swissmedic

Date: 6 November 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lytgobi

International non-proprietary name: futibatinib

Pharmaceutical form: film-coated tablets

Dosage strength(s): 4 mg

Route(s) of administration: oral

Marketing authorisation holder: Taiho Oncology Europe GmbH

Marketing authorisation no.: 69714

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 08 October 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for futibatinib in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 19 March 2024.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

2.2.2 Approved indication

Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Presence of FGFR2 gene fusions or rearrangements should be confirmed by an appropriate diagnostic test prior to initiation of Lytgobi therapy.
The recommended starting dose is 20 mg futibatinib taken orally once daily.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	25 April 2024
Formal control completed	29 April 2024
Preliminary decision	2 July 2024
Response to preliminary decision	28 August 2024
Labelling corrections and/or other aspects	16 September 2024
Response to labelling corrections and/or other aspects	20 September 2024
Final decision	8 October 2024
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority European Medicines Agency (EMA). This SwissPAR relates to the publicly available EMA assessment report for Lytgobi, published 26 April 2023, Procedure No. EMEA/H/C/005627/0000.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority European Medicines Agency (EMA). The SwissPAR relating to quality aspects refers to the publicly available EMA assessment report for Lytgobi, published 26 April 2023, Procedure No. EMEA/H/C/005627/0000.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority European Medicines Agency (EMA). The nonclinical aspects in this SwissPAR refer to the publicly available EMA assessment report for Lytgobi, published 26 April 2023, Procedure No. EMEA/H/C/005627/0000.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority European Medicines Agency (EMA). The clinical aspects in this SwissPAR refer to the publicly available EMA assessment report for Lytgobi, published 26 April 2023, Procedure No. EMEA/H/C/005627/0000.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Lytgobi was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

LYTGOBI has been authorised temporarily, see “Indications/Uses” section.

LYTGOBI

Composition

Active substances

Futibatinib.

Excipients

Tablet core: Mannitol (E421), Maize starch, Lactose monohydrate, Sodium laurilsulfate, Cellulose, microcrystalline, Crospovidone, Hydroxypropylcellulose (E463), Magnesium stearate

Film-coating: Hypromellose (E464), Macrogol 6000, Titanium dioxide (E171)

Lustering agent: Magnesium stearate

Each film-coated tablet contains 5.4 mg lactose (as monohydrate).

Each film-coated tablet contains 0.3 mg sodium.

Pharmaceutical form and active substance quantity per unit

4 mg film-coated tablet (tablet).

Round (6 mm), white, film-coated tablet debossed on one side with “4MG” and “FBN” on the reverse.

Indications/Uses

LYTGOBI monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

Dosage/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 a validated diagnostic

test prior to initiation of LYTGOBI therapy.

Usual dosage

The recommended starting dose is 20 mg futibatinib taken orally once daily.

If a dose of futibatinib is missed by more than 12 hours or if 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 mineralisation, including cutaneous calcification, vascular calcification, and myocardial calcification (see section “Warnings and precautions”).

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

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 (see sections “Warnings and precautions” and “Interactions”). 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 sections “Warnings and precautions” and “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 to ≤7 mg/dL	• Initiate phosphate lowering therapy and monitor serum phosphate weekly • Futibatinib should be continued at current dose
Serum phosphate >7 mg/dL to ≤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 reduced dose – 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 “Warnings and Precautions”

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 Reactions	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 the 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).

Special populations

Elderly

No specific dose adjustment is required for elderly patients (≥65 years) (see section "Pharmacodynamics").

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 "Pharmacokinetics").

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. However, there are no safety data in cancer patients with severe hepatic impairment (see section “Pharmacokinetics”).

Paediatric population

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

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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Excipients”.

Warnings and precautions

Hyperphosphatemia

Hyperphosphatemia is a pharmacodynamic effect expected with futibatinib administration (see section “Pharmacodynamics”). Prolonged hyperphosphatemia may cause soft tissue mineralisation, including cutaneous calcification, vascular calcification, and myocardial calcification, anaemia, hyperparathyroidism, and hypocalcemia that may cause muscle cramps, QT interval prolongation, and arrythmias (see section “Dosage/Administration”).

