▼ 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.

AUSTRALIAN PRODUCT INFORMATION – LYTGOBI (FUTIBATINIB) TABLETS

1 NAME OF THE MEDICINE

Futibatinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LYTGOBI 4 mg film-coated tablet contains 4 mg of futibatinib.

Excipients with known effect:
Lactose monohydrate

For the list of excipients, see *section 6.1 List of excipients*.

3 PHARMACEUTICAL FORM

LYTGOBI 4 mg film-coated tablets are white, round, film-coated tablets debossed with “4MG” on one side and “FBN” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LYTGOBI monotherapy has **provisional approval** in Australia for the treatment of adult patients with locally advanced or metastatic intrahepatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy. The decision to approve this indication has been made on the basis of the favourable objective 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

LYTGOBI therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with biliary tract cancer.

Presence of FGFR2 gene fusions or rearrangements should be confirmed by an appropriate diagnostic test prior to initiation of LYTGOBI therapy.

Dosage (dose and interval)

Dose

The recommended starting dose is 20 mg futibatinib (5 x 4 mg tablets) taken orally once daily.

If a dose of futibatinib is missed by more than 12 hours or vomiting occurs after taking a dose, an additional dose should not be taken, and treatment should be resumed with the next scheduled dose.

Treatment should be continued until disease progression or unacceptable toxicity.

In all patients, dietary restrictions that limit phosphate intake are recommended as part of hyperphosphatemia management. A phosphate-lowering therapy should be initiated when serum phosphate level is ≥ 5.5 mg/dL. If the serum phosphate level is > 7 mg/dL, the dose of futibatinib should be modified based on the duration and severity of hyperphosphatemia (see Table 2). Prolonged hyperphosphatemia can cause soft tissue mineralization, including cutaneous calcification, vascular calcification, and myocardial calcification (see *section 4.4 Special warnings and precautions for use*).

If LYTGOBI treatment is stopped or serum phosphate level falls below normal range, phosphate-lowering therapy and diet should be discontinued. Severe hypophosphatemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and haemolytic anaemia.

Method of administration

LYTGOBI is for oral use. The tablets should be taken with or without food at about the same time each day. The tablets should be swallowed whole to ensure that the full dose is administered.

Dose modification guidelines

Dose adjustment due to drug interaction

- *Concomitant use of futibatinib with strong CYP3A/P-gp inhibitors*

Co-administration of futibatinib with strong CYP3A4/P-gp inhibitors, such as itraconazole, should be avoided. If this is not possible, based on careful monitoring of tolerability, a futibatinib dose reduction to the next lower level should be considered.

- *Concomitant use of futibatinib with strong or moderate CYP3A/P-gp inducers*

Co-administration of futibatinib with strong or moderate CYP3A4/P-gp inducers, such as rifampicin, should be avoided (see *section 4.4 Special warnings and precautions for use* and *section 4.5 Interactions with other medicines and other forms of interactions*). If this is not possible, gradually increasing the futibatinib dose based on careful monitoring of tolerability should be considered.

Management of toxicities

Dose modifications or interruption of dosing should be considered for the management of toxicities. The recommended dose reduction levels are provided in Table 1.

Table 1: Recommended futibatinib dose reduction levels

Dose	Dose reduction levels	
20 mg taken orally once daily	**First**	**Second**
	16 mg taken orally once daily	12 mg taken orally once daily

Treatment should be permanently discontinued if patient is unable to tolerate 12 mg futibatinib once daily.

Dose modifications for hyperphosphatemia are provided in Table 2.

