PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PR PEMAZYRE™

Pemigatinib tablets
Tablets, 4.5 mg, 9 mg, and 13.5 mg, Oral
Protein Kinase Inhibitor (L01EX20)

PEMAZYRE™ is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

PEMAZYRE™ has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of authorization. For further information for PEMAZYRE™, please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PEMAZYRE™ (pemigatinib) is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement.

Clinical effectiveness of PEMAZYRE™ is based on overall response rate (ORR) and duration of response (DoR) from a single-arm Phase 2 trial in patients with specific FGFR2 rearrangements (see **14 CLINICAL TRIALS**).

Treatment with PEMAZYRE™ should be initiated following confirmation of a FGFR2 fusion or rearrangement using a validated test (see **14 CLINICAL TRIALS**).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see **7 WARNINGS AND PRECAUTIONS**, Special Populations).

1.2 Geriatrics

Geriatrics (≥65 years of age): Of the 146 patients treated with PEMAZYRE™ in study FIGHT-202, 46 (31.5%) were ≥65 years. No overall differences in safety or effectiveness were observed between elderly and younger patients.

2 CONTRAINDICATIONS

PEMAZYRE™ is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients must be selected for the treatment of locally advanced or metastatic cholangiocarcinoma with PEMAZYRE™ based on the confirmation of an FGFR2 fusion or rearrangement by a validated test (see **7 WARNINGS AND PRECAUTIONS, General and 14 CLINICAL TRIALS**).
- Avoid concomitant use of strong or moderate CYP3A4 inhibitors with PEMAZYRE™. Reduce the PEMAZYRE™ dose if co-administration with a strong or moderate CYP3A inhibitor cannot be avoided (see **9 DRUG INTERACTIONS**).
- Avoid concomitant use of strong or moderate CYP3A4 inducers with PEMAZYRE™ (see **9 DRUG INTERACTIONS**).

Dose reduction of PEMAZYRE™ is required in patients with severe renal or hepatic impairment (see **4 DOSAGE AND ADMINISTRATION, Special Populations**).

Risk management for hyperphosphatemia

- In all patients, initiate a low phosphate diet when phosphate level is >5.5 mg/dL and consider adding a phosphate lowering therapy when level is >7 mg/dL. Adjust the dose of phosphate lowering therapy until phosphate level returns to <7 mg/dL. Consider discontinuing phosphate lowering therapy during PEMAZYRE™ treatment breaks or if phosphate level falls below normal (see Table 1).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of PEMAZYRE™ is 13.5 mg orally once daily for 14 consecutive days followed by 7 days off therapy, in 21-day cycles. Continue treatment until disease progression or unacceptable toxicity.

Health Canada has not authorized an indication for pediatric use (see **1 INDICATIONS, Pediatrics**).

Dose Modifications

The recommended dose reductions for adverse reactions are:

First dose reduction: PEMAZYRE™ 9 mg taken orally once daily, 14 days on, 7 days off therapy.

Second dose reduction: PEMAZYRE™ 4.5 mg taken orally once daily, 14 days on, 7 days off therapy.

Permanently discontinue if unable to tolerate PEMAZYRE™ 4.5 mg once daily.

See Table 1.

Table 1: Dosage Modifications for Toxicities

Guidance for Interruption/Discontinuation of PEMAZYRE™	
Adverse Reaction	**PEMAZYRE™ Dose Modification**
Hyperphosphatemia	
>5.5 mg/dL – ≤7 mg/dL	• Continue PEMAZYRE™ at current dose. • Initiate a low phosphate diet.
>7 mg/dL – ≤10 mg/dL	• Continue PEMAZYRE™ at current dose, continue a low phosphate diet, and initiate phosphate-binding therapy. • Monitor serum phosphate weekly, and adjust dose of phosphate lowering therapy as needed until level returns to <7 mg/dL. • Withhold PEMAZYRE™ if serum phosphate levels do not return to <7 mg/dL within 2 weeks of starting a phosphate lowering therapy. Restart PEMAZYRE™ at the same dose when serum phosphate level returns to <7 mg/dL. • Upon recurrence of serum phosphate at >7 mg/dL with phosphate-lowering therapy, reduce PEMAZYRE™ 1 dose level.
>10 mg/dL	• Continue PEMAZYRE™ at current dose, maintain a low-phosphate diet, and adjust phosphate-binding therapy. • Continue to monitor serum phosphate weekly and adjust dose of phosphate lowering therapy as needed until serum phosphate level returns to <7 mg/dL. • Withhold PEMAZYRE™ if serum phosphate levels continue >10 mg/dL for 1 week. • Restart PEMAZYRE™ 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, permanently discontinue PEMAZYRE™.
Serous Retinal Detachment	
Educational material to assist healthcare professionals with the diagnosis and management of serous retinal detachment is available through the manufacturer.	
Asymptomatic and stable on serial examination	• Continue PEMAZYRE™ at current dose. Monitor as described in Warnings and Precautions (Section 7).
Symptomatic or worsening on serial examination	• Withhold PEMAZYRE™. • If asymptomatic and improved on subsequent examination, resume PEMAZYRE™ at next lower dose level. • If symptoms persist, consider permanent discontinuation of PEMAZYRE™.
Other Adverse Reactions	
Grade 1 or Grade 2	Continue PEMAZYRE™ treatment and treat the toxicity; monitor as medically indicated.

Guidance for Interruption/Discontinuation of PEMAZYRE™	
Grade 3	• Interrupt PEMAZYRE™ up to 2 weeks (14 days) until the toxicity has resolved to ≤Grade 1. • Restart PEMAZYRE™ at next lower dose if adverse reaction resolves within 2 weeks; monitor as medically indicated. • Permanently discontinue PEMAZYRE™ if adverse reaction does not resolve within 2 weeks. • Permanently discontinue PEMAZYRE™ for recurrent Grade 3 adverse reaction after 2 dose reductions.
Grade 4	Permanently discontinue PEMAZYRE™.

Special Populations

Renal impairment: For patients with severe renal impairment (GFR <30 mL/min), the starting dose of PEMAZYRE™ should be reduced to 9 mg. No dose adjustment is required for patients with end stage renal disease who are receiving dialysis (see **10 CLINICAL PHARMACOLOGY, Pharmacokinetics**). No dose adjustment is recommended for patients with mild or moderate renal impairment (glomerular filtration rate (GFR) ≥30 to <90 mL/min estimated by Modification of Diet in Renal Disease (MDRD) equation).

