TIBSOVO®
ivosidenib tablets 250mg

TIBSOVO® PRODUCT GUIDE FOR CHOLANGIOCARCINOMA (CCA) TREATMENT

INDICATION

TIBSOVO is indicated for patients with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated..

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (eg, anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

TIBSOVO® EFFICACY RESULTS

TIBSOVO delivered a significant improvement in PFS

TIBSOVO was studied in a phase 3, randomized (2:1), double-blind, placebo-controlled, multicenter trial of 185 adult patients with locally advanced or metastatic m*IDH1* cholangiocarcinoma whose disease had progressed following at least 1 but not more than 2 prior regimens, including at least one gemcitabine- or 5-FU-containing regimen. Patients were randomized to receive either TIBSOVO 500 mg QD orally or matched placebo. The primary endpoint was PFS. Crossover from placebo to TIBSOVO was permitted after confirmed disease progression.

Efficacy results in patients with locally advanced or metastatic cholangiocarcinoma[1]

ENDPOINT	TIBSOVO (500 mg DAILY)	PLACEBO
Progression-free survival by IRC assessment	**n=124**	**n=61**
Events, n (%)	76 (61)	50 (82)
Progressive disease	64 (52)	44 (72)
Death	12 (10)	6 (10)
Hazard ratio (95% CI)[a]	0.37 (0.25, 0.54)	
***P* value[b]**	<0.0001	
Objective response rate, n (%)	**3 (2.4)**	**0**
Overall survival[c]	**n=126**	**n=61**
Deaths, n (%)	100 (79)	50 (82)
Hazard ratio (95% CI)[a]	0.79 (0.56, 1.12)	
***P* value[b]**	0.093	

CI, confidence interval; PFS, progression-free survival.
[a]Hazard ratio was calculated from stratified Cox regression model. Stratification factor is the number of prior lines of therapy.
[b]*P* values were calculated from the one-sided stratified log-rank test. Stratification factor is the number of prior lines of therapy.
[c]Overall survival (OS) results were based on the final analysis of OS (based on 150 deaths), which occurred 16 months after the final analysis of PFS. The median OS (95% CI) for TIBSOVO was 10.3 (7.8, 12.4) months and placebo was 7.5 (4.8, 11.1) months without adjusting for crossover. In the analysis of OS, 70% of the patients randomized to placebo had crossed over to receive TIBSOVO after radiographic disease progression.

Median treatment duration was 2.8 months with TIBSOVO (range, 0.1 to 34.4 months) and 1.6 months with placebo (range, 0 to 6.9 months)[1,2]

IRC, independent review committee; mIDH1, mutated IDH1; QD, once a day.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

RECOMMENDED DOSING

TIBSOVO® should be taken orally, with or without food, at about the same time each day[1]

500 mg
(2 x 250-mg film-coated tablets)

Tablets not shown at actual size.

- If a dose is missed or not taken at the usual time, patients should take the missed dose as soon as possible and at least 12 hours prior to the next scheduled dose. They should return to the normal schedule the following day. They should not take 2 doses within 12 hours. If a dose is vomited, patients should not take a replacement dose; they should wait until the next scheduled dose is due
- TIBSOVO tablets should not be split, crushed, or chewed
- TIBSOVO can be taken with or without food but should not be taken with a high-fat meal because of an increase in ivosidenib concentration[a]

Treatment with TIBSOVO has not been studied in patients with preexisting severe renal or hepatic impairment. For patients with preexisting severe renal or hepatic impairment, consider the risks and potential benefits before initiating treatment with TIBSOVO.

[a]An example of a high-fat meal includes 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk (approximately 1000 calories and 58 grams of fat).[1]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Guillain-Barré Syndrome: Guillain-Barré syndrome can develop in patients treated with TIBSOVO. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

ADVERSE REACTIONS

- **In patients with cholangiocarcinoma,** the most common adverse reactions (≥15%) were fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash. The most common laboratory abnormalities (≥10%) were hemoglobin decreased, aspartate aminotransferase increased, and bilirubin increased.

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DRUG-DRUG INTERACTIONS

Strong or moderate CYP3A4 inhibitors[1]

- Coadministration increased ivosidenib plasma concentrations, which may increase the risk of QTc interval prolongation
- Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors
- If coadministration of a strong CYP3A4 inhibitor is unavoidable, reduce TIBSOVO® to 250 mg once daily. If the strong inhibitor is discontinued, increase the TIBSOVO dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended dose of 500 mg once daily
- Monitor patients for increased risk of QTc interval prolongation

Strong CYP3A4 inducers[1]

- Coadministration decreased TIBSOVO plasma concentrations
- Avoid coadministration

QTc interval–prolonging drugs[1]

- Coadministration may increase the risk of QTc interval prolongation
- Avoid coadministration with TIBSOVO or replace with alternative therapies
- If coadministration is unavoidable, monitor patients for increased risk of QTc interval prolongation

Effect of TIBSOVO on other drugs[1]