Table 2: Dose modifications for hyperphosphatemia

Adverse reaction	Futibatinib dose modification
Serum phosphate ≥5.5 mg/dL - ≤ 7 mg/dL	• Initiate phosphate lowering therapy and monitor serum phosphate weekly • Futibatinib should be continued at current dose
Serum phosphate >7 mg/dL - ≤ 10 mg/dL	• Initiate/intensify phosphate lowering therapy and monitor serum phosphate weekly AND • Dose reduce futibatinib to next lower dose – If the serum phosphate resolves to ≤7.0 mg/dL within 2 weeks after dose reduction, continue at this reduceddose – If serum phosphate is not ≤ 7.0 mg/dL within 2 weeks, further reduce futibatinib to the next lower dose – If serum phosphate is not ≤ 7.0 mg/dL within 2 weeks after the second dose reduction, withhold futibatinib until serum phosphate is ≤ 7.0 mg/dL and resume at the dose prior to suspending
Serum phosphate >10 mg/dL	• Initiate/intensify phosphate lowering therapy and monitor serum phosphate weekly AND • Suspend futibatinib until phosphate is ≤ 7.0 mg/dL and resume futibatinib at the next lower dose • Permanently discontinue futibatinib if serum phosphate is not ≤ 7.0 mg/dL within 2 weeks following 2 dose reductions

Dose modifications for serous retinal detachment are provided in Table 3.

Table 3: Dose modifications for serous retinal detachment

Adverse reaction	Futibatinib dose modification
Asymptomatic	• Continue futibatinib at current dose. Monitoring should be performed as described in *section 4.4 Special warnings and precautions for use*.

Adverse reaction	Futibatinib dose modification
Moderate decrease in visual acuity (best corrected visual acuity 20/40 or better or ≤ 3 lines of decreased vision from baseline); limiting instrumental activities of daily living	• Withhold futibatinib. If improved on subsequent examination, futibatinib should be resumed at the next lower dose level. • If symptoms recur, persist or examination does not improve, permanent discontinuation of futibatinib should be considered based on clinical status.
Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or >3 lines decreased vision from baseline up to 20/200); limiting activities of daily living	• Withhold futibatinib until resolution. If improved on subsequent examination, futibatinib may be resumed at 2 dose levels lower. • If symptoms recur, persist or examination does not improve, permanent discontinuation of futibatinib should be considered based on clinical status.
Visual acuity worse than 20/200 in affected eye; limiting activities of daily living	• Permanent discontinuation of futibatinib should be considered based on clinical status.

Dose modifications for other adverse reactions are provided in Table 4.

Table 4: Dose modifications for other adverse reactions

Other Adverse Reaction	Grade 3[a]	• Withhold futibatinib until toxicity resolves to Grade 1 or baseline, then resume futibatinib – for haematological toxicities resolving within 1 week, at the dose prior to suspending. – for other adverse reactions, at next lower dose.
	Grade 4[a]	• Permanently discontinue futibatinib

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

4.3 CONTRAINDICATIONS

LYTGOBI is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in *section 6.1 List of excipients.*

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperphosphatemia

Hyperphosphatemia is a pharmacodynamic effect expected with futibatinib administration (see *section 5.1 Pharmacodynamic properties*). Prolonged hyperphosphatemia may cause soft tissue mineralization, including cutaneous calcification, vascular calcification, and myocardial calcification, anaemia, hyperparathyroidism, and hypocalcemia that may cause muscle cramps, QT interval prolongation, and arrythmias (see *section 4.2 Dose and method of administration*).

Recommendations for management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see *section 4.2 Dose and method of administration*).

Phosphate-lowering therapy was used by 83.4 % of patients during treatment with futibatinib (see *section 4.8 Adverse effects (Undesirable effects)*).

Serous retinal detachment

Futibatinib can cause serous retinal detachment, which may present with symptoms such as blurred vision, visual floaters, or photopsia (see *section 4.8 Adverse effects (Undesirable effects)*). This can moderately influence the ability to drive and use machines (see *section 4.7 Effects on ability to drive and use machines*).

Perform a comprehensive ophthalmological examination, including optical coherence tomography (OCT) of the macula, prior to initiation of therapy, every 2 months for the first 6 months, and every 3 months thereafter. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of LYTGOBI. For serous retinal detachment reactions, the dose modification guidelines should be followed (see *section 4.2 Dose and method of administration*).