Hepatic impairment: For patients with severe hepatic impairment (total bilirubin > 3 × ULN with any AST), the starting dose of PEMAZYRE™ should be reduced to 9 mg (see **10 CLINICAL PHARMACOLOGY, Pharmacokinetics**). No dose adjustment is recommended for patients with mild (total bilirubin > upper limit of normal (ULN) to 1.5 × ULN or AST > ULN) or moderate hepatic impairment (total bilirubin > 1.5–3 × ULN with any AST).

Pediatric patients (<18 years of age): Health Canada has not authorized an indication for pediatric use.

Geriatric patients (≥65 years of age): No overall differences in efficacy or safety were detected between these patients and in patients <65 years of age. No specific dose adjustments are considered necessary for elderly patients (see **10 CLINICAL PHARMACOLOGY, Pharmacokinetics**).

4.3 Missed Dose

If the patient misses a dose of PEMAZYRE™ by 4 or more hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day. If vomiting occurs any time after taking PEMAZYRE™, the next dose should be taken at the next scheduled time.

5 OVERDOSAGE

There is no information on overdosage with PEMAZYRE™.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/ Composition	Non-medicinal Ingredients
Oral	Tablet 4.5 mg, 9 mg, 13.5 mg	Magnesium stearate, Microcrystalline cellulose, Sodium starch glycolate

PEMAZYRE™ 4.5 mg tablets are round, white to off-white debossed on one side with "I" and "4.5" on the other side.

PEMAZYRE™ 9 mg tablets are oval, white to off-white debossed on one side with "I" and "9" on the other side.

PEMAZYRE™ 13.5 mg tablets are round, white to off-white debossed on one side with "I" and "13.5" on the other side.

PEMAZYRE™ 4.5 mg, 9 mg, and 13.5 mg tablets are available as a 14-day supply provided in blister packs (14 tablets).

7 WARNINGS AND PRECAUTIONS

General

Before taking PEMAZYRE™, patients must have confirmation of an FGFR2 fusion or other rearrangement by a validated test. In the FIGHT-202 clinical trial, qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene, leaving the FGFR2 kinase domain intact (see **14 CLINICAL TRIALS**).

Driving and Operating Machinery

No studies to establish the effects of pemigatinib on the ability to drive and use machines have been conducted. However, eye disorders such as central serous retinopathy have been noted with FGFR inhibitors and with PEMAZYRE™ treatment. If patients experience symptoms affecting their vision, it is recommended that they do not drive or use machines until the effect subsides.

Endocrine and Metabolism

Hyperphosphatemia

An increase in phosphate levels is a pharmacodynamic effect of PEMAZYRE™ (see **10 CLINICAL PHARMACOLOGY, Pharmacokinetics**). Hyperphosphatemia was reported in 59% of all patients treated with PEMAZYRE™ in clinical trials, with a median time to onset of 14 days. Phosphate lowering therapy was used by 29% of patients during treatment with PEMAZYRE™.

Soft tissue mineralization, including cutaneous calcification, calcinosis, and non-uremic calciphylaxis may be associated with hyperphosphatemia and has been observed with PEMAZYRE™ treatment (see **8 ADVERSE REACTIONS**).

Serum phosphate concentrations should be monitored, and a low phosphate diet should be initiated when serum phosphate level is >5.5 mg/dL (see **7 WARNINGS AND PRECAUTIONS**, Monitoring and Laboratory Tests, and **4 DOSAGE AND ADMINISTRATION**, Table 1). Recommendations for additional management of hyperphosphatemia include administration of phosphate-lowering therapy, and dose modification when required. Calcium-based antacids and phosphate-based supplements should be avoided.

Hypophosphatemia

In the FIGHT-202 clinical trial, hypophosphatemia was reported in 22.6% of patients, with ≥Grade 3 reactions in 12.3% of patients. Dose interruption occurred in 1.4% of participants. None of the events were serious, led to discontinuation or to dose reduction.

Severe hypophosphatemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and hemolytic anemia. Discontinuing phosphate-lowering therapy and diet should be considered during pemigatinib treatment breaks or if serum phosphate level falls below normal range.

For patients presenting with hyperphosphatemia or hypophosphatemia, additional close monitoring and follow-up is recommended regarding dysregulation of bone mineralization.

Monitoring and Laboratory Tests

Serum Phosphate

Phosphate concentrations should be assessed 14 days after initiating PEMAZYRE™ and then monitored every 2 cycles (approximately 6 weeks) thereafter. For elevated phosphate concentrations, follow dose modification guidelines in Table 1 (see **4 DOSAGE AND ADMINISTRATION**).

Ocular Testing

Perform ophthalmological examination including visual acuity test, slit-lamp examination, fundoscopy, and OCT prior to initiation of therapy, and every 2 months for the first 6 months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms.

Increased Creatinine

Pemigatinib may increase serum creatinine due to a blockade of tubular secretion via renal transporters OCT2 and MATE1. Within the first treatment cycle of PEMAZYRE™ 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. Alternative markers of renal function should be considered if persistent elevations in serum creatinine are observed.

Ophthalmologic

Serous Retinal Detachment

PEMAZYRE™ can cause serous retinal detachment events, which may present with symptoms such as blurred vision, visual floaters, or photopsia.

Serous retinal detachment events occurred in 7.5% of all patients treated with PEMAZYRE™. Events were generally Grade 1 or 2 (6.9%) in severity and nonserious; ≥ Grade 3 events included detachment of retinal pigment epithelium in 1 patient (0.2%) and retinal detachment in 2 patients (0.4%). Serous retinal detachment events led to discontinuation of PEMAZYRE™ in 2 patients (0.4%). Serous

retinal detachment events leading to PEMAZYRE™ dose interruption occurred in 1.7% of all patients and events leading to dose reduction occurred in 0.4% of patients. In about 50% of the patients with an event, the events were self-limiting or resolved following PEMAZYRE™ interruption, reduction, or discontinuation.

Perform ophthalmological examination including visual acuity test, slit-lamp examination, fundoscopy, and OCT prior to initiation of therapy, and every 2 months for the first 6 months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms.

Educational materials to assist healthcare professionals with the diagnosis and management of serous retinal detachment are available through the manufacturer.

For serous retinal detachment events, follow the dose modification guidelines in Table 1 (see **4 DOSAGE AND ADMINISTRATION**).

Reproductive Health: Female and Male Potential

Fertility

No animal studies have been performed to evaluate whether or not PEMAZYRE™ affects fertility in females or males.

Teratogenic Risk

Based on the mechanism of action and findings in an animal reproduction study, PEMAZYRE™ may cause fetal harm when administered to a pregnant woman. In an embryo-fetal toxicity study, oral administration of pemigatinib to pregnant rats during the period of organogenesis caused malformations and embryo-fetal death at maternal exposures that were less than the human exposure at the maximum recommended human dose based on area under the curve (AUC).

Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PEMAZYRE™ and for 1 month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PEMAZYRE™ and for 1 month after the last dose.

7.1 Special Populations

7.1.1 Pregnant Women

PEMAZYRE™ may cause fetal harm and potential loss of pregnancy when administered to pregnant women. There are no clinical data on the use of PEMAZYRE™ in pregnant women.

Verify pregnancy status of females of reproductive potential prior to initiating PEMAZYRE™. PEMAZYRE™ should not be used during pregnancy. If PEMAZYRE™ is used during pregnancy, or if the patient becomes pregnant while taking PEMAZYRE™, advise the patient of the potential hazard to the fetus and counsel the patient about her clinical and therapeutic options. Advise patients to contact their healthcare professional or if they become pregnant or pregnancy is suspected while being treated with PEMAZYRE™ and up to 1 month afterwards.

7.1.2 Breast-feeding

There are no data on the presence of pemigatinib or its metabolites in human milk or their effects on either the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children with PEMAZYRE™, advise women not to breastfeed during treatment and for 1 month after the final dose.

7.1.3 Pediatrics (<18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics (≥65 years of age)

Of the 146 patients treated with PEMAZYRE™ in study FIGHT-202, 31.5% were 65 years and older. No overall difference in safety was observed between elderly and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reactions Overview

Based on the safety database of 146 patients with previously treated, advanced or metastatic cholangiocarcinoma treated with pemigatinib monotherapy, the most common adverse reactions (≥15%) were hyperphosphatemia, alopecia, diarrhea, fatigue, nail toxicity, dysgeusia, nausea, constipation, stomatitis, dry mouth, decreased appetite, vomiting, dry eye, arthralgia, abdominal pain, hypophosphatemia, dry skin, oedema peripheral, weight decreased, headache, urinary tract infection, dehydration, hypercalcemia, and palmar-plantar erythrodysaesthesia syndrome.

Grade ≥3 adverse events were reported in 64% of patients, most frequently (≥5%) hypophosphatemia (12.3%), arthralgia (6.2%), hyponatremia (5.5%), and stomatitis (5.5%).

Serious adverse events were reported in 45% of patients. The most common serious adverse events (≥2%) were abdominal pain (4.8%), pyrexia (4.8%), cholangitis (3.4%), pleural effusion (3.4%), acute kidney injury (2.1%), cholangitis infective (2.1%), failure to thrive (2.1%), hypercalcemia (2.1%), hyponatremia (2.1%), small intestinal obstruction (2.1%), and urinary tract infection (2.1%).

Dose interruptions and dose reductions of pemigatinib due to adverse events occurred in 43% and 14% of patients, respectively. Dose modifications (interruptions and/or reductions) due to adverse events were most commonly due to stomatitis (7.5%), palmar-plantar erythrodysesthesia syndrome (5.5%), arthralgia (4.8%), and fatigue (4.1%). Permanent discontinuation of pemigatinib due to adverse events occurred in 8.9% of patients, most commonly (≥1%) due to intestinal obstruction and acute kidney injury (2 patients each, 1.4%).

Fatal adverse reactions occurred in 4.1% of patients, including failure to thrive (2 patients, 1.4%), and bile duct obstruction, cholangitis, sepsis, and pleural effusion (1 patient each, 0.7%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety data described below reflect exposure to PEMAZYRE™ in Study FIGHT-202. This was a Phase 2 study of 146 patients with previously treated, advanced, or metastatic cholangiocarcinoma. Patients were treated with PEMAZYRE™ in 21-day cycles consisting of 13.5 mg oral dosing once daily for 14 days on / 7 days off therapy. The median duration of treatment was 181 days (range: 7 to 730 days).

Treatment-emergent adverse events (TEAEs) reported in ≥15% of patients in FIGHT-202 are presented in Table 3.

Table 3: Adverse Reactions (≥15%) in Patients Receiving PEMAZYRE™ in FIGHT-202

	PEMAZYRE™ N=146	
Adverse Reaction	**All Grades[a] (%)**	**Grades ≥3* (%)**
Metabolism and nutrition disorders		
Hyperphosphatemia[b]	60	0
Hypophosphatemia[c]	23	12
Decreased appetite	33	1.4
Dehydration	15	2.1
Hypercalcemia	15	2.1
Skin and subcutaneous tissue disorders		
Alopecia	49	0
Nail toxicity[d]	43	2.1
Dry skin	20	0.7
Palmar-plantar erythrodysaesthesia syndrome	15	4.1
Gastrointestinal disorders		
Diarrhea	47	2.7
Nausea	40	2.1
Constipation	35	0.7
Stomatitis	35	5.5
Dry mouth	34	0
Vomiting	27	1.4
Abdominal pain	23	4.8
General disorders		
Fatigue	42	4.8
Edema peripheral	18	0.7
Nervous system disorders		
Dysgeusia	40	0
Headache	16	0
Eye disorders		
Dry eye[e]	35	0.7

	PEMAZYRE™ N=146	
Adverse Reaction	**All Grades[a] (%)**	**Grades ≥3* (%)**
Musculoskeletal and connective tissue disorders		
Arthralgia	25	6.2
Back pain	20	2.7
Pain in extremity	19	2.1
Infections and Infestations		
Urinary Tract Infection	16	3.4
Investigations		
Weight decreased	16	2.1

* Only Grades 3–4 were identified.

[a] Graded per NCI CTCAE 4.03.

[b] Includes hyperphosphatemia and blood phosphorous increased; graded based on clinical severity and medical interventions taken according to the "investigations-other, specify" category in NCI CTCAE v4.03.

[c] Includes hypophosphatemia and blood phosphorous decreased.

[d] Includes nail toxicity, nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia.

[e] Includes dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis.

The following adverse reactions were reported with the administration of PEMAZYRE™ in FIGHT-202 and other clinical trials:

Hyperphosphatemia

Prolonged hyperphosphatemia can cause precipitation of calcium-phosphate crystals that can lead to hypocalcemia, soft tissue mineralization, muscle cramps, seizure activity, QT interval prolongation, and arrhythmias.

Hyperphosphatemia was reported in 59% of all patients treated with PEMAZYRE™ in clinical trials, with 2 patients (0.5%) reporting a serious event. The median time to onset for any grade of hyperphosphatemia was 14 days, with 60.3% of patients reporting first occurrences of hyperphosphatemia during the first 6 months of pemigatinib exposure. Hyperphosphatemia above 7 mg/dL and 10 mg/dL was experienced by 27% and 0% of patients, respectively. Adverse events of hyperphosphatemia led to dose interruption or dose reduction in 3.6% and 0.9% of patients, respectively, in PEMAZYRE™ clinical trials.

