

Attachment 1: Product information for AusPAR – Truseltiq - infigratinib - Adjutor Healthcare Pty Ltd - PM-2020-06031-1-4 FINAL 8 December 2022. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-one>>

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## AUSTRALIAN PRODUCT INFORMATION TRUSELTIQ™ (infigratinib) hard capsules

### 1 NAME OF THE MEDICINE

Infigratinib

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TRUSELTIQ™ 25 mg hard capsule contains 25 mg of infigratinib (as phosphate) [see Section 6.5 Nature and Contents of Container].

Each TRUSELTIQ™ 100 mg hard capsule contains 100 mg of infigratinib (as phosphate) [see Section 6.5 Nature and Contents of Container].

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

### 3 PHARMACEUTICAL FORM

TRUSELTIQ™ 25 mg is a hard gelatin capsule having a white opaque body and grey opaque cap, with 'INFI 25mg' printed in black on the body.

TRUSELTIQ™ 100 mg is a hard gelatin capsule having a white opaque body and light orange opaque cap, with 'INFI 100mg' printed in black on the body.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

TRUSELTIQ™ has **provisional approval** in Australia 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 [see Section 4.2 Dose and Method of Administration]. The decision to approve this indication has been made on the basis of overall response rate and duration of response in a single arm trial. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

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## 4.2 DOSE AND METHOD OF ADMINISTRATION

### Patient Selection

Select patients for the treatment of unresectable locally advanced or metastatic cholangiocarcinoma with TRUSELTIQ™ based on the presence of an FGFR2 fusion or rearrangement, as detected by a validated test [see Section 5.1 Clinical Trials].

### Recommended Dosage

The recommended dose of TRUSELTIQ™ is 125 mg (one 100 mg hard capsule and one 25 mg hard 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.

### Method of Administration

Hard capsules should be taken on an empty stomach at least 1 hour before or 2 hours after a meal, at approximately the same time each day (preferably in the morning). Swallow the hard capsules whole with a large glass of water. Do not open, crush, chew, or dissolve the hard capsules.

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.

### Dose Modification for Adverse Reactions

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

**Table 1: Recommended Dose Reductions for TRUSELTIQ™ for Adverse Reactions**

Dose	1 <sup>st</sup> Dose Reduction	2 <sup>nd</sup> Dose Reduction	3 <sup>rd</sup> Dose Reduction
125 mg (one 100 mg and one 25 mg hard capsule)	100 mg (one 100 mg hard capsule)	75 mg (three 25 mg hard capsules)	50 mg (two 25 mg hard capsules)

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

**Table 2: Recommended Dose Modifications for TRUSELTIQ™ for Adverse Reactions**

Adverse Reaction	TRUSELTIQ™ Dose Modifications
<b>Ocular Disorders</b> [see Section 4.4 Special Warnings and Precautions for Use]	
<b>Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED)</b>	
Grade 2 and 3 CSR/RPED and CSR/RPED-like events	Withhold TRUSELTIQ™ until resolved to Grade ≤1 and continue periodic ophthalmic evaluation. <ul style="list-style-type: none"> <li>• If resolved within ≤14 days, resume TRUSELTIQ™ at the next lower dose level.</li> <li>• If not resolved after 14 days, permanently discontinue TRUSELTIQ™.</li> </ul>

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Grade 4 CSR/RPED and CSR/RPED-like events	Permanently discontinue TRUSELTIQ™.
<b>Hyperphosphataemia</b> [see Section 4.4 Special Warnings and Precautions for Use]	
Serum phosphate >5.5 – ≤7.5 mg/dL	Continue TRUSELTIQ™ at current dose. Initiate or dose adjust phosphate lowering therapy according to respective product information. <i>Phosphate binder dosing should be held during the week off TRUSELTIQ™ therapy each cycle (Days 22-28) and during TRUSELTIQ™ dose interruptions for non-hyperphosphataemia adverse events.</i>
Serum phosphate >7.5 mg/dL <b>Or</b> Single serum phosphate >9.0 mg/dL regardless of duration or dose of phosphate lowering therapy.	Withhold TRUSELTIQ™ until level returns to serum phosphate ≤5.5 mg/dL. Resume TRUSELTIQ™ as below, with maximal phosphate binder dosing: <ul style="list-style-type: none"> <li>• If the patient did not receive maximal phosphate binder dosing for serum phosphate &gt;7.5 mg/dL or if serum phosphate &gt;7.5 mg/dL occurred for less than 7 days: Restart TRUSELTIQ™ at the same dose.</li> <li>• If the patient had received maximal phosphate lowering therapy for serum phosphate &gt;7.5 mg/dL for &gt;7 days or if patient had a one-time serum phosphate of &gt;9.0 mg/dL: Resume TRUSELTIQ™ at the next lower dose level.</li> </ul> It is recommended that phosphate binder dosing continues during TRUSELTIQ™ dose interruptions for hyperphosphataemia and that serum phosphate values be monitored frequently, eg, every 2-3 days. <i>Phosphate binder dosing should be held during the week off TRUSELTIQ™ therapy each cycle (Days 22-28) and during TRUSELTIQ™ dose interruptions for non-hyperphosphataemia adverse events.</i>
Serum phosphate with life-threatening consequences; urgent intervention indicated (eg, dialysis)	Permanently discontinue TRUSELTIQ™.
<b>Other adverse reactions<sup>a</sup></b>	
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™.