During the conduct of the clinical study, there was no routine monitoring, including OCT, to detect asymptomatic serous retinal detachment; therefore, the incidence of asymptomatic serous retinal detachment with futibatinib is unknown.

Careful consideration should be taken with patients that have clinically significant medical eye disorders, such as retinal disorders, including but not limited to, central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment.

Dry eye

Futibatinib can cause dry eye (see section 4.8 *Adverse effects (Undesirable effects)*). Patients should use ocular demulcents, in order to prevent or treat dry eye, as needed.

Embryofetal toxicity

Based on the mechanism of action and findings in an animal study (*section 4.6 Fertility, pregnancy and lactation*), futibatinib can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the fetus. An effective method of contraception should be used in women of childbearing potential and in men with women partners of childbearing potential during treatment with LYTGOBI and for 1 week following completion of therapy, barrier methods should be applied as a second form of contraception to avoid pregnancy (see *section 4.6 Fertility, pregnancy and lactation*). A pregnancy test should be performed before treatment initiation to exclude pregnancy.

Combination with strong CYP3A/P-gp inhibitors

Concomitant use of strong CYP3A/P-gp inhibitors should be avoided because it may increase futibatinib plasma concentration (see *section 4.2 Dose and method of administration* and *section 4.5 Interactions with other medicines and other forms of interactions*).

Combination with strong or moderate CYP3A/P-gp inducers

Concomitant use of strong or moderate CYP3A/P-gp inducers should be avoided because it may decrease futibatinib plasma concentration (see *section 4.2 Dose and method of administration* and *section 4.5 Interactions with other medicines and other forms of interactions*).

Lactose

LYTGOBI contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

LYTGOBI contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

Use in renal impairment

Dose adjustment is not required for patients with mild and moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min estimated by Cockcroft-Gault). There are no data in patients with severe renal impairment (CLcr < 30 mL/min) or for patients with end-stage renal disease receiving intermittent haemodialysis and therefore no dosing recommendation can be made (see *section 5.2 Pharmacokinetic properties*).

Use in hepatic impairment

No dose adjustment is required when administering futibatinib to patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), or severe (Child-Pugh class C) hepatic impairment. There are limited data in patients treated with LYTGOBI with total bilirubin >1.5 x ULN, and patients with cholangiocarcinoma with total bilirubin >3 x ULN were excluded from enrolment in clinical trials. Patients with cirrhosis and total bilirubin >1.5 x ULN to 3 x ULN may have the potential for increased adverse reactions compared to patients with normal hepatic function due to higher unbound futibatinib exposure (see *section 5.2 Pharmacokinetic properties*).

Use in the elderly

No specific dose adjustment is required for elderly patients (≥ 65 years) (see *section 5.1 Pharmacodynamic properties*).

Paediatric use

The safety and efficacy of futibatinib in children less than 18 years of age have not been established. No data are available.

Effects on laboratory tests

See *Section 4.8 Adverse effects (undesirable effects)*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on futibatinib

CYP3A/P-gp inhibitors

Co-administrations of multiple doses of 200 mg itraconazole, a strong CYP3A/P-gp inhibitor, increased futibatinib C_{max} by 51% and AUC by 41% following a single oral dose of 20 mg futibatinib. Therefore, the concomitant use of strong CYP3A/P-gp inhibitors (e.g., clarithromycin, itraconazole) may increase futibatinib plasma concentration and should be avoided. If this is not possible, a reduction in the futibatinib dose to the next lower dose level based on tolerability observed should be considered (see *section 4.2 Dose and method of administration* and *section 4.4 Special warnings and precautions for use*).

CYP3A/P-gp inducers

Co-administrations of multiple doses of 600 mg rifampin, a strong CYP3A/P-gp inducer, decreased futibatinib C_{max} by 53% and AUC by 64% following a single oral dose of 20 mg futibatinib.