Serous retinal detachment

PEMAZYRE™ can cause serous retinal detachment (SRD), which may cause symptoms such as blurred vision, visual floaters, or photopsia. Clinical trials of PEMAZYRE™ did not conduct routine monitoring including optical coherence tomography (OCT) to detect asymptomatic SRD; therefore, the incidence of asymptomatic SRD with PEMAZYRE™ is unknown.

Adverse reactions of SRD occurred in 7.5% of all patients treated with PEMAZYRE™ in clinical trials. SRD events included serous retinal detachment, retinal detachment, detachment of retinal pigmented epithelium, retinal thickening, subretinal fluid, chorioretinal folds, chorioretinal scar, and maculopathy. Events were generally Grade 1 or 2 (6.9%) in severity and non-serious; ≥ Grade 3 events included detachment of retinal pigment epithelium in 1 patient (0.2%) and retinal detachment in 2 patients (0.4%). Almost all first occurrences (93%) of SRD occurred during the first 6 months of pemigatinib exposure.

Nail disorders

Nail toxicity events, most frequently reported as events of nail discoloration, onychomadesis, and onycholysis, were common for patients treated with PEMAZYRE™ in clinical trials, reported by 35.0% of patients. Nail toxicity events led to pemigatinib dose interruption in 4.7% of patients and dose reduction in 3.2% of patients. The median time to first nail toxicity event was 3.7 months in patients treated with pemigatinib on an intermittent schedule (14 days on therapy, followed by 7 days off treatment, in 21 day cycles), with approximately half of all first events occurring during the first 6 months of pemigatinib exposure.

8.3 Less Common Clinical Trial Adverse Reactions

The following are clinically significant adverse reactions reported in less than 15% of patients receiving PEMAZYRE™:

Blood and lymphatic disorders: anemia

Eye disorders: serous retinal detachment, retinal detachment, detachment of retinal pigmented epithelium, retinal thickening, subretinal fluid, chorioretinal folds, chorioretinal scar, and maculopathy

Gastrointestinal disorders: gastroesophageal reflux disease

General disorders: pyrexia

Musculoskeletal and connective tissue disorders: musculoskeletal stiffness, myalgia

Nervous system disorders: dizziness

Respiratory, thoracic and mediastinal disorders: epistaxis

Skin and subcutaneous tissue disorders: hair growth abnormal, trichiasis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Abnormal laboratory findings are presented in Table 4.

Table 4. Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Receiving PEMAZYRE™ in FIGHT-202

	PEMAZYRE™[a] N=146	
Laboratory Abnormality	**All Grades[b] (%)**	**Grades ≥3 (%)**
Hematology		
Decreased hemoglobin	43	5.5
Decreased lymphocytes	36	8.2
Decreased platelets	28	3.4
Increased leukocytes	27	0.7
Decreased leukocytes	18	1.4
Chemistry		
Increased phosphate[c]	94	0
Decreased phosphate	68	38
Increased alanine aminotransferase	43	4.1
Increased aspartate aminotransferase	43	6.2
Increased calcium	43	4.1
Increased alkaline phosphatase	41	11
Increased creatinine[d]	41	1.4
Decreased sodium	39	12
Increased glucose	36	0.7
Decreased albumin	34	0
Increased urate	30	10
Increased bilirubin	26	5.5
Decreased potassium	26	4.8
Decreased calcium	17	2.7
Increased potassium	12	2.1
Decreased glucose	11	1.4

[a] The denominator used to calculate the rate varied from 142-146 based on the number of patients with a baseline value and at least one post-treatment value.

[b] Graded per NCI CTCAE 4.03.

[c] Based on CTCAE 5.0 grading.

[d] Graded based on comparison to upper limit of normal.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Pemigatinib is primarily metabolized in humans by CYP3A4. Unchanged pemigatinib was the major drug-related moiety in plasma, with only minor circulating metabolites.

CYP3A inhibitors

Co-administration of moderate or strong CYP3A inhibitors is predicted to increase the steady-state exposure of pemigatinib. Co-administration of PEMAZYRE™ with moderate or strong CYP3A inhibitors should be avoided. Reduce the PEMAZYRE™ dose if co-administration with a strong or moderate CYP3A inhibitor cannot be avoided. For patients who are taking PEMAZYRE™ 13.5 mg QD, reduce the PEMAZYRE™ dose to 9 mg QD and for patients who are taking PEMAZYRE™ 9 mg QD, reduce PEMAZYRE™ dose to 4.5 mg QD.

CYP3A inducers

Co-administration of moderate or strong CYP3A inducers is predicted to decrease the steady-state exposure of pemigatinib. Co-administration of PEMAZYRE™ with moderate or strong CYP3A inducers should be avoided.

9.4 Drug-Drug Interactions

The drugs listed in Table 5 are based on clinical trial or theoretical based on physiologically-based pharmacokinetic (PBPK) modeling.

Table 5: Established or Potential Drug-Drug Interactions

Proper/ Common Name	Source of Evidence	Effect	Clinical comment
Effect of CYP3A inhibitors on pemigatinib:			
Strong CYP3A inhibitor (e.g., itraconazole, ketoconazole, clarithromycin)	CT, T	Increase in pemigatinib exposure • Mean ratio (90% CI) for C_{max} was 117% (107, 129) • Mean ratio (90% CI) for AUC was 188% (175, 203)	• May lead to increased drug-related toxicity. • Avoid co-administration with strong CYP3A inhibitors. • If co-administration cannot be avoided, reduce the dose of PEMAZYRE™.

Proper/ Common Name	Source of Evidence	Effect	Clinical comment
Moderate CYP3A inhibitor (e.g., erythromycin, diltiazem)	T	Pemigatinib exposure increased by approximately 50% when co-administered with moderate CYP3A4 inhibitors.	• May lead to increased drug-related toxicity. • Avoid co-administration with moderate CYP3A inhibitors. • If co-administration cannot be avoided, reduce the dose of PEMAZYRE™.
Weak CYP3A inhibitor (e.g., fluvoxamine)	T	No drug-drug interaction was predicted.	• No dose adjustment is recommended.
Effect of CYP3A inhibitors on pemigatinib:			
Strong CYP3A inducer (e.g., rifampin)	CT	Decrease in pemigatinib exposure • Mean ratio (90% CI) for C_{max} was 38% (33.2, 43.5) • Mean ratio (90% CI) for AUC was 14.9% (13.9, 16.1)	• May lead to decreased activity. • Avoid co-administration of strong CYP inducers.
Moderate CYP3A inducer (e.g., efavirenz)	T	Pemigatinib exposure decreased by more than 50% when co-administered with moderate CYP3A4 inducers.	• May lead to decreased activity. • Avoid co-administration of moderate CYP inducers.
Weak CYP3A inducer (e.g., dexamethasone)	T	No drug-drug interaction was predicted.	• No dose adjustment is recommended.
Acid-lowering medications			
Proton pump inhibitors (e.g., esomeprazole)	CT	• Mean ratio (90% CI) for C_{max} was 65.3% (54.7, 78.0) when co-administered with esomeprazole • Mean ratio (90% CI) for AUC was 92.1% (88.6, 95.8) when co-administered with esomeprazole. No clinically important change in pemigatinib exposure.	• No dose adjustment is recommended.