<sup>a</sup> Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

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### **Dose Modifications for Mild and Moderate Renal Impairment**

The recommended dosage 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 Section 4.4 Special Warnings and Precautions for Use and Section 5.2 Pharmacokinetic Properties].

### **Dose Modifications for Moderate Hepatic Impairment**

The recommended dosage of TRUSELTIQ™ 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 to 3 × ULN with any AST) is as follows [see 4.4 Special Warnings and Precautions for Use].

- 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.

## **4.3 CONTRAINDICATIONS**

TRUSELTIQ™ is contraindicated in patients with hypersensitivity to infigratinib or to any other ingredients in TRUSELTIQ™ hard capsules.

## **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

### **Ocular Disorder**

#### Central Serous Retinopathy/Retinal Pigment Epithelial Detachment (CSR/RPED)

TRUSELTIQ™ can cause CSR/RPED, which may cause symptoms such as blurred vision. All clinical trials of TRUSELTIQ™ conducted frequent routine ophthalmic monitoring to detect asymptomatic CSR/RPED.

Among 351 patients who received TRUSELTIQ™ across clinical trials, CSR/RPED occurred in 11% of patients. The median time to first onset of CSR/RPED was 26 days. CSR/RPED led to dose interruption/reduction of TRUSELTIQ™ 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™.

If a patient loses visual acuity with corresponding changes on macular OCT (PED-like or CSR-like chorioretinopathy) continue current dose and review in 14 days. If resolving chorioretinopathy continue infigratinib, if getting worse or not resolving, reduce dose or cease treatment in conjunction with treating physician.

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### Dry Eye

Among 351 patients who received TRUSELTIQ™ across clinical trials, dry eye occurred in 24% of patients, including Grade 3 in 0.3% of patients. No Grade 4 dry eye was observed. Treat patients with ocular demulcents as needed.

### **Hyperphosphataemia and Soft Tissue Mineralisation**

TRUSELTIQ™ can cause hyperphosphatemia leading to soft tissue mineralisation, cutaneous calcinosis, non-uremic calciphylaxis, vascular calcification, and myocardial calcification. Increases in phosphate levels may occur as a pharmacodynamic effect of TRUSELTIQ™ [see Section 5.1 Pharmacodynamic properties]. Among 351 patients who received TRUSELTIQ™ across clinical trials, hyperphosphataemia was reported in 82% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphataemia was 8 days (range 1-349). Phosphate-lowering therapy was received by 83% of patients who received TRUSELTIQ™.

Monitor for hyperphosphataemia throughout treatment. Initiate phosphate lowering therapy when serum phosphate is >5.5 mg/dL. For serum phosphate >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 Section 4.2 Dose and Method of Administration].

### **Patients of Reproductive Potential**

#### Pregnancy Testing

In females of reproductive potential, pregnancy should be verified and excluded prior to initiating treatment with TRUSELTIQ™ [see Section 4.6 Fertility, Pregnancy and Lactation].

#### Contraception

TRUSELTIQ™ may cause embryo-fetal harm when administered to a pregnant woman [see Section 4.6 Fertility, Pregnancy and Lactation].

#### Females

Females of reproductive potential must be advised to use effective contraception during treatment with TRUSELTIQ™ and for 1 month after the last dose.

#### Males

Males that are partnered with females of reproductive potential must be advised to use effective contraception during treatment with TRUSELTIQ™ and for 1 month after the last dose.