Therefore, the concomitant use of strong and moderate CYP3A/P-gp inducers (e.g., carbamazepine, phenytoin, phenobarbital, efavirenz, rifampin) may decrease futibatinib plasma concentration and should be avoided. If this is not possible, gradually increasing the futibatinib dose based on careful monitoring of tolerability should be considered (see *section 4.2 Dose and method of administration* and *section 4.4 Special warnings and precautions for use*).

Proton pump inhibitors

Futibatinib geometric mean ratios for C_{max} and AUC were 108 % and 105 %, respectively, when co-administered in healthy subjects with lansoprazole (a proton pump inhibitor) relative to futibatinib alone. Co-administrations of a proton pump inhibitor (lansoprazole) did not result in a clinically important change in futibatinib exposure.

Effects of futibatinib on other medicinal products

Effect of futibatinib on CYP3A substrate

Midazolam (a CYP3A sensitive substrate) geometric mean ratios for C_{max} and AUC were 95 % and 91 %, respectively, when co-administered in healthy subjects with futibatinib relative to midazolam alone. Co-administrations of futibatinib had no clinically significant impact on midazolam exposure.

Effect of futibatinib on P-gp and BCRP substrates

In vitro, futibatinib is an inhibitor of P-gp and BCRP. Co-administration of futibatinib with P-gp (e.g., digoxin, dabigatran, colchicine) or BCRP (e.g., rosuvastatin) substrates may increase their exposure.

Effect of futibatinib on CYP1A2 substrates

In vitro studies indicate that futibatinib has the potential to induce CYP1A2. Co-administration of futibatinib with CYP1A2 sensitive substrates (e.g., olanzapine, theophylline) may decrease their exposure and therefore may affect their activity.

Effect of futibatinib on other CYP enzymes

In vitro studies indicate that futibatinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or systemic CYP3A, and does not induce CYP2B6 or CYP3A4 at clinically relevant concentrations.

Effect of futibatinib on drug transporters

In vitro studies indicated that futibatinib inhibited P-gp and BCRP, but did not inhibit OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1 or MATE2K at clinically relevant concentrations. Futibatinib is a substrate of P-gp and BCRP *in vitro*. Inhibition of BCRP is not expected to result in clinically relevant changes in the exposure of futibatinib.

Hormonal contraceptives

It is currently unknown whether futibatinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method during LYTGOBI treatment and for at least 1 week after the last dose (see *section 4.6 Fertility, pregnancy and lactation*).

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential/Contraception in males and females

An effective method of contraception should be used in women of childbearing potential and in men with women partners of childbearing potential during treatment with LYTGOBI and for 1 week following completion of therapy. Since the effect of futibatinib on the metabolism and efficacy of contraceptives has not been investigated, barrier methods should be applied as a second form of contraception to avoid pregnancy.

Effects on fertility

There are no data on the effect of futibatinib on human fertility. Animal fertility studies have not been conducted with futibatinib. Based on the pharmacology of futibatinib, impairment of male and female fertility cannot be excluded.

Use in pregnancy – Pregnancy Category D

There are no available data from the use of futibatinib in pregnant women.
Based on animal data and the pharmacology of futibatinib, LYTGOBI use during pregnancy may cause embryofetal harm or loss. Advise pregnant women and women of reproductive potential of the potential risk to the fetus. A pregnancy test should be performed before treatment initiation to exclude pregnancy.

Oral administration of futibatinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at 10 mg/kg per day (5 times the recommended human dose of 20 mg based on body surface area, BSA). At all tested doses (≥0.05 mg/kg/day; 0.02 times the recommended human dose of 20 mg based on BSA), there was an increased incidence of fetal skeletal and visceral malformations including major blood vessel variations.

Use in lactation

It is unknown whether futibatinib or its metabolites are excreted in human milk. A risk to the breast-fed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with LYTGOBI and for 1 week after the last dose.

