZYRE 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 should be permanently discontinued if patient is unable to tolerate 4.5 mg PEMAZYRE once daily.

Dose modifications for hyperphosphataemia are provided in Table 2.

Table 2: Dose modifications for hyperphosphataemia

Adverse reaction	PEMAZYRE dose modification
> 5.5 mg/dL - ≤ 7 mg/dL	• PEMAZYRE should be continued at current dose.
> 7 mg/dL - ≤ 10 mg/dL	• PEMAZYRE 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. • PEMAZYRE should be withheld if levels do not return to < 7 mg/dL within 2 weeks of starting a phosphate lowering therapy. PEMAZYRE 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, PEMAZYRE should be reduced 1 dose level.
> 10 mg/dL	• PEMAZYRE 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. • PEMAZYRE should be withheld if levels continue > 10 mg/dL for 1 week. PEMAZYRE 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, PEMAZYRE 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	PEMAZYRE dose modification
Asymptomatic	• PEMAZYRE should be continued at current dose. Monitoring should be performed as described in Section 4.4 Special warnings and precautions for use.
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	• PEMAZYRE should be withheld until resolution. If improved on subsequent examination, PEMAZYRE should be resumed at the next lower dose level. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of PEMAZYRE 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	• PEMAZYRE should be withheld until resolution. If improved on subsequent examination, PEMAZYRE may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of PEMAZYRE should be considered, based on clinical status.
Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	• PEMAZYRE should be withheld until resolution. If improved on subsequent examination, PEMAZYRE may be resumed at 2 dose levels lower. • If it recurs, symptoms persist or examination does not improve, permanent discontinuation of PEMAZYRE should be considered, based on clinical status.

Special populations

Elderly patients
The dose of PEMAZYRE is the same in elderly patients as younger adult patients (see Section 5.1 Pharmacodynamic properties).

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 PEMAZYRE once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg PEMAZYRE once daily should be reduced to 4.5 mg once daily (see Section 5.2 Pharmacokinetic properties).

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 PEMAZYRE once daily should be reduced to 9 mg once daily and the dose of patients who are taking 9 mg PEMAZYRE once daily should be reduced to 4.5 mg once daily (see Section 5.2 Pharmacokinetic properties).

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

4.3 CONTRAINDICATIONS

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

Concomitant use with St John's wort (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperphosphataemia

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

Recommendations for management of hyperphosphataemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see Section 4.2 Dose and method of administration).
Phosphate-lowering therapy was used by 19.0 % of patients during treatment with PEMAZYRE (see Section 4.8 Adverse effects (undesirable effects)).

Hypophosphataemia

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 4.2 Dose and method of administration). 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 mineralisation.

Serous retinal detachment

PEMAZYRE can cause serous retinal detachment reactions, which may present with symptoms such as blurred vision, visual floaters, or photopsia (see Section 4.8 Adverse effects (undesirable effects)). This can moderately influence the ability to drive and use machines (see Section 4.7 Effects on 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 (see Section 4.2 Dose and method of administration).

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 PEMAZYRE 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

PEMAZYRE can cause dry eye (see Section 4.8 Adverse effects (undesirable effects)). Patients should use ocular demulcents, in order to prevent or treat dry eye, as needed.

Embryo-fetal toxicity

Based on the mechanism of action and findings in an animal reproduction study (see Section 5.3 Preclinical safety data), PEMAZYRE can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the fetus. 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 PEMAZYRE and for at least 1 week after the last dose (see Section 4.6 Effects on fertility, pregnancy and lactation).

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 Adverse effects (undesirable effects)). Alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed.

Combination with strong and moderate CYP3A4 inhibitors

Concomitant use of PEMAZYRE with strong and moderate CYP3A4 inhibitors requires dose adjustment (see Sections 4.2 Dose and method of administration and 4.5 Interactions with other medicines and other forms of interactions). 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 PEMAZYRE with strong or moderate CYP3A4 inducers is not recommended (see Section 4.5 Interactions with other medicines and other forms of interactions).

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 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 Fertility, pregnancy and lactation).

Pregnancy test

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

Use In the elderly

Refer to Section 4.2 Dose and Method of Administration and Section 5.1 Clinical trials.

Paediatric use

The safety and efficacy of PEMAZYRE in patients less than 18 years of age has not been established. No data is available.