### **Use in hepatic impairment**

Reduce the dosage of TRUSELTIQ™ 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. The recommended dosage of TRUSELTIQ™ has not been established in patients with severe (total bilirubin > 3 × ULN with any AST) hepatic impairment [see Section 4.2 Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties].

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### **Use in renal impairment**

Reduce the dosage of TRUSELTIQ™ for patients with mild or moderate renal impairment (creatinine clearance [CL<sub>cr</sub>] 30 to 89 mL/min estimated by Cockcroft-Gault). The effect of severe renal impairment (CL<sub>cr</sub> < 30 mL/min) or renal dialysis in end-stage renal disease on infigratinib exposure is unknown [see Section 5.2 Pharmacokinetic Properties].

### **Use in the elderly**

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 effectiveness were observed between these patients and younger patients.

### **Paediatric use**

The safety and effectiveness of TRUSELTIQ™ in paediatric patients with cancer have not been established.

### **Effects on laboratory tests**

No data available.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

### Strong and moderate CYP3A4 Inhibitors

Concomitant use of TRUSELTIQ™ with a strong or moderate CYP3A4 inhibitor may increase infigratinib plasma concentrations [see Section 5.2 Pharmacokinetic Properties], which may increase the risk of adverse reactions. Avoid concomitant use of TRUSELTIQ™ with strong or moderate CYP3A4 inhibitors.

Coadministration of multiple doses of itraconazole (strong CYP3A4 inhibitor) increased infigratinib AUC<sub>0-inf</sub> by 622% and C<sub>max</sub> by 164%, increased BHS697 AUC<sub>0-inf</sub> by 174%, and decreased CQM157 C<sub>max</sub> by 69% respectively.

### Strong and moderate CYP3A4 Inducers

Concomitant use of TRUSELTIQ™ with a strong or moderate CYP3A4 inducer may decrease infigratinib plasma concentrations [see Section 5.2 Pharmacokinetic Properties], which may reduce TRUSELTIQ™ anti-tumour activity. Avoid concomitant use of TRUSELTIQ™ with strong or moderate CYP3A4 inducers.

Coadministration of multiple doses of rifampin (strong CYP3A4 inducer) decreased infigratinib AUC<sub>0-inf</sub> by 56% and C<sub>max</sub> by 44%, decreased BHS697 AUC<sub>0-inf</sub> by 65% and C<sub>max</sub> by 27%, and decreased CQM157 AUC<sub>0-inf</sub> by 76% and C<sub>max</sub> by 50% respectively.

### Gastric Acid Reducing Agents

The coadministration of TRUSELTIQ™ with a gastric acid reducing agent may decrease the concentration of infigratinib, which may reduce TRUSELTIQ™ anti-tumour activity

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Avoid concomitant use of TRUSELTIQ™ with proton pump inhibitors (PPIs), H<sub>2</sub>-antagonists, and locally acting antiacids. If coadministration of H<sub>2</sub>-antagonists or locally acting antiacids cannot be avoided, stagger administration of TRUSELTIQ™.

Coadministration of multiple doses of lansoprazole (proton pump inhibitor) decreased ifigRatinib AUC<sub>0-inf</sub> by 45% and C<sub>max</sub> by 49%, decreased BHS697 AUC<sub>0-inf</sub> by 32% and C<sub>max</sub> by 44%, and decreased CQM157 AUC<sub>0-inf</sub> by 72% and C<sub>max</sub> by 55% respectively.

TRUSELTIQ™ should be taken ≥2 hours before or 10 hours after dosing with H<sub>2</sub>-antagonists. Antacids should be taken at least 2 hours before or after TRUSELTIQ™ dosing.

#### Sensitive CYP3A4 Substrate

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

#### In Vitro Studies

*Effects of ifigRatinib on CYP substrates:* IfigRatinib does not induce CYP1A2, CYP2B6, CYP2C9 or CYP3A4. IfigRatinib, BHS697, or CQM157 do not inhibit major CYP isozymes at clinically relevant concentrations.

*Effects of transporters on ifigRatinib:* IfigRatinib is a substrate for P-gp/BCRP.

*Effects of ifigRatinib on transporters:* IfigRatinib has a low potential to inhibit P-gp, BSEP, OCT1, OCT2, and MATE-2K at clinically relevant concentrations. IfigRatinib inhibited BCRP and MATE1; clinical interactions with sensitive BCRP and MATE1 probes cannot be excluded. The metabolites BHS697 and CQM157 have a low potential to inhibit OATP1B1, OATP1B3, P-gp, or BCRP at clinically relevant concentrations.