Proper/ Common Name	Source of Evidence	Effect	Clinical comment
Histamine-2 antagonists (e.g., ranitidine)	CT	• Mean ratio (90% CI) for C_{max} was 97.9% (77.0, 124) when co-administered with ranitidine relative to pemigatinib alone. • Mean ratio (90% CI) for AUC was 103% (93.1, 114) when co-administered with ranitidine relative to pemigatinib alone. No clinically important change in pemigatinib exposure.	• No dose adjustment is recommended.

Legend: CT = Clinical Trial; T = Theoretical (simulation).

Effect of Pemigatinib on 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, 2B6, and 3A4.

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.

Pemigatinib is an inhibitor of P-gp, OCT2, and MATE1. PBPK modeling suggests pemigatinib does not result in a clinically important change in exposure of P-gp or OCT2/MATE1 substrates. Inhibition of OCT2/MATE1 may increase serum creatinine.

9.5 Drug-Food Interactions

PEMAZYRE™ can be administered with or without food (see **10 CLINICAL PHARMACOLOGY, Pharmacokinetics**). Grapefruit, grapefruit juice, and products containing grapefruit extract may increase pemigatinib plasma concentrations and should be avoided.

9.6 Drug-Herb Interactions

Drug-herb interactions have not been studied (see **9 Drug Interactions, Drug-Drug Interactions**).

St. John's Wort (Hypericum perforatum) is an inducer of CYP3A that may decrease pemigatinib plasma concentrations and should be avoided.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Pemigatinib is a small molecule kinase inhibitor of FGFR1, 2 and 3. Pemigatinib inhibits FGFR phosphorylation and signaling and selectively decreases cell viability in cancer cell lines with activating FGFR genetic alterations, including point mutations, amplifications, and fusions or rearrangements. These genetic alterations in FGFR genes result in activation of FGFR signaling that supports the proliferation and survival of malignant cells. In FGFR-activated cancer cell lines, the concentration required for 50% inhibition (IC_{50}) was less than 2 nM. In preclinical studies, pemigatinib exhibited anti-tumor activity in mouse xenograft models of human tumors with FGFR1, FGFR2, or FGFR3 activation including a patient-derived xenograft model of cholangiocarcinoma that expressed an oncogenic FGFR2-Transformer-2 beta homolog (TRA2b) fusion protein.

10.2 Pharmacodynamics

Cardiac Electrophysiology

A dedicated QT study has not been conducted. Based on evaluation of QTc interval in 116 patients in an open-label, dose escalation study, pemigatinib did not exhibit a large effect (i.e., >20 ms) on the QTc interval.

Serum Phosphate

Pemigatinib increased serum phosphate level due to FGFR inhibition. In patients, the increase in serum phosphate with pemigatinib was exposure-dependent, with increased risk of hyperphosphatemia with higher pemigatinib exposure. In pemigatinib clinical trials, phosphate-lowering therapy and dose modifications were permitted to manage hyperphosphatemia. To manage phosphate elevation, refer to Table 1 (see **4 DOSAGE AND ADMINISTRATION**).

10.3 Pharmacokinetics

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. Table 6 provides the pemigatinib steady-state pharmacokinetic parameters for 13.5 mg once daily in cancer patients.

Table 6: Geometric Mean (CV%) Pharmacokinetic Parameters of Pemigatinib at Steady-State Following Administration of 13.5 mg QD PEMAZYRE™ in Patients with Cancer

	C_{max} (nM)	T_{max} (h)	$t_{½}$ (h)	AUC_0-(nM·h)	CL/F (L/h)	V_z/F (L)
Steady-State	236 nM (56.4)	1.1(0.5-6) h	15.4 (51.6)	2620 (54.1)	10.6 (54.1)	235 (60.8)

T_{max} is presented as median (range).

Absorption: The median time to achieve peak pemigatinib plasma concentration (T_{max}) was 1.13 (0.50–6.00) hours.

Effect of Food:

No clinically meaningful differences with pemigatinib pharmacokinetics were observed following administration of a high-fat and high-calorie meal (approximately 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500–600 calories from fat in patients with cancer.

Distribution: Pemigatinib is 90.6% bound to human plasma proteins, predominantly to albumin. The estimated apparent volume of distribution was 235 L (60.8%) in patients with cancer following a 13.5 mg oral dose.

Metabolism: Pemigatinib is predominantly metabolized by CYP3A4 *in vitro*. Following oral administration of a single 11 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: The geometric mean elimination half-life ($t_{½}$) of pemigatinib was 15.4 (51.6% CV) hours and the geometric mean apparent clearance (CL/F) was 10.6 L/h (54% CV) at 13.5 mg QD in patients with advanced cancer.

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).

Special Populations and Conditions

***Pediatrics (<18 years of age)*:** The pharmacokinetics of pemigatinib has not been studied in pediatric patients.

***Geriatrics (≥65 years of age)*:** In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between pemigatinib oral clearance and patient age.

***Effect of weight, gender and race*:** Population PK analysis showed that there are no clinically relevant effects of body weight, gender or race on pemigatinib PK parameters.

***Pregnancy and Breast-feeding*:** The pharmacokinetics of pemigatinib in patients who are pregnant or breast-feeding has not been studied.

***Hepatic Insufficiency*:** The population PK analysis shows that the clearance in participants with mild or moderate hepatic impairment is not statistically significantly different from the clearance in participants with normal hepatic function. A hepatic impairment study showed that the geometric mean of C_{max} and $AUC_{0-\infty}$ of pemigatinib in participants with moderate hepatic impairment was 3.3% lower and 46% higher, respectively, than in healthy-matched participants. The geometric mean C_{max} and $AUC_{0-\infty}$ of pemigatinib in participants with severe hepatic impairment was 5.8% lower and 74% higher, respectively, than in healthy-matched participants. The data from this study indicate that there is evidence of a clinically significant pemigatinib AUC increase for participants with severe hepatic impairment, and the dose of PEMAZYRE™ should be reduced in these patients (see **4 DOSAGE AND ADMNISTRATION, Special Populations**). The exposure difference between participants with moderate hepatic impairment and healthy–matched participants is not considered clinically meaningful.