4.7 Effects on ability to drive and use machines

Futibatinib has moderate influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or operating machines in case they experience fatigue or visual disturbances during the treatment with LYTGOBI (see *section 4.4 Special warnings and precautions for use*).

4.8 Adverse effects (Undesirable effects)

Summary of the safety profile

The safety of LYTGOBI was evaluated in the Phase 1 Expansion portion and Phase 2 portion of Study TAS-120-101, which included 145 patients with intrahepatic cholangiocarcinoma (iCCA) harbouring *FGFR2* rearrangement, exposed to LYTGOBI at starting dose of 20mg QD.

The most common (≥20%) adverse events were hyperphosphatemia (89.7%), nail disorders (44.1%), constipation (37.2%), alopecia (35.2%), diarrhoea (33.8%), dry mouth (31.0%), fatigue (31.0%), nausea (28.3%), dry skin (27.6%), increased AST (26.9%), abdominal pain (24.8%), stomatitis (24.8%), vomiting (23.4%), palmar-plantar erythrodysaesthesia syndrome (22.8%), arthralgia (21.4%), and decreased appetite (20.0%).

The most common serious adverse reactions were intestinal obstruction (1.4%) and migraine (1.4%). Uncommon adverse reactions by System Organ Class (SOC) are endocrine disorders (0.7%) and injury, poisoning and procedural complications (0.7%).

Permanent discontinuation due to adverse reactions was reported in 7.6% of patients; the most common adverse reaction which led to dose discontinuation was stomatitis (1.4%), all other adverse reactions were single occurrence.

Tabulated list of adverse events

Table 5 summarises the adverse events by Preferred Term (PT) occurring in 145 patients treated in the indicated population of Study TAS-120-101. AEs were reported for all patients (n=145, 100.0%) with iCCA who received a starting dose of 20 mg QD futibatinib; of these, 111 patients (76.6%) experienced at least 1 Grade ≥3 TEAE. Hyperphosphataemia [Note 2)] (n=124, 85.5%) and constipation (n=54, 37.2%) of any grade were the most frequently reported AEs.

Table 5: Summary of Adverse Events (AEs) Occurring in ≥15% of Participants by MedDRA Preferred Term in TAS-120-101 study (N=145)

MedDRA Preferred Term [Note 1)]	Safety Data Group 1 (iCCA)	
	20 mg QD (N=145)	
	Any Grade n (%)	Grade ≥3 n (%)
Patients with Any AEs	**145 (100.0)**	**111 (76.6)**
Hyperphosphataemia [Note 2)]	124 (85.5)	39 (26.9)
Constipation	54 (37.2)	0
Alopecia	51 (35.2)	0
Diarrhoea	49 (33.8)	1 (0.7)
Dry mouth	45 (31.0)	0
Fatigue	45 (31.0)	11 (7.6)
Nausea	41 (28.3)	2 (1.4)
Dry skin	40 (27.6)	0
Aspartate aminotransferase increased	39 (26.9)	13 (9.0)
Abdominal pain	36 (24.8)	5 (3.4)
Stomatitis	36 (24.8)	9 (6.2)
Vomiting	34 (23.4)	1 (0.7)
Palmar-plantar erythrodysaesthesia syndrome	33 (22.8)	8 (5.5)
Arthralgia	31 (21.4)	0

MedDRA Preferred Term [Note 1)]	Safety Data Group 1 (iCCA)	
	20 mg QD (N=145)	
	Any Grade n (%)	Grade ≥3 n (%)
Decreased appetite	29 (20.0)	3 (2.1)
Alanine aminotransferase increased	28 (19.3)	9 (6.2)
Weight decreased	27 (18.6)	5 (3.4)
Dysgeusia	26 (17.9)	0
Dry eye	25 (17.2)	1 (0.7)
Hypercalcaemia	25 (17.2)	3 (2.1)
Anaemia	24 (16.6)	8 (5.5)
Back pain	24 (16.6)	3 (2.1)

