PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTRUSELTIQ™

Infigratinib capsules

Capsules, 25 mg and 100 mg infigratinib (as infigratinib phosphate), Oral

Antineoplastic agent

(ATC Code: L01EN03)

"TRUSELTIQ™, indicated for:

- the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement 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 the authorization. For further information for TRUSELTIQ™ 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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Date of Initial Authorization:
[September 21, 2021]

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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.

RECENT MAJOR LABEL CHANGES

Not applicable.	

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PART I: HEALTH PROFESSIONAL INFORMATION

NOC/c

1 INDICATIONS

TRUSELTIQ™ (infigratinib) 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.

Prior to initiation of TRUSELTIQ™ therapy, FGFR2 fusion or rearrangement should be established using a validated test.

Clinical effectiveness of TRUSELTIQ™ 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).

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.

1.2 Geriatrics

Geriatrics (>65 years of age): Of the 351 patients treated with TRUSELTIQ™ in clinical studies, 33% were 65 years or older and 10% were 75 years or older. No overall differences in safety and efficacy were observed between these patients and younger patients.

2 CONTRAINDICATIONS

- Infigratinib 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.

NOC/c

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- A validated assay is required for the selection of patients with an FGFR2 fusion or other rearrangement.
- Avoid concomitant use with strong or moderate CYP3A4 inhibitors [see 9 DRUG INTERACTIONS].
- Avoid concomitant use with strong or moderate CYP3A4 inducers [see 9 DRUG INTERACTIONS].
- Avoid administration of proton pump inhibitors, H2-antagonists, and locally-acting antacids with TRUSELTIQ™. If coadministration of gastric acid reducing agents cannot be avoided, use an H2-receptor antagonist or locally- acting antacid and stagger administration of TRUSELTIQ™. TRUSELTIQ™ should be taken ≥2 hours before or 10 hours after administration of H2-antagonists. Locally-acting antacids should be taken at least 2 hours before or after TRUSELTIQ™ dosing. see 9 DRUG INTERACTIONS.
- TRUSELTIQ™ dose adjustment is required in patients with mild or moderate hepatic impairment

and in patients with mild or moderate renal impairment. (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, special populations).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dose of TRUSELTIQ™ is 125 mg (one 100 mg capsule and one 25 mg capsule) orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. Continue treatment until disease progression or unacceptable toxicity.

Dosage Adjustment

The recommended dose reductions for adverse reactions are listed in Table 1.

Table 1: Recommended Dose Reduction for TRUSELTIQ™ for Adverse Reactions

Dose	1st dose reduction	2nd dose reduction	3rd dose reduction
125 mg (one 100 mg and one 25 mg capsule)	100 mg (one 100 mg capsule)	75 mg (three 25 mg capsules)	50 mg (two 25 mg capsules)

The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for TRUSELTIQ™ Adverse Reactions

Adverse Reaction	TRUSELTIQ™ Dose Modifications
Ocular Disorder [see 7 WARNINGS and PRECAUTIONS, Ophthalmologic]	
Retinal pigment epithelial detachment (RPED)	• Continue TRUSELTIQ™ at the current dose and continue periodic ophthalmic evaluation: • If resolving within 14 days, continue TRUSELTIQ™ at the current dose. • If not resolving within 14 days, withhold TRUSELTIQ™ until resolving; then resume TRUSELTIQ™ at previous or a lower dose.
Hyperphosphatemia [see 7 WARNINGS and PRECAUTIONS, Hyperphosphatemia]	
Serum phosphate >5.5 to ≤7.5 mg/dL	Continue TRUSELTIQ™ at current dose and initiate or dose adjust phosphate lowering therapy according to respective label. Monitor serum phosphate weekly. *Phosphate binder dosing should be held during the week off TRUSELTIQ™ therapy each cycle (Days 22 to 28) and during TRUSELTIQ™ dose interruptions for non-hyperphosphatemia adverse events.*
Serum phosphate >7.5 mg/dL OR	Withhold TRUSELTIQ™ until level returns to serum phosphate ≤5.5 mg/dL.

Adverse Reaction	TRUSELTIQ™ Dose Modifications
Single serum phosphate >9.0 mg/dL regardless of duration or dose of phosphate lowering therapy	Resume TRUSELTIQ™ as below, with maximal phosphate binder dosing: • If serum phosphate >7.5 mg/dL occurred for less than 7 days: Restart TRUSELTIQ™ at the same dose. • If serum phosphate >7.5 mg/dL for >7 days or if patient had a one-time serum phosphate of >9.0 mg/dL: Resume TRUSELTIQ™ at the next lower dose level.
Serum phosphate with life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Permanently discontinue TRUSELTIQ™.
Other adverse reactions[a]	
Grade 3	Withhold dose of TRUSELTIQ™ until resolved to CTCAE Grade ≤1, then resume at the next lower dose level of TRUSELTIQ™. If not resolved within ≤14 days, permanently discontinue TRUSELTIQ™.
Grade 4	Permanently discontinue TRUSELTIQ™.

[a] Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

Educational material to assist healthcare professionals with the diagnosis and management of retinal pigment epithelial detachment is available through the manufacturer.

Special Populations

Pediatrics (<18 years old): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years old): No dose adjustment is required in patients ≥65 years of age [see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions].

Renal Impairment: The recommended dose of TRUSELTIQ™ for patients with mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min, estimated by Cockcroft-Gault) is 100 mg once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles [see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions].

TRUSELTIQ™ has not been studied in patients with severe (CrCl < 30 mL/min) renal impairment.

Hepatic Impairment: For patients with mild (total bilirubin > upper limit of normal [ULN] to 1.5 × ULN or AST > ULN) or moderate (total bilirubin >1.5 to 3 × ULN with any AST) hepatic impairment, reduce the recommended dose as follow:

• Mild Hepatic Impairment: 100 mg once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles.

• Moderate Hepatic Impairment: 75 mg once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles.

[see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions].

TRUSELTIQ™ has not been studied in patients with severe hepatic impairment per NCI-ODWG criteria (total bilirubin > 3 x ULN with any AST).

4.4 Administration

The recommended dose of TRUSELTIQ™ is 125 mg (one 100 mg capsule and one 25 mg capsule) orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. Continue treatment until disease progression or unacceptable toxicity.

Capsules should be taken on an empty stomach at least 1 hour before or 2 hours after food, at approximately the same time each day. Swallow capsules whole with a large glass of water. Do not open, crush, chew, or dissolve capsules.

4.5 Missed Dose

If a dose of TRUSELTIQ™ is missed by ≥4 hours or if vomiting occurs, resume the regular daily dose schedule for TRUSELTIQ™ the next day.