***Renal Insufficiency*:** Population PK analysis shows that the clearance in participants with mild or moderate renal impairment is not statistically significantly different from the clearance in participants with normal renal function. A renal impairment study showed that the geometric mean of C_{max} and $AUC_{0-\infty}$ of pemigatinib in participants with severe renal impairment was 35.4% lower and 59% higher, respectively, than healthy-matched participants. The geometric mean C_{max} and $AUC_{0-\infty}$ of pemigatinib in participants with end-stage renal disease (ESRD) before hemodialysis (HD) was 22.5% and 23.2% lower than healthy-matched participants, respectively. The geometric mean C_{max} and $AUC_{0-\infty}$ of pemigatinib in participants with ESRD after HD was 10.0% and 8.7% lower than healthy-matched participants, respectively. The data from this study indicate that there is evidence of a clinically significant pemigatinib AUC increase for participants with severe renal impairment and and the dose of PEMAZYRE™ should be reduced in these patients (see **4 DOSAGE AND ADMINISTRATION, Special Populations**). The exposure difference between participants with ESRD before or after HD and healthy-matched participants is not clinically meaningful.

11 STORAGE, STABILITY AND DISPOSAL

Store PEMAZYRE™ tablets at room temperature (15–30°C).

PEMAZYRE™ must be kept out of the reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

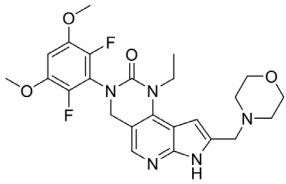
Drug Substance

Proper/Common name: pemigatinib

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

Molecular formula and molecular mass: $C_{24}H_{27}F_2N_5O_4$ 487.5 g/mole

Structural formula:



Physicochemical properties: Pemigatinib is a white to off-white solid that is not hygroscopic. Pemigatinib has low aqueous solubility (dose/solubility volume >250 mL at 37°C) above pH 4. The aqueous solubility of pemigatinib is pH dependent with decreasing solubility observed with increasing pH in the physiologic range.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 7: Summary of patient demographics for the clinical trial in previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
INCB 54828-202 (FIGHT-202) (NCT02924376)	Multicenter, non-randomized, open-label, multi-cohort trial	13.5 mg PEMAZYRE™, oral, once-daily (QD) for 14 days followed by no dose for 7 days, in 3-week cycles. PEMAZYRE™ was administered until disease progression or unacceptable toxicity.	107	56 years (26–77 years)	42 male 65 female

The efficacy population of Study FIGHT-202 (NCT02924376) consisted of 107 patients with locally advanced or metastatic cholangiocarcinoma that had progressed on or after at least 1 prior therapy and who had an FGFR2 fusion or rearrangement. Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene, leaving the FGFR2 kinase domain intact. Fibroblast growth factor receptor (FGFR) mutation status for screening and enrolment of patients was determined by a validated clinical trial assay.

A summary of the demographics and baseline characteristics for the main efficacy cohort (Cohort A) is shown in Table 8.

Table 8: Summary of Patient Demographics for Clinical Trials in INCB 54828-202 (FIGHT-202) in Cholangiocarcinoma

Variable	Cohort A N=107 (%)
Age (years)	55.3 (12.02)
Mean (STD)	56.0
Median (range)	26-77

Variable	Cohort A N=107 (%)
Age group, n (%)	
<65 years	82 (76.6)
≥65 years	25 (23.4)
Sex, n (%)	
Male	42 (39.3)
Female	65 (60.7)
Race, n (%)	
White	79 (73.8)
Black or African American	7 (6.5)
Asian	11 (10.3)
Other[a]	4 (3.7)
Missing	6 (5.6)
ECOG status at baseline, n (%)	
0	45 (42.1)
1	57 (53.3)
2	5 (4.7)
Renal impairment grade at baseline[b]	
Normal	42 (39.3)
Mild	47 (43.9)
Moderate	18 (16.8)
Severe	0
Hepatic impairment grade at baseline[c]	
Normal	48 (44.9)
Mild	52 (48.6)
Moderate	7 (6.5)
Cholangiocarcinoma location	
Intrahepatic	105 (98.1)
Extrahepatic	1 (0.9)
Other	0
Missing	1 (0.9)[d]
Metastatic disease[e]	88 (82.2)
Locally advanced disease	16 (15.0)

Variable	Cohort A N=107 (%)

Note: Cohort determination is based on tumor FGF/FGFR status from central genomics laboratory. Cohort A = FGFR2 rearrangements or fusions.

[a] Includes Hispanic, Latino, or Spanish or not reported.

[b] Baseline renal impairment grade (normal, mild, moderate, or severe) based on eGFR (calculated using the MDRD equation): normal renal function = eGFR ≥90 mL/min/1.73 m^2; mild renal impairment = eGFR ≥60 and <90 mL/min/1.73 m^2; moderate renal impairment = eGFR ≥30 to <60 mL/min/1.73 m^2; severe renal impairment = eGFR <30 mL/min/1.73 m^2.

[c] Degree of hepatic impairment based on National Cancer Institute Hepatic Working Group Criteria.

[d] At baseline, this participant had stage 4 cholangiocarcinoma (T3 N0 M1), presumed intrahepatic, with current sites of disease in liver, omentum, and peritoneum.

[e] Metastatic information was not able to be confirmed for one participant and missing for two participants.

The FGF/FGFR fusions or rearrangements analysed in Cohort A are provided in Table 9.

Table 9: FGF/FGFR Genetic Alterations Identified by Central Genomics Laboratory in ≥2 Participants (Cohort A)

FGF/FGFR Alteration, n	Cohort A (N=107)
FGFR2-BICC1	31
FGFR2-N/A[a]	5
FGFR2-KIAA1217	4
FGFR2-AHCYL1	3
FGFR2-ARHGAP24	2
FGFR2-AFF4	2
FGFR2-CCDC6	2
FGFR2-MACF1	2
FGFR2-NOL4	2
FGFR2-NRAP	2
FGFR2-PAWR	2
FGFR2-SLMAP	2

[a] FGFR2 rearrangement confirmed but gene partner not identified/available.

14.2 Study Results

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 duration of therapy was 6.0 months, and the median duration of efficacy follow up was 15.4 months.

Efficacy results are summarized in Table 10.