Recommendations for management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required (see section “Dosage/Administration”). Phosphate-lowering therapy was used by 83.4% of patients during treatment with futibatinib (see section “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 “Adverse effects”). This can moderately influence the ability to drive and use machines (see section “Effects on the ability to drive and use machines”).

Ophthalmological examination should be performed prior to initiation of therapy, 6 weeks thereafter, and urgently at any time for visual symptoms. For serous retinal detachment reactions, the dose modification guidelines should be followed (see section “Dosage/Administration”).

During the conduct of the clinical study, there was no routine monitoring, including optical coherence tomography (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 who 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 “Adverse effects”). Patients should use ocular demulcents in order to prevent or treat dry eye as needed.

Embryo-foetal toxicity

Based on the mechanism of action and findings in an animal study (see section “Preclinical data”), futibatinib can cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus. 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 at least 1 week following completion of therapy, barrier methods should be applied as a second form of contraception to avoid pregnancy (see section “Pregnancy, 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 sections “Dosage/Administration” and “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 sections “Dosage/Administration” and “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”.

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 sections “Dosage/Administration” and “Warnings and precautions”).

CYP3A/P-gp inducers

Co-administration 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 sections “Dosage/Administration” and “Warnings and precautions”).

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-administration of a proton pump inhibitor (lansoprazole) did not result in a clinically important change in futibatinib exposure.

Drug transporters

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.

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 CYP enzymes

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

Effect of futibatinib on drug transporters

In vitro studies indicate that futibatinib does not inhibit OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K at clinically relevant concentrations.

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 “Pregnancy, lactation”).

Pregnancy, 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 the 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.

Pregnancy

There are no available data from the use of futibatinib in pregnant women. Studies in animals have shown embryo-foetal toxicity (see section “Preclinical data”). LYTGOBI should not be used during pregnancy unless the potential benefit for the woman justifies the potential risk to the foetus.

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.

Fertility

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

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 “Warnings and precautions”).

Undesirable effects

Summary of the safety profile

The safety profile is based on pooled data from 318 patients with advanced solid tumours treated with futibatinib monotherapy at the recommended dose of 20 mg once daily, including 145 cholangiocarcinoma patients harbouring a FGFR2 fusion or rearrangement in the main study TAS-120-101. The most common (≥20%) adverse reactions were hyperphosphatemia (88.1%), constipation (34.9%), diarrhoea (33.3%), nail disorders (29.6%), nausea (27.0%), fatigue (26.4%), , increased AST (26.1%), decreased appetite (24.8%), vomiting (23.0%), alopecia (22.0%), and dry mouth (22.0%).

The most common serious adverse reaction was intestinal obstruction (2.2%)

Permanent discontinuation due to adverse reactions was reported in 9.1% of patients; the most common adverse reaction leading to dose discontinuation were anaemia (0.6%), decreased appetite (0.6%), diarrhoea (0.6%), intestinal obstruction (0.6%), muscular weakness (0.6%), and stomatitis (0.6%); all other adverse reactions were single occurrence.

Tabulated list of adverse reactions

Adverse reactions reported in 318 patients treated with Lytgobi are listed according to MedDRA system organ class (SOC). Frequency categories are very common (≥1/10) and common (≥1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions in patients treated with Lytgobi monotherapy at 20 mg QD (n=318)

System Organ Class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Very common	Hyperphosphatemia Decreased appetite Hypercalcaemia
	Common	Hyponatraemia Hypophosphataemia
Nervous system disorders	Very common	Dysgeusia
	Common	Migraine
Eye disorders	Very common	Dry eye
	Common	Serous retinal detachment[a]
Gastrointestinal disorders	Very common	Stomatitis Diarrhoea Nausea Constipation Dry mouth Vomiting
	Common	Intestinal obstruction

System Organ Class	Frequency	Adverse reactions
Skin and subcutaneous tissue disorders	Very common	Palmar-plantar erythrodysaesthesia syndrome[b] Nail disorders[c] Dry skin Alopecia
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
	Common	Myalgia
General disorders and administration site conditions	Very common	Fatigue Asthenia
Investigations	Very common	Liver transaminases increased

[a] Includes serous retinal detachment, detachment of retinal pigment epithelium, subretinal fluid, chorioretinopathy, macular oedema, and maculopathy. See below section "*Serous retinal detachment.*"

[b] Includes palmar-plantar erythrodysaesthesia syndrome, palmar erythema, and plantar erythema.