5 OVERDOSAGE

There is no experience with overdose in clinical trials with TRUSELTIQ™. There is no known specific antidote for TRUSELTIQ™ overdose. In the event of suspected overdose, interrupt TRUSELTIQ™, undertake general supportive measures, and observe until clinical stabilization.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules, 25 mg and 100 mg infigratinib (as infigratinib phosphate).	Black iron oxide, colloidal silicon dioxide, crospovidone, gelatin, hypromellose, lactose monohydrate, magnesium stearate (from vegetable source), microcrystalline cellulose, pharmaceutical grade printing ink, red iron oxide, titanium dioxide, and yellow iron oxide.

- TRUSELTIQ™ (infigratinib) hard gelatin capsules are supplied as 25 mg, white opaque body with gray opaque cap imprinted with “INFI 25mg” on the body.

- TRUSELTIQ™ (infigratinib) hard gelatin capsules are supplied as 100 mg, white opaque body with light orange opaque cap imprinted with "INFI 100mg" on the body.

Packaging: TRUSELTIQ™ capsules are supplied in 21-day dose pack configurations as follows:

- Blister pack for 125 mg daily dose (Contains 21 doses of 100 mg and 25 mg capsules. Dosage equal to 125 mg per day).
- Blister pack for 100 mg daily dose (Contains 21 doses of 100 mg capsules).
- Blister pack for 75 mg daily dose (Contains 21 doses of three 25 mg capsules. Dosage equal to 75 mg per day).
- Blister pack for 50 mg daily dose (Contains 21 doses of two 25 mg capsules. Dosage equal to 50 mg per day).

NOC/c 7 WARNINGS AND PRECAUTIONS

General

Before taking TRUSELTIQ™, patients must have confirmation of FGFR gene fusion or rearrangement by a validated test. Patients enrolled in Study CBGJ398X2204 were required to have confirmation of an FGFR2 fusion (n=88) or other rearrangement (n=20) in tumor tissues.

Table 4: FGFR2 fusions and rearrangements in patients treated with infigratinib (identified in ≥ 2 Participants)

FGFR Alteration	N**
FGFR2-BICC1	27
FGFR2 rearrangement intron 17	9
FGFR2 rearrangement*	5
FGFR2-AHCYL1	4
FGFR2-CCDC6	3
FGFR2-KIAA1217	3
FGFR2-WAC	3
FGFR2-KIAA1598	2
FGFR2-NRAP	2
FGFR2-RBM20	2
FGFR2-PAWR	2
FGFR2-PHLDB2	2

*No partner gene identified

** This table represents FGFR2 fusions and rearrangements that were identified in ≥ 2 participants in Study CBGJ398X2204

Driving and Operating Machinery

No studies to establish the effects of TRUSELTIQ™ 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 TRUSELTIQ™ treatment. If patients experience symptoms affecting their vision, it is recommended that they do not drive or use machines until the effect subsides.

Monitoring and Laboratory Tests

Serum Phosphate

Monitor for hyperphosphatemia 7-14 days after initiating TRUSELTIQ™ treatment, after the first cycle, and continue to monitor monthly thereafter. For elevated phosphate concentrations, follow dose modification guidelines in Table 2. (see 4 DOSAGE AND ADMINISTRATION, Dose Adjustment)

Ocular Testing

Perform a comprehensive ophthalmic examination including optical coherence tomography (OCT) prior to initiation of TRUSELTIQ™, at 1 month, at 3 months, and then every 3 months thereafter during treatment. Refer patients for ophthalmic evaluation urgently for onset of visual symptoms, and follow-up every 3 weeks until resolution or discontinuation of TRUSELTIQ™.

Endocrine and Metabolism

Hyperphosphatemia and Soft Tissue Mineralization

TRUSELTIQ™ can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcinosis, nonuremic calciphylaxis, vascular calcification, and myocardial calcification. Increases in phosphate levels are a pharmacodynamic effect of TRUSELTIQ™ [see 10.2 Pharmacodynamics]. Among 351 patients who received TRUSELTIQ™ across clinical trials, hyperphosphatemia was reported in 82% of patients based on laboratory values above the upper limit of normal. The median time to onset of reported hyperphosphatemia event was 8 days (range 1 to 349). Phosphate-lowering therapy was received by 83% of patients who received TRUSELTIQ™.

Among 108 patients who received TRUSELTIQ™ in CBGJ398X2204, hyperphosphatemia was reported in 89% of patients based on laboratory values above the upper limit of normal with ≥Grade 3 reactions in 13% of patients. Dose interruption occurred in 25% and none led to dose discontinuation.

Monitor for hyperphosphatemia throughout treatment. Initiate phosphate lowering therapy when serum phosphate level is >5.5 mg/dL. For serum phosphate level >7.5 mg/dL, withhold TRUSELTIQ™ and initiate phosphate lowering therapy. Withhold, dose reduce, or permanently discontinue TRUSELTIQ™ based on duration and severity of hyperphosphatemia. [see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment].

Hypophosphatemia

Severe hypophosphatemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and hemolytic anemia. Among 351 patients who received TRUSELTIQ™ across clinical trials, hypophosphatemia was reported in 48 % of patients based on laboratory values below the lower limit of normal. The median time to onset of reported hypophosphatemia event was 85 days (range 1 to 610).

Among 108 patients who received TRUSELTIQ in CBGJ398X2204, hypophosphatemia was reported in 63% of patients based on laboratory values below the lower limit. Hypophosphatemia was the second most commonly reported ≥Grade 3 TEAE at 13% with SAEs occurring in 2% subjects. Dose interruption occurred in 4% and none led to dose discontinuation. Most of the reported events of hypophosphatemia recovered.

Most cases of hypophosphatemia occurred following the phosphate binder treatment (i.e., was due to unintended overcorrection of hyperphosphatemia). Monitor for hypophosphatemia throughout the treatment.

Ophthalmologic

Retinal Pigment Epithelial Detachment (RPED)

TRUSELTIQ™ can cause RPED, which may cause symptoms such as blurred vision.

Among 351 patients who received TRUSELTIQ™ across clinical trials, RPED occurred in 11% of patients, including patients with asymptomatic RPED. The median time to first onset of RPED was 26 days.

Among the 108 patients with cholangiocarcinoma enrolled in CBGJ398X2204, RPED was reported in 17% of patients. RPED led to dose interruption/reduction of infigratinib in 3.4% of patients and permanent discontinuation in 0.6% of patients.