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

Table 10: Efficacy Results

	Cohort A (FGFR2 Fusion or Rearrangement) Efficacy Evaluable Population (N=107)
ORR (95% CI)	35.5% (26.5, 45.4)
Complete response	2.8%
Partial response	32.7%
Median duration of response (months) (95% CI)[a]	9.1 (6.0, 14.5)

[a] The 95% CI was calculated using the Brookmeyer and Crowley method.

ORR = CR+PR.

CI = Confidence Interval.

Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Rats

In a 3-month repeat-dose toxicity study, once daily oral pemigatinib was administered to rats at doses up to 1.05 mg/kg/day (resulting in systemic exposure of approximately 2 times the AUC in patients who received the recommended dose of 13.5 mg). Deaths were observed at the highest dose level (1.05 mg/kg/day). Toxicity was observed at all dose levels and included weight loss, bilateral corneal crystals, soft tissue and vascular mineralization, hyperphosphatemia and physeal and teeth dysplasia. Soft tissue mineralization included the heart, lung, stomach, duodenum, kidney, skeletal muscle, spinal cord and eyes. Teeth dysplasia was clinically manifested by missing or broken incisors. Phosphate aberrations and corneal crystallization showed evidence of recovery after 6 weeks, whereas tissue mineralization, physeal and teeth dysplasia, and weight loss did not.

Cynomolgus Monkeys

In a 3-month repeat-dose toxicity study, once daily oral pemigatinib was administered to monkeys at doses up to 1 mg/kg/day (resulting in systemic exposure of approximately 60% of the AUC in patients who received the recommended dose of 13.5 mg). Toxicity was observed at all dose levels and included hyperphosphatemia and physeal dysplasia. Recovery was evident, but not complete 6 weeks after cessation of dosing. Soft tissue mineralization in monkeys was observed at 3 mg/kg/day in the 10-day range finding study; this dose was not tolerated and resulted in exposure approximately 2.7 times higher than the AUC in patients administered who received the recommended dose of 13.5 mg.

Carcinogenicity

Carcinogenicity studies with pemigatinib have not been conducted.

Genotoxicity

Pemigatinib was not mutagenic in a bacterial mutagenicity assay, and was not clastogenic in an *in vitro* chromosome aberration assay or in an *in vivo* micronucleus assay in rats.10.2 Pharmacodynamics

Reproductive and Developmental Toxicology

Impairment of Fertility

No dedicated animal studies with pemigatinib have been conducted to evaluate the effects of pemigatinib on fertility in females or males.

Developmental Toxicity

Pemigatinib was evaluated in rats in a dose range-finding embryo-fetal developmental and toxicokinetic study, in which pregnant rats received once daily oral doses of 0.1, 0.3, and 1.0 mg/kg/day of pemigatinib during the period of organogenesis from gestational day 6 to 17. Treatment with pemigatinib at dose levels ≥0.3 mg/kg caused 100% embryo-fetal mortality due to post-implantation loss. Pemigatinib reduced maternal body weight at dose levels ≥0.3 mg/kg and gravid uterine weight at dose levels ≥0.1 mg/kg. At the 0.1 mg/kg dose level, pemigatinib reduced fetal body weight and caused vertebral anomalies, major blood vessel variations and reduced ossification of ribs and presacral vertebrae. Systemic exposure (AUC) in rats at doses of 0.1 mg/kg and 0.3 mg/kg is approximately 20% and 60% of the AUC in patients who received the recommended dose of 13.5 mg pemigatinib, respectively.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PRPEMAZYRE™

pemigatinib tablets

Read this carefully before you start taking **PEMAZYRE™** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PEMAZYRE™**.

What is PEMAZYRE™ used for?

For the following indication, PEMAZYRE™ has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

PEMAZYRE™ is used to treat adults with a type of cancer called cholangiocarcinoma (bile duct cancer) when it:

- has a type of abnormality in a specific gene called Fibroblast Growth Factor Receptor 2 (FGFR2); **and**
- has been treated previously
- cannot be removed with surgery
- is at an advanced stage or has spread to other parts of the body (called metastatic).

A test will be done to find out if the cancer has an FGFR2 gene abnormality. This is to make sure that PEMAZYRE™ is right for you.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's

performance after it has been sold, and to report their findings to Health Canada.

How does PEMAZYRE™ work?

Fibroblast growth factor receptors (FGFRs) are proteins found on cells. These help cells grow and divide. Some people with bile duct cancer have FGFRs that are more active than normal. PEMAZYRE™ works by blocking the activity of FGFRs. This should slow down the growth and spread of bile duct cancer cells.

What are the ingredients in PEMAZYRE™?

Medicinal ingredients: pemigatinib

Non-medicinal ingredients: magnesium stearate, microcrystalline cellulose, sodium starch glycolate

PEMAZYRE™ comes in the following dosage forms:

Tablets, 4.5 mg, 9 mg, and 13.5 mg

Do not use PEMAZYRE™ if:

- you are allergic to pemigatinib or to any of the other ingredients in PEMAZYRE™ including any part of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PEMAZYRE™. Talk about any health conditions or problems you may have, including if you:

- have problems swallowing tablets
- have severe liver problems
- have severe kidney problems

Other warnings you should know about:
Treatment with PEMAZYRE™ can cause serious side effects, including:

- **Hyperphosphatemia** (high phosphate levels in your blood) or **hypophosphatemia** (low levels of phosphate in your blood): Your healthcare professional will do blood tests to check levels of phosphate in your blood. These tests will be done 14 days after you start PEMAZYRE™. They will be repeated about every 6 weeks. If your levels are too high or too low, you may need to:
  - change the amount of phosphate you eat in your diet;
  - change your dose of PEMAZYRE™, or
  - start or stop taking other medications that affect the amount of phosphate in your blood.

  Because of the risk for hyperphosphatemia, avoid using antacids that contain calcium and supplements that are phosphate-based.

- **High levels of creatinine in your blood**, which may be a sign that you are having kidney problems.
- **Eye and vision problems**, including:
  - dry eye. If this happens you may need to use artificial tears or something similar.
  - inflamed eyes (including inflammation of the cornea, which is the front part of the eye)
  - increased tears
  - **serious retinal detachment**. This is when fluid builds up in the eye and causes the retina to detach. Your healthcare professional will check your eyes and vision before you start taking PEMAZYRE™, every 2 months for the first 6 months of your treatment and then every 3 months thereafter. If you develop any changes in your vision during your treatment with PEMAZYRE™ such as: blurred vision, flashes of light, or seeing black spots, tell your healthcare professional. You may need to see an eye specialist (an ophthalmologist) right away.