Effects on laboratory tests

See Section 4.8 Adverse effects (undesirable effects).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on PEMAZYRE

Strong and Moderate 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 PEMAZYRE.

Concomitant use of a strong or moderate CYP3A4 inhibitor with PEMAZYRE increases pemigatinib plasma concentrations, which may increase incidence and severity of adverse reactions. Avoid concomitant use of strong and moderate CYP3A4 inhibitors with PEMAZYRE. Reduce PEMAZYRE dosage if concomitant use of strong and moderate CYP3A4 inhibitors cannot be avoided.

Patients who are taking 13.5 mg PEMAZYRE once daily should have their dose reduced to 9 mg once daily and patients who are taking 9 mg PEMAZYRE once daily should have their dose reduced to 4.5 mg once daily (see Section 4.2 Dose and method of administration).

Strong and Moderate CYP3A4 Inducers

A strong CYP3A4 inducer (rifampicin 600 mg once daily) decreased pemigatinib AUC geometric mean by 85 % (90 % CI of 84 %, 86 %), which may decrease the efficacy of PEMAZYRE.

Concomitant use of PEMAZYRE with a strong or moderate CYP3A4 inducer decreases plasma concentrations, which may reduce the efficacy of PEMAZYRE. Avoid concomitant use of strong and moderate CYP3A4 inducers with PEMAZYRE.

Concurrent use of strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin) should be avoided during treatment with PEMAZYRE (see Section 4.4 Special warnings and precautions for use).

Concomitant use of PEMAZYRE with St John's wort is contraindicated (see Section 4.3 Contraindications*).* 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 PPI) 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.

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 PEMAZYRE 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 PEMAZYRE with P-gp substrates (e.g. digoxin, dabigatran, colchicine) may increase their exposure and thus their toxicity. PEMAZYRE 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, CYP2B6 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the impact of PEMAZYRE on human fertility. Animal fertility studies have not been conducted with pemigatinib. In repeated dose toxicity studies, oral administration of pemigatinib did not result in any dose-related adverse effects on male and female reproductive organs. Based on the pharmacology of pemigatinib, impairment of male and female fertility cannot be excluded.

Use in pregnancy – Pregnancy Category D

There are no available data from the use of PEMAZYRE in pregnant women. An embryofetal developmental study in rats has shown reproductive toxicity. Once daily oral administration of pemigatinib during the period of organogenesis resulted in 100 % post implantation loss at doses ≥ 0.3 mg/kg (approximately 0.3 times the human exposure based on AUC at the clinical dose of 13.5 mg). Fetal survival was not affected at 0.1 mg/kg/day; however, once daily oral administration of pemigatinib at the 0.1 mg/kg dose level (approximately 0.1 times the human exposure based on AUC at the clinical dose of 13.5 mg) resulted in an increase in fetal skeletal and visceral malformations, major blood vessels variations, reduced ossification and decrease fetal body weight.

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

Contraception in men and women/women of childbearing potential

Based on findings in an animal study and its mechanism of action, pemigatinib can cause fetal harm when administered to a pregnant woman. Women of childbearing potential 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. Since the effect of PEMAZYRE 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.

Use in lactation

There are no data on 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse reactions such as fatigue and visual disturbances have been associated with PEMAZYRE. Therefore, caution should be recommended when driving or operating machines (see Section 4.4 Special warnings and precautions for use).

4.8 ADVERSE EFFECTS (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 palmarplantar erythrodysaesthesia syndrome (16.3 %).

The most common serious adverse reactions were hyponatremia (2.0 %) and blood creatinine increase (1.4 %). No serious adverse reaction led to pemigatinib dose reduction. One serious adverse reaction of hyponatremia (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) 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, 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 Dose and method of administration and 4.4 Special warnings and precautions for use.

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 Dose and method of administration and 4.4 Special warnings and precautions for use.

Description of selected adverse events

Acute Kidney Injury

Serious and ≥ Grade 3 events of acute kidney injury occurred in 2% of patients treated with pemigatinib, respectively. Acute kidney injury led to dose interruption and discontinuation of pemigatinib in 1.4% of patients, respectively.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at https://www.hsa.gov.sg/adverse-events.