Perform a comprehensive ophthalmic examination including optical coherence tomography (OCT) prior to initiation of TRUSELTIQ™, at 1 month, at 3 months, and then every 3 months thereafter during treatment. Refer patients for ophthalmic evaluation urgently for onset of visual symptoms, and follow-up every 3 weeks until resolution or discontinuation of TRUSELTIQ™.

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

See 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.

Dry Eye

Among 351 patients who received TRUSELTIQ™ across clinical trials, dry eye occurred in 29% of patients. Treat patients with ocular demulcents as needed.

Reproductive Health: Female and Male Potential

- **Fertility**

  No human data on the effect of TRUSELTIQ™ on fertility are available.

- **Teratogenic Risk**

  Based on findings in animal studies and its mechanism of action, TRUSELTIQ™ may cause fetal harm when administered to a pregnant woman. Oral administration of infigratinib to pregnant rats and rabbits during the period of organogenesis caused malformations, fetal growth retardation, and embryo-fetal death at maternal exposures lower than the human exposure based on area under the curve (AUC) at the clinical dose of 125 mg.

  Advise women of reproductive potential to use effective contraception during treatment with TRUSELTIQ™ and for 1 month after the last dose. Advise men who are partnered with women of reproductive potential to use effective contraception during treatment with TRUSELTIQ™ and for

1 month after the last dose. [see 7.1 WARNINGS AND PRECAUTIONS, Special Populations and 16 NON-CLINICAL TOXICOLOGY].

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data on TRUSELTIQ™ use in pregnant women to inform a drug-associated risk.

Based on the mechanism of action and findings in animal reproduction studies, TRUSELTIQ™ can cause embryo-fetal harm or loss of pregnancy when administered to a pregnant woman [see 16 NON-CLINICAL TOXICOLOGY].

Verify pregnancy status in females of reproductive potential prior to initiating TRUSELTIQ™. TRUSELTIQ™ should not be used during pregnancy. If TRUSELTIQ™ is used during pregnancy, or if the patient becomes pregnant while taking TRUSELTIQ™, advise the patient of the potential hazard to the fetus and counsel the patient about her clinical and therapeutic options.

7.1.2 Breast-feeding

There are no data on the presence of infigratinib 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 from TRUSELTIQ™, advise women not to breastfeed during treatment and for 1 month after the last dose.

7.1.3 Pediatrics

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

Of the 351 patients treated with TRUSELTIQ™ in clinical studies, 33% were 65 years or older, and 10% were 75 years or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

NOC/c 8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Based on the safety database of 108 patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement, the most common adverse reactions (≥20%) in patients receiving TRUSELTIQ™ included hyperphosphatemia, nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodyesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred and vomiting.

Serious adverse reactions occurred in 32% of patients receiving TRUSELTIQ™. Serious adverse reactions in ≥2% of patients who received TRUSELTIQ™ included infection, anemia, pyrexia, hypercalcemia, and sepsis. Fatal adverse reactions occurred in 0.9% of patients and included sepsis.

The following adverse reactions are discussed elsewhere in the labeling:

- Hyperphosphatemia and Soft Tissue Mineralization [see 7 WARNINGS AND PRECAUTIONS]; and
- Ocular Toxicity [see 7 WARNINGS AND PRECAUTIONS].

Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received TRUSELTIQ™. Adverse reactions requiring permanent discontinuation in 2% of patients were blood creatinine increased, fatigue, and subretinal fluid and calcinosis.

Dosage reductions due to an adverse reaction occurred in 60% of patients who received TRUSELTIQ™. Adverse reactions requiring dosage reductions in ≥2% of patients who received TRUSELTIQ™ included hyperphosphatemia (26%), stomatitis (12%), palmar-plantar erythrodysesthesia syndrome (8%), increased blood creatinine (4%), increased lipase (4%), hypercalcemia (3%), and onycholysis (3%).

Dosage interruptions due to an adverse reaction occurred in 64% of patients who received TRUSELTIQ™. Adverse reactions requiring dosage interruption in ≥5% of patients included hyperphosphatemia , hypercalcemia , palmar-plantar erythrodysesthesia syndrome , stomatitis , and diarrhea and blood creatinine increased.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of TRUSELTIQ™ was evaluated in Study CBGJ398X2204, which included 108 patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement.

Patients were treated orally with TRUSELTIQ™ 125 mg once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles, until disease progression or unacceptable toxicity. The median duration of treatment was 5.52 months (range: 0.03 to 28.29 months).

Table 5 summarizes the adverse reactions in study CBGJ398X2204.

Table 5: Adverse Reactions (≥15%) in Patients Receiving TRUSELTIQ™ in Study CBGJ398X2204

Adverse Reaction	TRUSELTIQ™ N=108	
	All Grades (%)	Grades ≥3[a] (%)
Blood and lymphatic system disorders		
Anemia	19	4
Eye disorders		
Dry eye[b]	44	2
Eyelash changes[c]	25	0
Vision blurred	21	0
Gastrointestinal disorders		
Stomatitis[d]	56	15
Constipation	30	1
Dry mouth	25	0
Diarrhea	24	3
Vomiting	21	1
Nausea	19	1
Abdominal pain	17	4
Dyspepsia	17	0
General disorders and administration site conditions		
Fatigue[e]	44	4
Edema	17	1
Pyrexia	15	1
Investigations		
Blood creatinine increased	24	0
Aspartate aminotransferase increased	21	2
Metabolism and nutrition disorders		
Hyperphosphatemia[f]	78	11
Hypercalcemia	25	6
Hypophosphatemia	22	13
Decreased appetite	22	1
Musculoskeletal and connective tissue disorders		
Arthralgia	32	0
Pain in extremity	17	2
Nervous system disorders		
Dysgeusia	32	0
Headache	17	1
Respiratory, thoracic and mediastinal disorders		
Epistaxis	18	0

Adverse Reaction	TRUSELTIQ™ N=108	
	All Grades (%)	Grades ≥3[a] (%)
Skin and subcutaneous tissue disorders		
Nail toxicity[g]	57	2
Alopecia	38	0
Palmar-plantar erythrodysesthesia syndrome	33	7
Dry skin	23	0

[a] Only Grades 3 and 4.
[b] Includes dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis.
[c] Includes blepharitis, eyelash changes, eyelash discoloration, growth of eyelashes, trichiasis, and trichomegaly.
[d] Includes mouth ulceration and stomatitis.
[e] Includes asthenia and fatigue.
[f] Includes hyperphosphatemia and blood phosphorous increased.
[g] Includes ingrown nail, nail bed bleeding, nail bed disorder, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail hypertrophy, nail infection, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia.