#### Food-drug interactions

Grapefruit products should be avoided during treatment with TRUSELTIQ™.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

#### Effects on fertility

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 ifigRatinib. In the embryo-fetal portion of the study, a decrease in the mean number of viable 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 at 1 and 3 mg/kg/day (exposures <0.1 times the human exposure at the clinical dose of 125 mg, based on AUC).

#### **Use in pregnancy – Pregnancy Category D**

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

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Based on the mechanism of action and findings in animal reproduction studies, TRUSELTIQ™ may cause embryo-fetal harm or loss of pregnancy when administered to a pregnant woman [see Effects on fertility]. Advise pregnant women and women of reproductive potential of the potential risk to the fetus.

Oral administration of infigratinib to pregnant rats and rabbits during the period of organogenesis at maternal exposures that were less than the human exposures at the clinical dose of 125 mg based on AUC resulted in malformations, fetal growth retardation, and embryo-fetal death.

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  $\geq 1$  mg/kg/day (exposures  $< 0.1$  times the human exposure at the clinical dose of 125 mg, based on AUC).

In rabbits, infigratinib administration resulted in reductions in maternal body weight gain at all doses (0.3 3 mg/kg/day) and reductions in fetal body weights at 3 mg/kg/day (exposures at 0.3 and 3 mg/kg/day, respectively,  $< 0.1$  and 2 times the human exposure at the clinical dose of 125 mg, based on AUC). Correlated with the reduction in fetal weights was a decrease in the numbers of ossification sites in some bones.

Advise pregnant women and women of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with TRUSELTIQ™ and for 1 month after the last dose [see Section 4.4 Special Warnings and Precautions for Use].

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 Section 4.4 Special Warnings and Precautions for Use].

#### **Use in lactation**

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.

#### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

Patients should be advised not to drive or operate machinery if they experience any adverse effects that cause visual disturbance while undergoing treatment with TRUSELTIQ™ [see Section 4.8 Adverse Effects (Undesirable Effects)].



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## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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 [see Section 5.1 Clinical Studies]. 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).

The median age of TRUSELTIQ™ treated patients was 53 years (range 23-81), 62% were females, and 72% were white.

Serious adverse reactions occurred in 32% of patients receiving TRUSELTIQ™. Serious adverse reactions in ≥2% of patients who received TRUSELTIQ™ included infections, anaemia, pyrexia, abdominal pain, hypercalcaemia, and sepsis. Fatal adverse reactions occurred in 0.9% of patients and included sepsis.

Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received TRUSELTIQ™. Adverse reactions requiring permanent discontinuation in ≥1% of patients were blood creatinine increased, fatigue, 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 hyperphosphataemia, stomatitis, palmar-plantar erythrodysesthesia syndrome, increased blood creatinine, increased lipase, hypercalcaemia, and onycholysis.

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 hyperphosphataemia, hypercalcaemia, palmar-plantar erythrodysesthesia syndrome, stomatitis, diarrhoea and blood creatinine increased.

Table 3 summarizes the adverse reactions in study CBGJ398X2204.

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**Table 3: Adverse Reactions (≥15%) in Patients Receiving TRUSELTIQ™ in Study CBGJ398X2204**

Adverse Reaction	TRUSELTIQ™ N=108	
	All Grades (%)	Grades ≥3 <sup>a</sup> (%)
Metabolism and nutrition disorders		
Hyperphosphataemia <sup>b</sup>	78	11
Hypercalcaemia	25	6
Hypophosphataemia	22	13
Decreased appetite	22	1
Skin and subcutaneous tissue disorders		
Nail toxicity <sup>c</sup>	57	2
Alopecia	38	0
Palmar-plantar erythrodysesthesia syndrome	33	7
Dry skin	23	0
Gastrointestinal disorders		
Stomatitis <sup>d</sup>	56	15
Constipation	30	1
Dry mouth	25	0
Diarrhoea	24	3
Vomiting	21	1
Nausea	19	1
Abdominal pain	17	4
Dyspepsia	17	0
Eye disorders		
Dry eye <sup>e</sup>	44	2
Eyelash changes <sup>f</sup>	25	0
Vision blurred	21	0
General disorders and administrative site conditions		
Fatigue <sup>g</sup>	44	4
Oedema <sup>h</sup>	17	1
Pyrexia	15	1
Musculoskeletal and connective tissue disorders		
Arthralgia	32	0
Pain in extremity	17	2
Nervous system disorders		