MedDRA Preferred Term [Note 1)]	Safety Data Group 1 (iCCA)	
	20 mg QD (N=145)	
	Any Grade n (%)	Grade ≥3 n (%)
Urinary tract infection	24 (16.6)	3 (2.1)
Onycholysis	22 (15.2)	0

Abbreviations: AE=adverse event; iCCA=intrahepatic cholangiocarcinoma; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with at least 1 event; N=number of patients in treatment group; N/A=not applicable; QD=once daily
Note 1): Only individual Preferred Term (PT) is reflected in Table 5. Nail disorders, comprising of PTs nail bed disorder, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail hypertrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, paronychia, with cumulative incidence of 44.1% is not reflected in Table 5.
Note 2): Hyperphosphatemia TEAE incidence only includes the PT of hyperphosphatemia (85.5%). Any Grade Blood phosphorus increased was reported for 8.3% of patients and Grade ≥3 Blood phosphorous increased was reported for 0.7% of patients.

Description of selected adverse events

Hyperphosphatemia

Hyperphosphatemia was reported in 89.7 % of patients treated with futibatinib and 27.6 % patients had Grade 3 events, defined as serum phosphate > 7 mg/dL and ≤ 10 mg/dL irrespective of clinical symptoms. The median time to onset of hyperphosphatemia of any grade was 6.0 days (range: 3.0 to 117.0 days).

None of the reactions were Grade 4 or 5 in severity, serious, or led to discontinuation of futibatinib. Dose interruption occurred in 18.6 % patients and reduction in 17.9 % of patients. Hyperphosphatemia was manageable with dietary phosphate restriction and/or administration of phosphate lowering therapy and/or dose modification.

Recommendations for management of hyperphosphatemia are provided in *section 4.2 Dose and method of administration* and *section 4.4 Special warnings and precautions for use*.

Serous retinal detachment *Note*

Serous retinal detachment occurred in 6.2 % of patients treated with futibatinib.
Note: Includes serous retinal detachment, detachment of retinal pigment epithelium, subretinal fluid, chorioretinopathy, and maculopathy

Reactions were all Grade 1 or 2 in severity. Dose interruption occurred in 2.1 % patients and reduction in 2.1 % of patients. None of the reactions led to discontinuation of futibatinib. Serous retinal detachment was generally manageable.

Recommendations for management of serous retinal detachment are provided in *section 4.2 Dose and method of administration* and *section 4.4 Special warnings and precautions for use*.

Post-marketing experience

There is limited post-marketing data available.

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.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

There is no information on overdose of futibatinib. In the event of overdose, the patient should be monitored for adverse events and supportive management is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EN04

Mechanism of action

Constitutive fibroblast growth factor receptor (FGFR) signalling can support the proliferation and survival of malignant cells. Futibatinib is a tyrosine kinase inhibitor that irreversibly inhibits FGFR 1, 2, 3, and 4 by covalent binding. Futibatinib exhibited *in vitro* inhibitory activity against FGFR2 resistance mutations (*N550H, V565I, E566G, K660M*).

Pharmacodynamic effects

Serum phosphate

Futibatinib increased serum phosphate level as a consequence of FGFR inhibition. Phosphate-lowering therapy and dose modifications are recommended to manage hyperphosphatemia: see *section 4.2 Dose and method of administration*, *section 4.4 Special warnings and precautions for use* and *section 4.8 Adverse effects (Undesirable effects)*.

Clinical trials

Clinical efficacy and safety

TAS-120-101 a multicentre, open-label, single-arm study evaluated the efficacy and safety of futibatinib in previously treated patients with unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma. Patients with prior FGFR-directed therapy were excluded. The efficacy population consists of 103 patients that had progressed on or after at least 1 prior gemcitabine and platinum-based chemotherapy and had FGFR2 fusion (77.7%) or rearrangement (22.3%), as determined by tests performed at central or local laboratories.