Note: Adverse reactions were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 4.03.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Not applicable.

8.3 Less Common Clinical Trial Adverse Reactions

The following are the less common clinical trial reactions occurring in <15% and >5% of patients receiving TRUSELTIQ™ in Study CBGJ398X2204:

Blood and lymphatic system disorders: lymphopenia, neutropenia, thrombocytopenia
Eye disorders: cataract, chorioretinopathy, subretinal fluid
Gastrointestinal disorders: abdominal pain upper, dysphagia, gastroesophageal reflux disease, oral pain
General disorders and administration site conditions: chills, non-cardiac chest pain,
Infections and Infestations: urinary tract infection
Investigations: alanine aminotransferase increased, blood alkaline phosphatase increased, weight decreased, lipase increased, blood bilirubin increased, amylase increased
Metabolism and nutrition disorders: dehydration, hyperkalemia, hypertriglyceridemia, hyperuricemia, hypokalemia, hypomagnesemia, hyponatremia
Musculoskeletal and connective tissue disorders: back pain, flank pain, muscular weakness, myalgia
Nervous system disorders: dizziness, peripheral sensory neuropathy
Psychiatric Disorders: insomnia
Respiratory, thoracic and mediastinal disorders: cough, dyspnea, oropharyngeal pain

Skin and subcutaneous tissue disorders: pruritus, rash, rash maculo-papular

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable.

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

Clinical Trial Findings

Table 6: Select Laboratory Abnormalities Worsening from Baseline Reported in ≥15% of Patients in Study CBGJ398X2204

Laboratory Abnormality	N=108	
	All Grades (%)	Grades ≥3 (%)
Hematology		
Hemoglobin decreased	51	5
Leukocytes decreased	30	3
Lymphocytes decreased	42	9
Platelets decreased	35	4
Chemistry		
Alanine aminotransferase increased	51	6
Albumin decreased	24	1
Alkaline phosphatase increased	52	8
Aspartate aminotransferase increased	37	4
Bilirubin increased	24	6
Calcium increased	50	11
Cholesterol increased	16	1
Creatinine increased	95	7
Lipase increased	45	8
Phosphate decreased	63	31
Phosphate increased[a]	89	13
Potassium decreased	22	3
Potassium increased	17	3
Sodium decreased	41	20
Triglycerides increased	38	2
Urate increased	36	36

The denominator used to calculate the rate varied from 94 to 107 based on the number of patients with a baseline value and at least one post-treatment value.
Graded per NCI CTCAE 4.03.
[a] NCI CTCAE 4.03 does not define grades for increased phosphate. Laboratory value shift table categories were used to assess increased phosphorus levels (Grades ≥3 defined as ≥9.0 mg/dL [≥2.907 mmol/L]).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

CYP3A4 Inhibitors

Concomitant use of a strong or moderate CYP3A4 inhibitor with TRUSELTIQ™ may increase infigratinib plasma concentrations, which may increase the incidence and severity of adverse reactions. Avoid concomitant use of strong or moderate CYP3A4 inhibitors with TRUSELTIQ™.

CYP3A4 Inducers

Concomitant use of TRUSELTIQ™ with a strong or moderate CYP3A4 inducer may decrease infigratinib plasma concentrations, which may reduce the efficacy of TRUSELTIQ™. Avoid concomitant use of strong or moderate CYP3A4 inducers with TRUSELTIQ™.

Gastric Acid Reducing Agents

The coadministration of TRUSELTIQ™ with a gastric acid reducing agent may decrease the concentration of infigratinib, which may reduce the efficacy of TRUSELTIQ™.

Proton pump inhibitors, histamine-2 (H2) receptor antagonists, and locally-acting antacids should be avoided. If coadministration of gastric acid reducing agents cannot be avoided, use an H2-antagonist or locally-acting antacid and stagger administration of TRUSELTIQ™. TRUSELTIQ™ should be taken ≥2 hours before or 10 hours after administration of H2-antagonists. Locally-acting antacids should be taken at least 2 hours before or after TRUSELTIQ™ dosing.

Drug Metabolizing Enzymes

No clinically significant differences in the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) were observed when co-administered after multiple doses of 125 mg TRUSELTIQ™.

Based on in vitro studies, infigratinib does not induce CYP1A2, CYP2B6, CYP2C9, or CYP3A4. Infigratinib, BHS697, or CQM157 do not inhibit major CYP isozymes at clinically relevant concentrations.

Drug Transporters

Based on in vitro studies, infigratinib inhibits MATE1 and BCRP. Infigratinib has a low potential to inhibit P-gp, BSEP, OCT1, OCT2 and MATE-2K at clinically relevant concentrations. Infigratinib is a substrate for P-gp and BCRP. The metabolites BHS697 and CQM157 have a low potential to inhibit OATP1B1, OATP1B3, P-gp, or BCRP at clinically relevant concentrations. The effect of these metabolites to inhibit MATE or OCT at clinically relevant concentrations is unknown.

Phosphate Binder

Based on population PK analysis, a 25% increase in infigratinib exposure (AUC) on Cycle 1 Day 1 was observed in cholangiocarcinoma patients who received phosphate binder with infigratinib on Cycle 1 Day 1. Due to limited data, the clinical relevance could not be established.

9.4 Drug-Drug Interactions

The drugs listed in Table 7 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 7: Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Strong CYP3A4 inhibitor	Clinical trial	Coadministration of multiple doses of itraconazole, a strong CYP3A4 inhibitor, with a single 75 mg infigratinib administration increased infigratinib AUC_{0-inf} by 622% and C_{max} by 164%, increased BHS697 (active metabolite) AUC_{0-inf} by 174%, and decreased CQM157 (active metabolite) C_{max} by 69%	Avoid concomitant use of strong CYP3A4 inhibitors with TRUSELTIQ™
Moderate CYP3A4 inhibitor	Predicted	The risk of a moderate CYP3A4 inhibitor affecting the pharmacokinetics of infigratinib has not been evaluated	Avoid concomitant use of moderate CYP3A4 inhibitors with TRUSELTIQ™
Strong CYP3A4 inducer	Clinical trial	Coadministration of multiple doses of rifampin, a strong CYP3A4 inducer, with a single 125 mg infigratinib administration decreased infigratinib AUC_{0-inf} by 56% and C_{max} by 44%, decreased BHS697 AUC_{0-inf} by 65% and C_{max} by 27%, and decreased CQM157 AUC_{0-inf} by 76% and C_{max} by 50%	Avoid concomitant use of strong CYP3A4 inducers with TRUSELTIQ™
Moderate CYP3A4 inducer	Predicted	The risk of a moderate CYP3A4 inducer affecting the pharmacokinetics of infigratinib has not been evaluated	Avoid concomitant use of moderate CYP3A4 inducers with TRUSELTIQ™

Gastric acid reducing agent	Clinical trial	Coadministration of multiple doses of lansoprazole, a proton pump inhibitor, with a single 125 mg infigratinib administration decreased infigratinib AUC_{0-inf} by 45% and C_{max} by 49%, decreased BHS697 AUC_{0-inf} by 32% and C_{max} by 44%, and decreased CQM157 AUC_{0-inf} by 72% and C_{max} by 55%	Proton pump inhibitors, H2-antagonists, and locally-acting antacids should be avoided. If coadministration of gastric acid reducing agents cannot be avoided, use an H2-receptor antagonist or locally- acting antacid and stagger administration of TRUSELTIQ™ (see 4 DOSAGE AND ADMINISTRATION).