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	TRUSELTIQ™ N=108	
<b>Adverse Reaction</b>	<b>All Grades (%)</b>	<b>Grades ≥3<sup>a</sup> (%)</b>
Dysgeusia	32	0
Headache	17	1
<b>Investigations</b>		
Blood creatinine increased	24	0
Aspartate aminotransferase increased	21	2
Weight decreased	15	2
<b>Blood and lymphatic system disorders</b>		
Anaemia	19	4
<b>Respiratory, thoracic and mediastinal disorders</b>		
Epistaxis	18	0

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 4.03).

- <sup>a</sup> Only Grades 3 and 4.
- <sup>b</sup> Includes hyperphosphataemia and blood phosphorous increased.
- <sup>c</sup> 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, onychoclasia, onycholysis, onychomadesis, onychomycosis, and paronychia.
- <sup>d</sup> Includes mouth ulceration and stomatitis.
- <sup>e</sup> Includes dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis.
- <sup>f</sup> Includes blepharitis, eyelash changes, eyelash discoloration, growth of eyelashes, trichiasis, and trichomegaly.
- <sup>g</sup> Includes asthenia and fatigue.
- <sup>h</sup> Includes oedema peripheral and oedema.

## Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of action

Infigratinib is a small molecule kinase inhibitor that targets FGFR1, FGFR2 and FGFR3 with *in vitro* IC<sub>50</sub> values of 1.1, 1.0, and 2.0 nM, respectively. *In vitro*, infigratinib inhibited the activity of FGFR1-3, but not FGFR4, KDR and other kinases, at clinically relevant concentrations. The major active metabolites of infigratinib, 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 signalling and decreased cell viability in cancer cell lines with activating FGFR amplifications, mutations and fusions that resulted in constitutive activation of FGFR signalling. Constitutive FGFR signalling can support the proliferation and survival of malignant cells. Infigratinib exhibited anti-tumour activity in mouse and rat xenograft models of human tumours with activating FGFR1, FGFR2, or FGFR3 alterations, including two patient-derived xenograft models of cholangiocarcinoma that expressed distinct FGFR2 fusion proteins. Infigratinib demonstrated brain-to-plasma concentration ratios (based on AUC<sub>0-inf</sub>) of 0.682 in rats after a single oral dose.

#### Cardiac Electrophysiology

Based on evaluation of QTc interval in two studies with 261 patients with cancer, at a dose up to 1.2 times the recommended dose, TRUSELTIQ™ does not result in a clinically relevant (i.e., >10 msec) mean increase on the QTc interval.

#### Serum Phosphate

TRUSELTIQ™ increased serum phosphate levels as a consequence of 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™.

#### **Clinical trials**

Study CBGJ398X2204 (NCT02150967), a multicenter, open-label single-arm Phase 2 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 a local or central laboratory using next generation sequencing (89%) or other nucleic-acid based tests (11%).

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.

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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 was confirmed in 104 enrolled subjects (96%) with local or central laboratory Next Generation Sequencing (NGS) testing. Eighty-eight (n=88) patients had in-frame FGFR2 fusions, with BICC1 the most commonly reported partner gene for FGFR2 fusions (n=27). Twenty (n=20) 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. In the 46% of patients with disease progression following one line of prior therapy, the ORR was 34% (95% CI: 21.2, 48.8) and median duration of response was 5.5 months (95% CI: 3.7, 9.5), per BICR. In 108 patients the disease control rate (complete response, partial response, and stable disease) was 84% (95% CI: 76.0, 90.6).

Efficacy results are summarised in Table 4. The median time to response was 3.6 months (range 1.4 – 7.4 months). Subgroup analyses are summarised in Table 5.

**Table 4: Efficacy Results in Study CBGJ398X2204**

Efficacy Parameter	TRUSELTIQ™ N=108	
	BICR Assessment	Investigator Assessment
<b>ORR (95% CI)</b>	<b>23.1%</b> (15.6, 32.2)	<b>30.6%</b> (22.1, 40.2)
Complete Response, n (%)	1 (1%)	0
Partial Response, n (%)	24 (22.2%)	33 (30.6%)
<b>Median DoR (months) (range)</b>	<b>5</b> (0.92+, 19.12)	<b>6</b> (0.95+, 19.12)
Patients with DoR ≥6 months, n (%)	8 (32%)	12 (36%)

Abbreviations: 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.

