NEW DRUG APPROVAL

Brand Name	Truseltiq™
Generic Name	infigratinib
Drug Manufacturer	QED Therapeutics, Inc.

New Drug Approval

FDA Approval Date: May 28, 2021
Review Designation: Priority; Orphan
Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214622
Dispensing Restrictions: Speciality Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Advanced, unresectable cholangiocarcinoma (CCA; also known as bile duct cancer) is a rare, aggressive malignancy with a poor prognosis. The incidence of cholangiocarcinoma ranges between 0.3 and 3.4 per 100,000 people in North America. It is estimated that approximately 8000 people in the United States are diagnosed annually; however, the actual number of CCA cases is likely to be higher because establishing an accurate diagnosis can be difficult.

Bile duct cancer is mainly seen in older people (average age of diagnosis in the United States is 70 years for those with cancer of the intrahepatic bile ducts and 72 years for cancer of the extrahepatic bile ducts). FGFR2 genetic aberrations are present in approximately 15% of people who have CCA.

Bile duct cancer may occur more frequently in patients with a history of primary sclerosing cholangitis, chronic ulcerative colitis, choledochal cysts, or infections with the liver fluke Clonorchis sinensis.

Efficacy

Study CBGJ398X2204 (NCT02150967), a multicenter open-label single-arm trial, evaluated the efficacy of Truseltiq™ in 108 patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement as determined for enrollment by local (89%) or central testing (11%). Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene that leaves the FGFR2 kinase domain intact.
Patients received Truseltiq™ at a dosage of 125 mg orally once daily for 21 consecutive days followed by 7 days off therapy, 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.

Efficacy Results in Study CBGJ398X2204

Efficacy Parameter	**Truseltiq™ N=108**
	BICR Assessment
ORR (95% CI)	23% (16, 32)
Complete Response, n (%)	1 (1%)
Partial Response, n (%)	24 (22%)
Median DoR (months) (95% CI)	5.0 (3.7, 9.3)

Patients with DoR ≥6 months, n (%)	8 (32%)
Patients with DoR ≥12 months, n (%)	1 (4%)

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

Safety

ADVERSE EVENTS

- Most common (≥20%) adverse reactions were nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred and vomiting.
- Most common laboratory abnormalities (≥20%) were increased creatinine, increased phosphate, decreased phosphate, increased alkaline phosphatase, decreased hemoglobin, increased alanine aminotransferase, increased lipase, increased calcium, decreased lymphocytes, decreased sodium, increased triglycerides, increased aspartate aminotransferase, increased urate, decreased platelets, decreased leukocytes, decreased albumin, increased bilirubin and decreased potassium.

WARNINGS & PRECAUTIONS

- **Ocular Toxicity**: Truseltiq™ can cause retinal pigment epithelial detachment (RPED). Perform comprehensive ophthalmic examination including optical coherence tomography (OCT) prior to initiation of Truseltiq™ and at 1 month, at 3 months, and then every 3 months thereafter during treatment. Withhold as recommended.
- **Hyperphosphatemia and Soft Tissue Mineralization:** Increases in phosphate levels can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcinosis, non-uremic calciphylaxis, vascular calcification, and myocardial calcification. Withhold, dose reduce, or permanently discontinue as recommended.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise patients of reproductive potential of the potential risk to the fetus and to use effective contraception.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Infigratinib is a small molecule kinase inhibitor of FGFR with IC50 values of 1.1, 1, 2, and 61 nM for FGFR1, FGFR2, FGFR3, and FGFR4, respectively. The major human metabolites of infigratinib, BHS697 and CQM157, have similar in vitro binding affinities for FGFR1, FGFR2, and FGFR3 compared to infigratinib. Infigratinib inhibited FGFR signaling and decreased cell proliferation in cancer cell lines with activating FGFR amplifications, mutations, or fusions. Constitutive FGFR signaling can support the proliferation and survival of malignant cells. Infigratinib had anti-tumor activity in mouse and rat xenograft models of human tumors with activating FGFR2 or FGFR3 alterations, including two patient-derived xenograft models of cholangiocarcinoma that expressed FGFR2-TTC28 or FGFR2-TRA2B fusions. Infigratinib demonstrated brain-to-plasma concentration ratios (based on $AUC_{0\text{-}inf}$) of 0.682 in rats after a single oral dose.

Dose & Administration

ADULTS

Confirm the presence of an FGFR2 fusion or rearrangement prior to initiation of treatment with Truseltiq™.

125 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles.
Take on an empty stomach at least 1 hour before or 2 hours after food, at approximately the same time each day.
Swallow capsules whole with a glass of water. Do not crush, chew or dissolve.

PEDIATRICS

The safety and effectiveness of Truseltiq™ in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Mild and Moderate Renal Impairment: The recommended dosage is 100 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles.

HEPATIC IMPAIRMENT

Mild Hepatic Impairment: The recommended dosage is 100 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles.
Moderate Hepatic Impairment: The recommended dosage is 75 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28 day cycles.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 25 mg and 100 mg.