9.5 Drug-Food Interactions

Administration of infigratinib with food (either a high-fat and high-calorie meal or a low-fat and low-calorie meal) was found to increase infigratinib exposure in healthy subjects [see 10 CLINICAL PHARMACOLOGY].

Grapefruit products should be avoided during treatment with TRUSELTIQ™.

Capsules should be taken on an empty stomach at least 1 hour before or 2 hours after food [see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY].

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

Avoid concomitant use of St. John's Wort, as this herb is a strong inducer of CYP3A.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

NOC/c 10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Infigratinib is a small molecule kinase inhibitor that targets of FGFR with in vitro IC_{50} values of 1.1, 1.0, and 2.0 nM and 61 nM for FGFR1, FGFR2, FGFR3 and FGFR4, respectively. The major active metabolites of TRUSELTIQ™, BHS697 and CQM157, showed similar in vitro binding activity as infigratinib towards FGFR1-3, with similar less potent activity toward FGFR4, in binding affinity studies. Infigratinib inhibited FGFR1-3 phosphorylation and signaling and decreased cell proliferation in cancer cell lines with activating FGFR amplifications, mutations, and fusions that resulted in constitutive activation of FGFR signaling. Constitutive FGFR signaling can support the proliferation and survival of malignant cells. Infigratinib exhibited anti-tumor activity in mouse and rat xenograft models of human tumors with activating FGFR2 or FGFR3 alterations, including two patient-derived xenograft models of cholangiocarcinoma that expressed FGFR2-TTC28 and FGFR2-TRA2B fusions. Infigratinib demonstrated

brain-to-plasma concentration ratios (based on AUC_{0-inf}) of 0.682 in rats after a single oral dose.

10.2 Pharmacodynamics

Cardiac Electrophysiology

According to a pharmacokinetic-pharmacodynamic analysis of pooled data from two open-label, uncontrolled studies with a combined total of 261 patients with advanced solid tumours, of whom 170 received infigratinib at a dose of 125 mg/day for 3 weeks on and 1 week off, large mean increases from baseline (i.e., >20 msec) in the QTc interval were not predicted for the reported C_{max} value of 295.3 ng/mL (geometric mean C_{max} for the 125 mg/day dose on day 15). The QT effect of infigratinib at higher exposures, such as those associated with CYP3A inhibition, has not been studied.

Serum Phosphate

TRUSELTIQ™ increased serum phosphate levels due to FGFR inhibition. In patients, the increase in serum phosphate observed after treatment with TRUSELTIQ™ was exposure-dependent across the dose range of 20 to 150 mg once daily (0.16 to 1.2 times the recommended dose), with increased risk of hyperphosphatemia with higher exposure to TRUSELTIQ™.

10.3 Pharmacokinetics

The pharmacokinetics of TRUSELTIQ™ and its active metabolites BHS697 and CQM157 have been studied in healthy subjects and oncology patients.

The infigratinib pharmacokinetic parameters are presented following administration of the approved recommended dosage in cholangiocarcinoma patients, unless otherwise specified.

After single and repeat once daily dosing, TRUSELTIQ™ exposure (C_{max} and AUC) increased more than proportionally across the dose range of 5 to 150 mg (0.04 to 1.2 times the maximum recommended dose). Steady state was achieved within 15 days with once daily dosing and the mean accumulation ratio was 8- and 5-fold for C_{max} and AUC, respectively.

Table 8: Summary of Steady State Pharmacokinetic Parameters of Infigratinib and its Metabolites (Mean (CV%)) in Patients with Cholangiocarcinoma Receiving TRUSELTIQ™

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_{0-24h} (ng•h/mL)	CL/F (L/h)	V/F (L)
Infigratinib	282.5 (54%)	6.0 (2-7)	33.5 (39%)	5742 (51%)	21.8 (51%)	1600 (33%)
BHS697	42.1 (65%)	4.0 (2-24)	47.6 (31%)	874 (68%)	NC	NC
CQM157	15.7 (92%)	5.1 (0.4-24)	76.4 (52%	371 (64)	NC	NC

AUC_{0-24h} = area under the plasma concentration-time curve from time 0 to 24 hours post dose; CL/F = apparent clearance; C_{max} = maximum plasma concentration; NC = not calculated; T_{max} = time to maximum plasma concentration; $t_{1/2}$ = half-life; V/F = apparent volume of distribution

Note: Pharmacokinetic parameters are described for steady state. AUC_{0-24h}, $C_{max,}$ T_{max} , and CL/F were calculated from observed data obtained in Study CBGJ398X2204. $T_{1/2}$ and V/F are population PK model predicted values. Values provided are geometric means except for T_{max} (median).

Absorption

Median time to achieve peak plasma concentration (t_{max}) was 6.0 hours (range: 2 to 7 hours).

Effect of Food

Administration of infigratinib with a high-fat and high-calorie meal (800 to 1000 calories with about 50% of total caloric content from fat) or a low-calorie, low-fat meal (330 calories with about 20% of total caloric content from fat) was found to increase infigratinib exposure by approximately two-fold in healthy subjects.

Distribution:

The geometric mean (CV%) apparent volume of distribution of infigratinib was 1600 L (33%CV) at steady state.

Infigratinib protein binding was 98% in patients, primarily to alpha-1-acid glycoprotein.

Metabolism:

Infigratinib is predominantly metabolized by CYP3A4. The contribution of CYP3A4 in the total clearance of infigratinib is estimated to be 94% and to a lesser extent by FMO3 estimated to be 6% in vitro. The major drug-related moiety in plasma was unchanged infigratinib (38% of dose) in a human [^{14}C] mass balance study, followed by two active metabolites, BHS697 and CQM157 (each at >10% of dose).