**Table 5: Subgroup Analyses in Study CBGJ398X2204**

POPULATION	TRUSELTIQ™		
	N (%)	ORR	95% CI
<b>LINES OF PRIOR THERAPY</b>			
≤1	50 (46.3)	34%	21.2, 48.8
>1	58 (53.7)	13.8%	6.1, 25.4
<b>GENDER</b>			
FEMALE	67 (62)	20.9%	11.9, 32.6

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MALE	41 (38)	26.8%	14.2, 42.9
<b>AGE</b>			
<65 YEARS	82 (75.9)	22%	13.6, 32.5
≥65 YEARS	26 (24.1)	26.9%	11.6, 47.8
<b>REGION</b>			
NORTH AMERICA	77 (71.3)	28.6%	18.8, 40
WESTERN EUROPE	24 (22.2)	8.3%	1, 27
ASIA	7 (6.5)	14.3%	0.4, 57.9

Abbreviations: CI=confidence interval; ORR=overall response rate.

Note: Data are according to RECIST v1.1. ORR is based upon confirmed complete and partial responses per BICR assessment.

## 5.2 PHARMACOKINETIC PROPERTIES

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

The mean (coefficient of variation [%CV]) steady-state maximum plasma concentration ( $C_{max}$ ) and area under the curve over a dosing interval ( $AUC_{0-24h}$ ) of infigratinib and active metabolites, BHS697 and CQM157, are presented in Table 6.

Table 6: Mean (%CV) Exposure of Infigratinib and Active Metabolites

	<b>Infigratinib</b>	<b>BHS697</b>	<b>CQM157</b>
$C_{max}$	282.5 ng/mL (54%)	42.1 ng/mL (65%)	15.7 ng/mL (92%)
$AUC_{0-24h}$	3780 ng•h/mL (59%)	717 ng•h/mL (55%)	428 ng•h/mL (72%)

Infigratinib  $C_{max}$  and AUC increased more than proportionally across the dose range of 5 to 150 mg (0.04 to 1.2 times the approved recommended dose). Steady state was achieved within 15 days and the mean accumulation ratio was 8- and 5-fold for  $C_{max}$  and AUC, respectively.

### Absorption

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

### Effect of Food

Following administration of TRUSELTIQ™ with a high-fat and high-calorie meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) in healthy subjects, the mean  $AUC_{inf}$  of infigratinib increased by 80%-120% and  $C_{max}$  increased by 60%-80%, the median  $T_{max}$  shifted from 4 hours to 6 hours. Following administration of TRUSELTIQ with a low-fat low-calorie meal (approximately 330 calories with 20% of total caloric content of the meal from fat), the mean  $AUC_{inf}$  of infigratinib increased by 70%,  $C_{max}$  increased by 90%, and the median  $T_{max}$  did not change.

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## **Distribution**

The geometric mean (CV%) apparent volume of distribution of infigratinib was 1600 L (33%) at steady state. The mean infigratinib protein binding was 96.8%, primarily to lipoprotein, and was dependent of drug concentration.

## **Metabolism**

Infigratinib is predominantly metabolised by CYP3A4. The contribution of CYP3A4 in the total clearance of infigratinib is estimated to be 94%. The major drug-related moiety in plasma was unchanged infigratinib (38% of dose) in a human [<sup>14</sup>C] mass balance study, followed by a 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.

## **Excretion**

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

The geometric mean (CV%) total apparent clearance (CL/F) of infigratinib was 33.1 L/h (59%CV) at steady state. The geometric mean (CV%) terminal half-life of infigratinib was 33.5 h (39%) at steady state.

## **Pharmacokinetics in special patient populations**

No clinically meaningful differences in the systemic exposure of infigratinib were observed based on age (19-86 years), sex, race/ethnicity, or body weight (36.4-169.0 kg). The effect of renal impairment or renal dialysis in end-stage renal disease on infigratinib exposure is unknown.

### Renal Impairment

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 severe renal impairment (CLcr < 30 mL/min) or renal dialysis in end-stage renal disease on infigratinib exposure is unknown.