[c] Includes nail toxicity, nail bed tenderness, nail disorder, nail discolouration, nail dystrophy, nail hypertrophy, nail infection, nail pigmentation, nail ridging, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis and paronychia.

Description of selected adverse reactions

Hyperphosphatemia

Hyperphosphatemia was reported in 88.1% of patients treated with futibatinib and 23.6% of 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 5.0 days (range: 3.0 to 117.0 days).

None of the reactions were Grade 4 or 5 in severity, serious, or led to the discontinuation of futibatinib. Dose interruption occurred in 21.1% of patients and reduction in 12.9% 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 sections "Dosage/Administration" and "Warnings and precautions."

Serous retinal detachment

Serous retinal detachment occurred in 8.5% of patients treated with futibatinib. Reactions were all Grade 1 or 2 in severity. Dose interruption occurred in 1.3% of patients and reduction in 1.6% of patients. None of the reactions led to the discontinuation of futibatinib. Serous retinal detachment was generally manageable.

Recommendations for management of serous retinal detachment are provided in sections "Dosage/Administration" and "Warnings and precautions."

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at *www.swissmedic.ch*.

Overdose

There is no information on overdose of futibatinib.

Properties/Effects

ATC code

L01 EN04

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*).

Pharmacodynamics

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 sections “Dosage/Administration”, “Warnings and precautions” and “Adverse effects”).

Clinical efficacy

TAS-120-101 is a multicentre, open-label, single-arm study that 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 who had progressed on or after at least 1 prior gemcitabine and platinum-based chemotherapy and had a 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, and 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 summarised in Table 6. The median time to response was 2.5 months (range 0.7–7.4 months).

Table 6: Efficacy results

	LYTGOBI (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.

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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with LYTGOBI in all subsets of the paediatric population in the treatment of cholangiocarcinoma. See section “Dosage/Administration” for information in paediatric use.

Pharmacokinetics

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 mg 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%).

Metabolism

Futibatinib is predominantly metabolised by CYP3A (40-50%) as well as glutathione conjugation (50-60%) *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 dose).

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%).

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.

Kinetics in special patient groups

No clinically meaningful differences in the systemic exposure (less than 25% difference in AUC) of futibatinib were observed based on age (18 to 82 years), sex, race/ethnicity, body weight (36 to 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 “Dosage/Administration”).

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 “Dosage/Administration”).

Exposure-response relationship

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

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

Preclinical 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, and 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 cell (CHL/IU), but negative in the bone marrow micronucleus assay in rat and did not induce DNA damage in comet assay in rats. Thus, futibatinib is overall non-genotoxic.

Carcinogenicity

Carcinogenicity studies with futibatinib have not been conducted.

Impairment of fertility

Dedicated fertility studies with futibatinib have not been conducted. In repeat dose toxicity studies, oral administration of futibatinib did not result in any dose-related findings likely to result in impaired fertility in male or female reproductive organs.

Developmental toxicity

Oral administration of futibatinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at 10 mg/kg per day (approximately 3.15 times the human exposure by AUC at the recommended clinical dose). At 0.5 mg/kg per day (approximately 0.15 times the human exposure by AUC at the recommended clinical dose), reduced mean foetal body weight and an increase in foetal skeletal and visceral malformations including major blood vessel variations were observed.

Other Information

Shelf life

Do not use this medicine after the expiry date marked as "EXP" on the pack.

Special precautions for storage

Store at room temperature (15-25°C).

Keep out of the reach of children.

Instructions for handling

No special requirements for disposal.

Authorisation number

69714 (Swissmedic)

Packs

PVC/PCTFE laminated blisters with aluminium foil backing with one tablet per cavity. Each blister contains a 7-day supply of film-coated tablets sealed inside a folding cardboard wallet in the following three-dose packs:

- 20 mg daily dose: Each wallet contains 35 tablets (5 tablets once daily). [A]
- 16 mg daily dose: Each wallet contains 28 tablets (4 tablets once daily). [A]
- 12 mg daily dose: Each wallet contains 21 tablets (3 tablets once daily). [A]

Marketing authorisation holder

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