BHS697 is mainly metabolized by CYP3A4 and CQM157 is metabolized through both Phase I and Phase II biotransformation pathways.

BHS697 and CQM157 contribute about 16% to 33% and 9% to 12% of overall pharmacologic activity, respectively.

Elimination

The geometric mean (CV%) total apparent clearance (CL/F) of infigratinib at steady state was 21.77 L/h (50.6%CV). The geometric mean (CV%) terminal half-life of infigratinib at steady state was 33.5 (39%) hours.

After a single oral 125 mg dose of radiolabeled infigratinib in healthy subjects, approximately 77% of the dose was recovered in feces (3.4% as unchanged) and 7.2% in urine (1.9% as unchanged).

Special Populations and Conditions

- **Geriatrics:** In the population PK analysis**,** no clinically meaningful differences in the systemic exposure of infigratinib were observed based on age (19 to 86 years).
- **Sex:** In the population PK analysis, no clinically meaningful differences in the systemic exposure of infigratinib were observed based on sex.
- **Ethnic Origin:** In the population PK analysis, no clinically meaningful differences in the systemic exposure of infigratinib were observed based on race/ethnicity.
- **Hepatic Insufficiency:** Based on a hepatic impairment study, mean exposure of infigratinib increased in subjects with mild (NCI-OWDG mild) and moderate (NCI-OWDG moderate) hepatic impairment. Infigratinib exposure increased by 52% (C_{max}) to 108% (AUC_{inf}) in subjects with mild hepatic impairment and increased by 123% (C_{max}) to 124% (AUC_{inf}) in subjects with moderate

hepatic impairment relative to subjects with normal liver function.

BHS697 exposure decreased by 21% in C_{max} to increase by 15% in AUC_{inf} in subjects with mild hepatic impairment and increased by 34% in C_{max} to 29% in AUC_{inf} in subjects with moderate hepatic impairment relative to subjects with normal liver function. Mean exposure of the CQM157 decreased by 40% in C_{max} to 37% in AUC_{inf} in subjects with mild hepatic impairment and increased by 13% in C_{max} and decreased by 51% in AUC_{inf} in subjects with moderate hepatic impairment relative to subjects with normal liver function

The effect of severe hepatic impairment on infigratinib exposure is unknown.

- **Renal Insufficiency:** Based on population PK analysis, the relative potency adjusted steady state AUC of infigratinib plus its active metabolites (BHS697, CQM157) in plasma increased by 32% and 37% in patients with mild (creatinine clearance [CLcr] 60 to 89 mL/min estimated by Cockcroft-Gault) and moderate renal impairment (CLcr 30 to 59 mL/min), respectively, relative to patients with normal renal function (CLcr ≥ 90 mL/min).

  The effect of renal impairment or renal dialysis in end-stage renal disease on infigratinib exposure is unknown.

- **Obesity:** In the population PK analysis, no clinically meaningful differences in the systemic exposure of infigratinib were observed based on body weight (36.4 to 169.0 kg).

11 STORAGE, STABILITY AND DISPOSAL

Store TRUSELTIQ™ at 15°C to 25°C.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

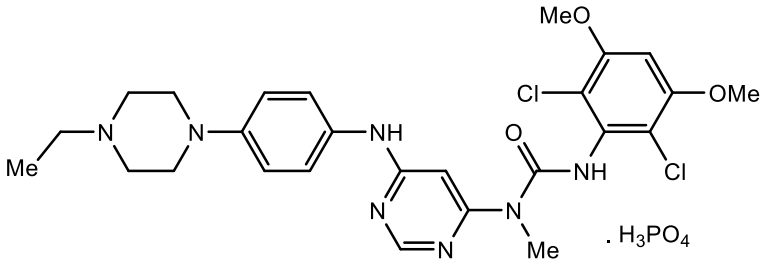
Drug Substance

Proper/Common name: Infigratinib phosphate

Chemical name: 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-{6-[4-(4-ethylpiperazin-1-yl)phenylamino]pyrimidin-4-yl}-1-methylurea phosphate (1:1)

Molecular formula and molecular mass: $C_{26}H_{31}Cl_2N_7O_3 \cdot H_3PO_4$ / 560.48 g/mol for the free base and 658.47 g/mol for the phosphate salt

Structural formula:



Physicochemical properties: Infigratinib phosphate is a white to off-white powder. It shows adequate solubility in water and 0.1N HCl. It is practically insoluble in pH 6.8 buffer and poorly soluble in common organic solvents.

NOC/c 14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 9: Summary of Patient Demographics for Patients with Previously Treated, Unresectable, Locally Advanced or Metastatic Cholangiocarcinoma with an FGFR2 Fusion or Other Rearrangement

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
CBGJ398 X2204	Multicentre, open-label, single-arm trial	125 mg TRUSELTIQ™, oral, once daily for 21 consecutive days / 7 days off therapy in 28-day cycles	108 cholangio-carcinoma subjects	53 years (23 to 81 years)	41 male / 67 female

Study CBGJ398X2204 (NCT02150967), a multicenter, open-label, single-arm trial, evaluated the efficacy of TRUSELTIQ™ in 108 patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement, as determined in laboratory using next generation sequencing (local or central lab) (89%) or other nucleic-acid based tests (local lab) (11%). Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene that leaves the FGFR2 kinase domain intact.

Patients received TRUSELTIQ™ as an oral monotherapy at 125 mg once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. TRUSELTIQ™ was administered in 28-day cycles until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR), as determined by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age was 53 years (range: 23 to 81 years), 62% were female, 72% were White, and 99% had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (42%) or 1 (57%). In-frame fusions and other rearrangements predicted to have breakpoint within intron 17/exon 18 of the FGFR2 gene that leaves the FGFR2 kinase domain intact were confirmed in 104 enrolled subjects (96%) with local or central laboratory Next Generation Sequencing (NGS) testing. Eighty-eight patients had in-

frame FGFR2 fusions, with BICC1 the most commonly reported partner gene for FGFR2 fusions (n=27, 25%). Twenty (19%) patients had other FGFR2 rearrangements that may not be in-frame with the partner gene or the partner gene was not identifiable.

Ninety-nine percent of patients had metastatic (Stage IV) disease at the time of study entry. All patients had received at least 1 prior line of systemic therapy, 32% had 2 prior lines of therapy, and 29% had 3 or more prior lines of therapy. Ninety-nine percent of patients received prior gemcitabine-based therapy and most (88%) had progressed on their prior gemcitabine-based therapy.