Patients received futibatinib orally once daily at a dose of 20 mg until disease progression or unacceptable toxicity. The primary efficacy outcome measure was objective response rate (ORR) as determined by an independent review committee (IRC) according to RECIST v1.1, with duration of response (DoR) as a key secondary endpoint.

The median age was 58 years (range: 22 to 79 years), 22.3% were ≥65 years, 56.3% were female, 49.5% were Caucasian. All (100 %) patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (46.6 %) or 1 (53.4 %). All patients had at least 1 prior line of systemic therapy, 30.1% had 2 prior lines of therapy, and 23.3% had 3 or more prior lines of therapy. All patients had received prior platinum-based therapy including 91% with prior gemcitabine/cisplatin.

Efficacy results are summarized in Table 6. The median time to response was 2.5 months (range 0.7 – 7.4 months).

Table 6: Efficacy results

	Efficacy Evaluable Population (N = 103)
ORR (95 % CI)[a]	42% (32, 52)
Partial response (N)	42% (43)
Median duration of response (months) (95% CI)[b]	9.7 (7.6, 17.1)
Kaplan-Meier estimates of duration of response (95 % CI)	
3 months	100 (100, 100)
6 months	85.1 (69.8, 93.1)
9 months	52.8 (34.2, 68.3)
12 months	37.0 (18.4, 55.7)

ORR = Complete Response + Partial Response
CI = Confidence Interval
Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.
[a] The 95 % CI was calculated using the Clopper–Pearson method.
[b] The 95% CI was constructed based on a log-log transformed CI for the survival function.

In addition to the primary analysis presented here, an interim analysis was conducted without plans to stop the study. Results from both analyses were consistent. The primary analysis for DoR included censoring for new anti-cancer treatment, progressive disease or death after two or more missed tumour assessments, or at least 21 days after treatment discontinuation.

Elderly patients
In the clinical study of futibatinib, 22.3% of patients were 65 years and older. No difference in efficacy was detected between these patients and in patients < 65 years of age.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of futibatinib were evaluated in patients with advanced cancer administered 20 mg once daily unless otherwise specified.

Futibatinib exhibits linear pharmacokinetics over the dose range of 4 to 24 mg. Steady-state was reached after the first dose with a geometric mean accumulation ratio of 1.03. The geometric mean steady-state AUC_{ss} was 790 ng·h/mL (44.7% gCV) and $C_{max,ss}$ was 144 ng/mL (50.3% gCV) at the recommended dosage of 20 mg once daily.

Absorption

Median time to achieve peak plasma concentration (t_{max}) was 2 (range: 1.2 to 22.8) hours.

No clinically meaningful differences in futibatinib pharmacokinetics were observed following administration of a high-fat and high-calorie meal (900 calories to 1000 calories with approximately 50% of total caloric content of the meal from fat) in healthy subjects.

Distribution

Futibatinib is approximately 95% bound to human plasma proteins, predominantly to albumin and α1-acid glycoprotein. The estimated apparent volume of distribution was 66.1 L (17.5% gCV).

Metabolism

Futibatinib is predominantly metabolised by CYP3A as well as glutathione conjugation *in vitro*. Following oral administration of a single 20 mg radiolabelled futibatinib dose in healthy adult male subjects, the main drug-related moiety in plasma was unchanged futibatinib (59.19% of the total sample radioactivity) in a human [^{14}C] mass balance study in healthy adult male subjects, followed by one inactive metabolite, a cysteinylglycine conjugate TAS-06-22952 (at >10% of the total sample radioactivity).

Excretion

Following a single oral dose of 20 mg radiolabelled futibatinib in healthy adult male subjects, approximately 64% of the dose was recovered in faeces and 6% in urine. Futibatinib excretion in unchanged form was negligible in either urine or faeces.