### Hepatic Impairment

The relative potency adjusted steady state AUC of infigratinib plus its active metabolites (BHS697, CQM157) in plasma increased by 47%-62% and 99% in patients with mild (total bilirubin > upper limit of normal [ULN] to 1.5 × ULN or AST > ULN) and moderate hepatic impairment (total

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bilirubin > 1.5 to 3 × ULN with any AST), respectively, relative to patients with normal hepatic function (total bilirubin ≤ ULN and AST ≤ ULN).

The effect of severe hepatic impairment (total bilirubin > 3 × ULN with any AST) on infigratinib exposure is unknown.

### **5.3 PRECLINICAL SAFETY DATA**

#### **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.

#### **Carcinogenicity**

Carcinogenicity studies have not been conducted with infigratinib.

#### **Repeat-Dose Toxicity**

In rat and dog repeat-dose toxicity studies ≥13 weeks in duration, toxicities in bones (rats and dogs) and teeth (rats) were observed at exposures less than the human exposure (AUC) at the clinical dose of 125 mg. Effects on the teeth, including incisor degeneration with degeneration of enamel and loss of ameloblast layer were observed in a 13-week rat study. Bone effects in lumbar vertebral bodies included decreased bone strength consistent with decreases in total bone mineral density in a 26-week rat study and increased growth plate thickness and fractures associated with increased physal thickness, focal mixed reaction, and bone loss in a 39-week dog study.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

25 mg hard capsules: Contains sugars as lactose monohydrate 23.25 mg

100 mg hard capsules: Contains sugars as lactose monohydrate 93.00 mg

Each TRUSELTIQ™ hard capsule contains the following inactive ingredients:

Hard capsule content:

- lactose monohydrate,
- microcrystalline cellulose,
- crospovidone,
- hypromellose,
- magnesium stearate (from vegetable source),
- colloidal anhydrous silica.

Hard capsule shell:

- gelatin (bovine),
- titanium dioxide,



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- iron oxide red (100 mg hard capsules only),
- iron oxide yellow (100 mg hard capsules only),
- iron oxide black (25 mg hard capsules only),

Printing ink:

- TekPrint SW-9049 Black Ink [Proprietary Ingredient ID: 12418]

## **6.2 INCOMPATIBILITIES**

No incompatibilities have been identified.

## **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store below 25°C.

## **6.5 NATURE AND CONTENTS OF CONTAINER**

Multi-day PVC/PCTFE blister packs with aluminum foil lidding with the following configurations:

- TRUSELTIQ™ 1 x 25 mg hard capsule and 1 x 100 mg capsule (125 mg daily dose composite pack)  
(Contains 21 x 25 mg and 21 x 100 mg hard capsules).
- TRUSELTIQ™ 1 x 100 mg hard capsule (100 mg daily dose)  
(Contains 21 x 100 mg hard capsules).
- TRUSELTIQ™ 3 x 25 mg hard capsules (75 mg daily dose)  
Pack 1 - Weeks 1-2 contains 42- x 25 mg hard capsules.  
Pack 2 - Weeks 3-4 contains 21 x 25 mg hard capsules.
- TRUSELTIQ™ 2 x 25 mg hard capsules (50 mg daily dose)  
(Contains 42 x 25 mg hard capsules)

## **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

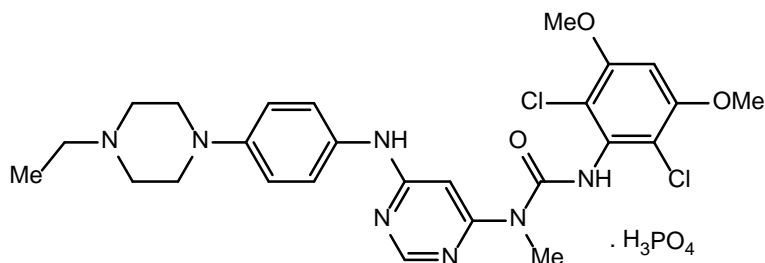
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## **6.7 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.

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## Chemical structure



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:  $C_{26}H_{31}Cl_2N_7O_3 \cdot H_3PO_4$

Molecular weight: 560.48 g/mol for the free base, 658.47 g/mol for the phosphate salt.

## CAS number

872511-34-7 (free base)

1310746-10-1 (phosphate salt)

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 –Prescription Only Medicine

## 8 SPONSOR

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Point Cook VIC 3030

Phone: 0418 314 763

## 9 DATE OF FIRST APPROVAL

05 November 2021

## 10 DATE OF REVISION

Not applicable.