14.2 Study Results

The primary endpoint (ORR assessed by BICR) was 23.1% (95% confidence interval [CI]: 15.6, 32.2) including 1 subject with a confirmed complete response (CR) and 24 subjects with confirmed partial response (PR) (Table 10). The Kaplan-Meier (K-M) estimate for median DoR assessed by BICR was 5 months (95% CI: 3.71, 9.26).

Efficacy results are summarized in Table 10. The median time to response was 3.6 months (range 1.4 to 7.4 months).

Table 10: Efficacy Results in Study CBGJ398X2204

Efficacy Parameter	TRUSELTIQ™ N=108 BICR Assessment
ORR (95% CI)	**23.1% (15.6, 32.2)**
Complete Response, n (%)	1 (1%)
Partial Response, n (%)	24 (22.2%)
Median DoR (months) (95% CI)	**5 (**(3.71, 9.26)**)**
Patients with DoR ≥6 months, n (%)	8 (32%)

BICR = blinded independent central review; CI = confidence interval; DoR = duration of response; ORR = overall response rate

Note: Data are according to RECIST v1.1, and complete and partial responses are confirmed.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Repeat-dose studies in rats and dogs were conducted for periods > 13-weeks.

In the 13-week study in rats, the highest dose tested was 10 mg/kg/day corresponding to a lower exposure than the clinical recommended dose of 125 mg, based on AUC. Observed toxicities included effects on teeth (including incisor degeneration with degeneration of enamel, loss of ameloblast layer and fractures), bones (growth plate thickening in femur and sternum), eye (keratopathy and corneal mineralization), kidney (mineralization), nasal cavity (chondrocytes hypertrophy), tongue and hard palate (decreased epithelium thickness). Recovery (following a 6-week recovery period) was observed

for most toxicities, with persisting effects on teeth and kidney and ocular mineralization. In this study, the NOAEL was considered 1 mg/kg/day.

In the 13-week dog study, at the highest dose of 10 mg/kg/day (lower than human exposure, based on AUC at the recommended dose), clinical signs included liquid feces, partially digested food and generalized thinness. Microscopic findings were observed in the sternum (growth plate thickening), in the meibomian glands (acinar atrophy and ducts dilatation), in the sebaceous glands (acinar atrophy) and skin (hyperkeratosis). All the changes were recoverable or showed ongoing recovery (sternum and meibomian glands). In this study, the NOAEL was considered 1 mg/kg/day.

Changes in appearance (longer hair, prominent backbone) and changes in plasma FGF23 levels (reversed after recovery period) were observed in both rats and dogs.

In a 26-week rat study, bone effects were observed in lumbar vertebral bodies including decreased bone strength consistent with decreases in total bone mineral density, at ≥ 1 mg/kg/day doses. Increased growth plate thickness and fractures associated with increased physeal thickness, focal mixed reaction, and bone loss were observed in a 39-week dog study, at 3 mg/kg/day.

In a 2-week repeat-dose mechanistic study investigating tissue mineralization, histopathological examination showed morphological changes in blood vessels, lungs, kidneys and bones at 20 mg/kg/day. Vascular changes included degeneration and mineralization in large blood vessels and in vessels of different organs (heart, GI-tract, kidneys and lungs). Bone changes were observed at doses >10 mg/kg/day. Reversibility or a tendency to reversibility was seen in all affected organs. Mineralization was not recoverable.

Carcinogenicity: Carcinogenicity studies have not been conducted with infigratinib.

Genotoxicity: Infigratinib was not mutagenic in a bacterial reverse mutation (Ames) assay and was not clastogenic in an in vitro human peripheral blood lymphocyte chromosome aberration assay. Infigratinib did not induce micronuclei in an in vivo rat bone marrow micronucleus assay. The major metabolites BHS697 and CQM157 were also not mutagenic.

Reproductive and Developmental Toxicology: Embryo-fetal development studies investigating the administration of infigratinib during the period of organogenesis were conducted in rats and rabbits. In rats, infigratinib administration resulted in an increase in embryo-fetal lethality at 10 mg/kg/day, and reductions in fetal body weights at 3 and 10 mg/kg/day. Fetal abnormalities (external, soft tissue, and skeletal) were increased at ≥1 mg/kg/day (maternal exposures < 0.1 times the recommended human dose of 125 mg, based on AUC). Once daily oral administration of infigratinib at ≥0.3 mg/kg/day to pregnant rabbits resulted in maternal toxicity and a corresponding reduction in fetal body weights (maternal exposures at all dose levels less than the human exposure (AUC) at the recommended human dose of 125 mg). Correlated with the reduction in fetal weights was a decrease in the numbers of ossification sites in some bones.

In a rat fertility study, there were no effects on mating or fertility, reproductive organ weights, or sperm motility, density, or morphology in males, and no effect on estrous cycling, mating, or fertility in females administered ≤3 mg/kg/day infigratinib. In the embryo-fetal portion of the study, a decrease in the mean number of embryos in females at 3 mg/kg/day was observed and associated with an increase in the number of nonviable embryos and in the percentage of post implantation loss. This dose corresponds to an exposure lower than human exposure, based on AUC at the clinical dose of 125 mg.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TRUSELTIQ™

Infigratinib Capsules

Read this carefully before you start taking **TRUSELTIQ™** 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 **TRUSELTIQ™**.

What is TRUSELTIQ™ used for?

For the following indication TRUSELTIQ™ 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.

TRUSELTIQ™ is used to treat adult patients 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,
- it cannot be removed with surgery, and
- 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 abnormality. This is to make sure that TRUSELTIQ 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 TRUSELTIQ™ work?

Fibroblast growth factor receptors (FGFRs) are proteins found on cells that help them grow and divide. People with bile duct cancer may have abnormalities in the FGFR2 gene. This causes their cancer cells

to grow and spread. TRUSELTIQ™ works by slowing down the growth and/or spread of cancer cells caused by the FGFR2 abnormality.

What are the ingredients in TRUSELTIQ™?

Medicinal ingredients: infigratinib (as infigratinib phosphate)

Non-medicinal ingredients: black iron oxide, colloidal silicon dioxide, crospovidone, gelatin, hypromellose, lactose monohydrate, magnesium stearate (from vegetable source), microcrystalline cellulose, pharmaceutical grade printing ink, red iron oxide, titanium dioxide, and yellow iron oxide.

TRUSELTIQ™ comes in the following dosage forms:

Capsules: 25 mg and 100 mg infigratinib (as infigratinib phosphate)

Do not use TRUSELTIQ™ if:

- You are allergic to infigratinib or any of the other ingredients in TRUSELTIQ™ in any part of the container.

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

- have liver problems.
- have kidney problems.