Elimination

The mean elimination half-life ($t_{1/2}$) of futibatinib was 2.94 (26.5% CV) hours and the geometric mean apparent clearance (CL/F) was 19.8 L/h (23.0% gCV).

Special populations

No clinically meaningful differences in the systemic exposure (less than 25% difference in AUC) of futibatinib were observed based on age (18 - 82 years), sex, race/ethnicity, body weight (36 - 152 kg), mild to moderate renal impairment, or hepatic impairment. The effect of severe renal impairment and renal dialysis in end-stage renal disease on futibatinib exposure is unknown (see *section 4.4 Special warnings and precautions for use*).

Hepatic impairment

Compared to subjects with normal hepatic function, systemic exposure following a single dose of futibatinib was similar in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), or severe (Child-Pugh class C) hepatic impairment (see *section 4.4 Special warnings and precautions for use*).

In patients with cirrhosis and total bilirubin >1.0 to 1.5 x ULN, mean unbound futibatinib AUC and C_{max} increased by 1.7-fold relative to subjects with normal hepatic function. In patients with cirrhosis and total bilirubin >1.5 x ULN, mean unbound futibatinib AUC and C_{max} increased by 3.2-fold and 2.4-fold, respectively, compared to values in healthy subjects.

Exposure-response relationship

Dose-dependent increase in blood phosphate levels was observed following once daily futibatinib 4 mg to 24 mg dose range.

No statistically significant exposure-efficacy relationships observed for ORR within the exposure range produced by futibatinib 20 mg once daily regimen.

5.3 PRECLINICAL SAFETY DATA

Repeat-dose toxicity

The main toxicological findings following repeat-dose administration of futibatinib in both rats and dogs were related to the pharmacological activity of futibatinib as an irreversible inhibitor of FGFR, including increased inorganic phosphorus and calcium in plasma, ectopic mineralisation in various organs and tissues, lesions in bone/cartilage at futibatinib exposures lower than the human exposure at the clinical dose of 20 mg. Corneal lesions were found only in rats. These effects were reversible with the exception of ectopic mineralisation.

Genotoxicity

Futibatinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay. It was positive in the *in vitro* chromosome aberration test in cultured Chinese hamster lung cells (CHL/IU), but negative in the bone marrow micronucleus assay in rat and did not induce DNA damage in the comet assay in rats. The weight of evidence from these studies suggests that futibatinib is not genotoxic.

Carcinogenicity

Carcinogenicity studies with futibatinib have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Mannitol
Maize starch
Lactose monohydrate
Sodium lauryl sulfate
Microcrystalline cellulose
Crospovidone
Hyprolose
Magnesium stearate

Film-coating

Hypromellose
Macrogol 6000
Titanium dioxide

Lustering agent

Magnesium stearate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.
Refer to *section 4.5 Interactions with other medicines and other forms of interactions.*

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

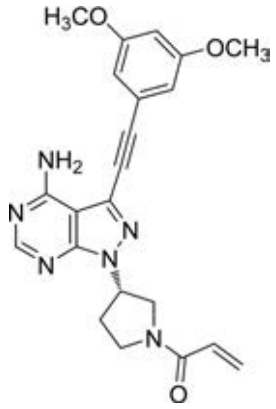
Tablets are supplied in PVC/PCTFE blister pack with aluminium foil lidding. Each blister strip contains five tablets. Pack size of 35 film-coated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular formula: $C_{22}H_{22}N_6O_3$
Relative molecular mass: 418.5

CAS number

1448169-71-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Taiho Pharma Oceania Pty Ltd
Three International Towers
300 Barangaroo Avenue
Sydney, NSW, 2000
Australia

TPOmedicalinfo@taiho.com.au
1800 955 777
www.taihopharmaoceania.com.au

9 DATE OF FIRST APPROVAL

17 April 2025

10 DATE OF REVISION

Not applicable.

SUMMARY TABLE OF CHANGES

Section(s) Changed	Summary of new information
All	New Product Information