See the Serious Side Effects and What To Do About Them table, below, for more information on these and other serious side effects.

Female patients – Pregnancy and breastfeeding:

- If you are pregnant, or are still able to get pregnant and/or breastfeed, there are specific risks you must discuss with your healthcare professional.
- You should not be pregnant while you are taking PEMAZYRE™. It may harm your unborn baby or make you lose the pregnancy.
- For females who are able to get pregnant:
  - Your healthcare professional will do a pregnancy test before you start treatment with PEMAZYRE™.
  - Use effective birth control during your treatment with PEMAZYRE™ and for 1 month after your last dose. Talk to your healthcare professional about available birth control methods.
  - If, during your treatment, you become pregnant or think you are pregnant, tell your healthcare professional right away.
- It is not known if PEMAZYRE™ passes into breastmilk. Do not breastfeed while you are taking PEMAZYRE™ and for 1 month after your last dose. Talk to your healthcare professional about the best way to feed your baby during this time.

Male patients – Pregnancy:

- Use effective birth control each time you have sex with a woman who can get pregnant. This is necessary during your treatment with PEMAZYRE™ and for 1 month after your last dose.

- If, during your treatment, your partner thinks she is pregnant, tell your healthcare professional right away.

Driving and using machines: Before you do tasks which may require special attention, wait until you know how you respond to PEMAZYRE™. If you experience vision problems, do not drive or use tools or machines until the side effect goes away.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PEMAZYRE™:

- Medicines to treat fungal infections called itraconazole and oral ketoconazole.
- Medicines to treat infections called clarithromycin and erythromycin.
- A medicine to treat HIV infection called efavirenz.
- A medicine to treat high blood pressure or chest pain called diltiazem.
- A medicine to treat tuberculosis or other bacterial infections called rifampin.
- An herbal remedy mainly used to treat depression called St. John's Wort.

Do not eat or drink grapefruit products or products that contain grapefruit extract during your treatment with PEMAZYRE™. These can affect the way the medicine works.

How to take PEMAZYRE™:

- Take exactly as your healthcare professional tells you. Check with your doctor or pharmacist if you are not sure.
- Take one tablet with or without food, once per day, at about the same time each day.
- Take your PEMAZYRE™ every day for 14 days (2-weeks) in a row. This is followed by 7 days (1-week) with no treatment (treatment-free week). Two weeks of treatment and one week with no treatment make up a 21-day cycle.
- Swallow tablets whole. Do not crush, chew, split or dissolve tablet

Usual dose: 13.5 mg per day for 14 days followed by 7 days with no treatment.

You may receive a lower dose if you are taking certain medications or have severe kidney or liver problems.

Your healthcare professional may change your dose of PEMAZYRE™, or may temporarily or completely stop your treatment. This may happen if you develop certain side effects or your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much PEMAZYRE™, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If it is 4 or more hours later than when you should have taken your PEMAZYRE™ dose, or if you vomit after taking your dose:

- do NOT make up the dose. Skip it and continue with your next dose at the usual time. Do not take an extra dose the next day to make up for the missed dose.

If it is less than 4 hours later than when you should have taken your dose, take it as soon as you remember. Continue with your next dose at the usual time.

What are possible side effects from using PEMAZYRE™?

These are not all the possible side effects you may feel when taking PEMAZYRE™. If you experience any side effects not listed here, contact your healthcare professional.

- hair loss
- abnormal hair growth
- feeling tired
- dizziness
- headache
- nose bleeds
- fever
- decreased appetite
- taste changes
- heartburn or indigestion
- dry mouth
- mouth sores
- nausea
- vomiting
- constipation
- diarrhea
- abdominal pain
- back pain
- pain in the arms or legs
- muscle pain and stiffness
- swelling of the arms and legs
- weight decreased

PEMAZYRE™ can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment and will interpret the results.

Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Hyperphosphatemia (high blood phosphate levels): muscle cramps and tingling		✓	
Hypophosphatemia (low blood phosphate levels): muscle weakness and pain, confusion, seizures, tea-colored urine, heart or breathing problems		✓	
Nail or skin problems: nails separating from the bed; nail pain, breaking of the nails, infected skin around the nails; color or texture changes, dry skin		✓	
Palmar-Plantar erythrodysaesthesia (hand-foot syndrome): swelling, peeling or tenderness, mainly on the hands and feet		✓	
Arthralgia: joint pain		✓	
Urinary tract infection (infection of the urinary system): pain or burning sensation while urinating, frequent urination, blood in the urine		✓	
Dehydration: feeling thirsty, infrequent urination, feeling dizzy or tired, dark yellow urine, dry mouth and lips		✓	
Hypercalcemia (high blood calcium levels): increase in urine production, increase in thirst, nausea, weakness, confusion		✓	
Anemia (decreased number of red blood cells): fatigue, weakness, loss of energy, fast heart rate, pale complexion, shortness of breath		✓	
Hyponatremia (low blood sodium levels): nausea, vomiting, fatigue, headache, confusion, seizure		✓	
COMMON			
Vision problems including serous retinal detachment (when fluid builds up under the retina): blurred vision, black spots, flashes of light, inflammation of the cornea, dry eye		✓	

Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Trichiasis: eyelashes grow inward to the eye		✓	
Kidney problems: passing low amounts of urine, nausea, swelling in legs and ankles, confusion, difficulty breathing		✓	
Cholangitis (infection of the biliary tract): abdominal pain, fever, chills, jaundice (yellowing of the skin or whites of the eyes), nausea, vomiting		✓	
Pleural effusion (a buildup of fluid between the tissues that line the lungs		✓	
Failure to thrive (a decline in adults, often associated with physical frailty, functional disability, and /or neuropsychiatric impairment): weight loss, weakness, decreased physical activity, difficulty in performing self-care, change in mental status		✓	
Sepsis (a serious condition caused by infection and the body's response to infection potentially leading to organ dysfunction): low blood pressure, fast heart rate, fever, decrease in urination, difficulty breathing, altered mental status.		✓	
Intestinal obstruction (an interruption to the flow of the intestines): abdominal pain or distention, nausea, vomiting		✓	
Bile duct obstruction (blockage of the bile duct that transports bile from the liver to the gallbladder and small intestine): abdominal pain, dark urine, fever, itching, jaundice (yellowing of the skin or whites of the eyes,) nausea, vomiting, pale colored stools		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store PEMAZYRE™ between 15°C to 30°C.

Keep out of sight and reach of children.

If you want more information about PEMAZYRE™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website (www.incytebiosciences.ca), or by calling 1-833-309-2759.

This leaflet was prepared by Incyte Corporation

Wilmington, Delaware 19803 USA

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