Other warnings you should know about:

Treatment with TRUSELTQ can cause serious side effects, including:

- **Hyperphosphatemia** (high phosphate levels in the blood) or **Hypophosphatemia** (low phosphate levels in the blood): Your healthcare professional will do blood tests to check levels of phosphate in your blood. These tests will be done 7-14 days after starting TRUSELTIQ™. They will be repeated after your first treatment cycle and then every month thereafter. If your levels are high, you may need:
  - changes to your dose of TRUSELTIQ™, or
  - additional medications to lower the amount of phosphate in your blood.
- **Eye and vision problems** including:
  - Dry eye. If this happens your healthcare professional may recommend that you use artificial tears or something similar.
  - **Retinal pigment epithelial detachment (RPED)**. This condition happens when fluid builds up inside the eye. It can lead to blurred vision.
  - Your healthcare professional will check your eyes and vision before you start taking TRUSELTIQ™, after your first month of treatment, after your first 3 months of treatment and then every 3 months thereafter. You may need to see an eye specialist (an ophthalmologist) during your treatment. This provider will help you to manage any eye or vision problems. Your healthcare professional will continue to check your eyes

and vision every 3 weeks until the side effect goes away or you stop taking TRUSELTIQ™.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Birth control, pregnancy and breastfeeding – information for women

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

Birth control and pregnancy – information for men:

- Use effective birth control each time you have sex with a woman who can get pregnant. This is necessary during your treatment with TRUSELTIQ™ and for 1 month after your last dose. If your sexual partner gets pregnant during this time, 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 TRUSELTIQ™. 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 TRUSELTIQ™:

- Medicines used to treat bacterial, viral and fungal infections including
    - rifampin, clarithromycin
    - indinavir, ritonavir
    - itraconazole, ketoconazole
- An herbal remedy typically used to treat depression called St. John's wort
- Medicines used to treat heartburn and acid reflux called histamine-2 (H2)-antagonists, proton pump inhibitors or antacids such as ranitidine, lansoprazole or calcium carbonate.
- Medicines used to lower the amount of phosphate.

Do not eat or drink grapefruit juice or products containing grapefruit during your treatment with TRUSLETIQ™. These can affect the way the medicine works.

How to take TRUSELTIQ™:

- Take TRUSELTIQ™ exactly as your healthcare provider professional tells you to. Check with your doctor or pharmacist if you are not sure.
- Do not separate the blister cards from the carton during your treatment.
- Take your dose once each day, at least 1 hour before or 2 hours after eating.
- Take TRUSELTIQ at about the same time each day.
- Swallow capsules whole with a glass of water. Do not open, crush, chew or dissolve capsules.
- You will take your TRUSELTIQ™ every day for 3 weeks in a row (days 1 to 21). This is followed by 1 week (days 22 to 28) with no doses (treatment-free week). Three weeks of treatment and 1 treatment-free week make up a 28-day cycle.
- Do not change your dose or stop taking TRUSELTIQ™ unless your healthcare provider tells you to.
- Avoid taking medications to treat heartburn or acid reflux while you are taking TRUSELTIQ. If you must take H2-antagonists or antacids, talk to your healthcare professional as there are specific instructions to follow.
  - If you take H2-antagonists: take your TRUSELTIQ™ 2 or more hours before or 10 hours after taking these medicines.
  - If you use antacids: take your TRUSELTIQ™ 2 hours before or 2 hours after taking these medicines.
- TRUSELTIQ™ is packaged in blister cards. To help track your doses, write the day you start each treatment cycle (start date) on the blister card. There is a spot for this information. For weeks 1, 2 and 3, push each cell to release the capsule. For week 4, use the peel away tabs to track the days of your treatment-free week.

Usual dose: 125 mg per day. This daily dose is made by taking one 25 mg capsule and one 100 mg capsule together each day for 3 weeks followed by a treatment free-week.

If you have kidney or liver problems, or you experience certain side effects, your healthcare professional may change your dose to one of the following:

100 mg per day: Take one 100 mg capsule each day.
75 mg per day: Take three 25 mg capsules together each day.
50 mg per day: Take two 25 mg capsules together each day.

Each of these daily doses is taken for 3 weeks followed by a treatment-free week.

Do not change your dose or stop taking TRUSELTIQ™ unless your healthcare professional tells you to. Your healthcare professional may temporarily or permanently stop your treatment. This may happen if you develop certain side effects or if your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much TRUSELTIQ™, 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 TRUSELTIQ™, or 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 TRUSELTIQ™, take it as soon as you remember. Continue with your next dose at the usual time.

What are possible side effects from using TRUSELTIQ™?

These are not all the possible side effects you may have when taking TRUSELTIQ™. If you experience any side effects not listed here, tell your healthcare professional.

- Feeling tired
- Fever
- Chills
- Nail changes
- Rash
- Itching
- Dry skin
- Eyelash changes
- Hair loss
- Redness, swelling, peeling or tenderness, mainly on the hands and feet (Hand-foot syndrome)
- Mouth sores
- Trouble swallowing
- Taste changes
- Constipation
- Dry mouth
- Diarrhea
- Decreased appetite
- Vomiting
- Nausea
- Heartburn or indigestion
- Mouth pain
- Joint, muscle, back or chest pain
- Pain in the extremities
- Muscle weakness
- Tingling and numbness in the hands and feet
- Pain or discomfort in stomach
- Swelling of the body parts
- Headache
- Dizziness
- Nose bleeds
- Trouble sleeping
- Cough
- Shortness of breath

TRUSELTIQ™ 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			
Eye and vision problems including retinal pigment epithelial detachment: vision changes, distorted vision, blurred vision, dry eye		✔	
Hyperphosphatemia (high blood phosphate levels): muscle cramps and tingling		✔	
COMMON			
Hypophosphatemia (low blood phosphate levels): muscle weakness and pain, confusion, seizures, tea-coloured urine, heart or breathing problems		✔	
Infection: Fever, burning or pain with urination		✔	
Anemia (decrease red blood cells): Fatigue, weakness		✔	
Blood creatinine increased: feeling tired, loss of appetite, nausea, itching		✔	
Sepsis (full-body response to infection): Fever, chills, shortness of breath and confusion		✔	
Hypercalcemia (increase in blood calcium): Bone pain, fatigue, headaches, lethargy		✔	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 TRUSELTIQ™ at 15°C to 25°C.

Keep out of reach and sight of children.

If you want more information about TRUSELTIQ™:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.qedtx.com, or by calling 1-905-477-4553.

This leaflet was prepared by QED Therapeutics., Inc.

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