4.9 OVERDOSE

There is no information on overdose of PEMAZYRE.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EN02

Pemigatinib is a small molecule kinase inhibitor of FGFR1, 2 and 3 with IC_{50} values of less than 2 nM. Pemigatinib also inhibited FGFR4 *in vitro* at a concentration approximately 100 times higher than those that inhibit FGFR1, 2, and 3. It inhibits FGFR 1-3 phosphorylation and signalling and decreases cell viability in cancer cells lines with activating FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements that resulted in constitutive activation of FGFR signalling. FGFR2 fusions/rearrangements are strong oncogenic drivers and are the most common FGFR alteration occurring, almost exclusively, in 10-16 % of intrahepatic cholangiocarcinoma (CCA). Constitutive FGFR signalling can support the proliferation and survival of malignant cells. Pemigatinib exhibited anti – tumour activity in mouse xenograft models of human tumours with FGFR1, FGFR2, or FGFR3 alterations resulting in constitutive FGFR activation including a patient- derived xenograft model of cholangiocarcinoma that expressed an oncogenic FGFR2-Transformer-2 beta homolog (TRA2b) fusion protein.

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 Dose and method of administration, 4.4 Special warnings and precautions for use and 4.8 Adverse effects (undesirable effects)).

Clinical trials

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. Eighty-six percent of patients had in-frame FGFR2 gene fusions and the most commonly identified FGFR2 fusion was FGFR2-BICC1 (34%). Fourteen percent of patients had other FGFR2 rearrangements that could not be confidently predicted to be in-frame fusions, including rearrangements without an identifiable partner gene.

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-five 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)
Stable disease (N)	49 % (45.4)
Median Disease control rate (95% CI)	82.2% (73.7, 89.0)
Median progression free survival (months) (95% CI)	7.03 (6.08, 10.48)
Median Overall. Survival (months) (95% CI)	17.48 (14.42, 22.93)
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.

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 at concentrations ranging from 1 to 10 µM, predominantly to albumin. The estimated apparent volume of distribution was 235 L (60.8 %) in patients with cancer.

Metabolism

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 feces (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 haemodialysis) and End Stage Renal Disease (ESRD) (GFR < 30 mL/min and on haemodialysis). 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 haemodialysis, 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 haemodialysis, 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, PEMAZYRE dose should be reduced for patients with severe renal impairment (see Section 4.2 Dose and method of administration).

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, PEMAZYRE dose should be reduced for patients with severe hepatic impairment (see Section 4.2 Dose and method of administration).

5.3 PRECLINICAL SAFETY DATA

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.

Systemic toxicity

The most prominent findings following repeat-dose oral 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 mineralisation; the findings were observed at exposure levels (AUC) less than at the human exposure at the recommended clinical dose of 13.5 mg. Mineralisation was observed in numerous tissues including kidneys, stomach, arteries, ovaries (monkey only), and eyes (cornea, rat only). Soft tissue mineralisation was not reversible, while physeal and cartilage findings were reversible. In addition, changes of the bone marrow (rats) and kidney lesions were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Sodium starch glycollate (Type A)
Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

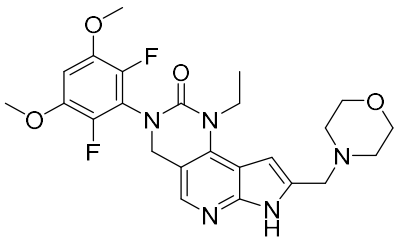
6.4 NATURE AND CONTENTS OF CONTAINER

ALCAR/PVC-Alu/paper blister containing 14 tablets. Carton box containing 14 or 28 tablets.

Not all pack sizes may be marketed.

6.5 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical name: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2*H*-pyrrolo[3',2':5,6]pyrido[4,3-*d*]pyrimidin-2-one

Molecular Formula: $C_{24}H_{27}F_2N_5O_4$

Molecular Weight: 487.5 g/mole

CAS number

1513857-77-6

7 MEDICINE SCHEDULE

PRESCRIPTION ONLY MEDICINE

8 MANUFACTURERS

Lonza Tampa LLC
5415 West Laurel Street,
Tampa, FL 33607 USA

PRODUCT REGISTRATION HOLDER:
Specialised Therapeutics Asia Pte Ltd
1 Harbourfront Avenue,
Keppel Bay Tower, #14-03/07,
Singapore 098632

9 DATE OF REVISION

28th June 2024