- Ivosidenib induces CYP3A4 and may induce CYP2C9
- Coadministration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease concentrations of drugs that are sensitive CYP2C9 substrates
- Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9
- Do not administer with itraconazole or ketoconazole (CYP3A4 substrates) due to expected loss of antifungal efficacy
- Coadministration may decrease the concentrations of hormonal contraceptives. Consider alternative methods of contraception
- If coadministration with sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

ADVERSE REACTIONS

The most common adverse reactions (≥15%) were fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash.[1]

Adverse reactions reported in ≥10% of patients receiving TIBSOVO®[1]

	TIBSOVO (500 mg DAILY) n=123		PLACEBO n=59	
Body system Adverse reaction	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
General disorders and administration site conditions				
Fatigue[a]	53 (43)	4 (3)	18 (31)	3 (5)
Gastrointestinal disorders				
Nausea	51 (41)	3 (2)	17 (29)	1 (2)
Diarrhea	43 (35)	0	10 (17)	0
Abdominal pain[b]	43 (35)	3 (2)	13 (22)	2 (3)
Ascites	28 (23)	11 (9)	9 (15)	4 (7)
Vomiting[c]	28 (23)	3 (2)	12 (20)	0
Respiratory, thoracic, and mediastinal disorders				
Cough[d]	33 (27)	0	5 (9)	0
Metabolism and nutrition disorders				
Decreased appetite	30 (24)	2 (2)	11 (19)	0
Blood and lymphatic system disorders				
Anemia	22 (18)	8 (7)	3 (5)	0
Skin and subcutaneous tissue disorders				
Rash[e]	19 (15)	1 (1)	4 (7)	0
Nervous system disorders				
Headache	16 (13)	0	4 (7)	0
Neuropathy peripheral[f]	13 (11)	0	0	0
Investigations				
Electrocardiogram QT prolonged	12 (10)	2 (2)	2 (3)	0

[a]Grouped term includes asthenia and fatigue.
[b]Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, epigastric discomfort, abdominal tenderness, and gastrointestinal pain.
[c]Grouped term includes vomiting and retching.
[d]Grouped term includes cough and productive cough.
[e]Grouped term includes rash, rash maculopapular, erythema, rash macular, dermatitis exfoliative generalized, drug eruption, and drug hypersensitivity.
[f]Grouped term includes neuropathy peripheral, peripheral sensory neuropathy, and paraesthesia.

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ADVERSE REACTIONS (cont'd)

Selected laboratory abnormalities reported in ≥10% of patients receiving TIBSOVO®[1]

	TIBSOVO (500 mg DAILY) n=123		PLACEBO n=59	
Parameter	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Aspartate aminotransferase increased	41 (34)	5 (4)	14 (24)	1 (2)
Bilirubin increased	36 (30)	15 (13)	11 (19)	2 (3)
Hemoglobin decreased	48 (40)	8 (7)	14 (25)	0

Dose reductions, interruptions, and discontinuations due to adverse events[1]

- Dose interruptions due to adverse reactions occurred in 29% of patients treated with TIBSOVO
  - The most common (>2%) adverse reactions leading to dose interruption were hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, ascites, and fatigue
- Dose reductions of TIBSOVO due to an adverse reaction occurred in 4.1% of patients
  - Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (3.3%) and neuropathy peripheral (0.8%)
- TIBSOVO was permanently discontinued in 7% of patients
  - The most common adverse reaction leading to permanent discontinuation was acute kidney injury (1.6%)

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation.

Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO.

Sensitive CYP3A4 Substrates: Avoid concomitant use with TIBSOVO.

QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

MANAGING ADVERSE REACTIONS

Periodic monitoring

- QTc prolongation: Obtain an electrocardiogram (ECG) prior to treatment initiation. Monitor ECGs at least once weekly for the first 3 weeks of therapy and then at least once monthly for the duration of therapy. Manage any abnormalities promptly
- Guillain-Barré syndrome: Monitor patients for onset of new signs or symptoms of motor and/or sensory neuropathy, such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing

Recommended dose modifications for TIBSOVO®[1]

Adverse reaction	Recommended action
QTc interval >480 msec to 500 msec	• Monitor and supplement electrolyte levels as clinically indicated • Review and adjust concomitant medications with known QTc interval-prolonging effects • Interrupt TIBSOVO • Restart TIBSOVO at 500 mg once daily after the QTc interval returns to ≤480 msec • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation
QTc interval greater than 500 msec	• Monitor and supplement electrolyte levels as clinically indicated • Review and adjust concomitant medications with known QTc interval–prolonging effects • Interrupt TIBSOVO • Resume TIBSOVO at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or ≤480 msec • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation • Consider re-escalating the dose of TIBSOVO to 500 mg daily if an alternative etiology for QTc prolongation can be identified
QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	• Discontinue TIBSOVO permanently
Guillain-Barré syndrome	• Discontinue TIBSOVO permanently
Other Grade 3[a] adverse reactions	• Interrupt TIBSOVO until toxicity resolves to Grade 1[a] or lower, or baseline, then resume at 500 mg daily (Grade 3 toxicity) or 250 mg daily (Grade 4 toxicity) • If Grade 3 toxicity recurs (a second time), reduce TIBSOVO dose to 250 mg daily until the toxicity resolves, then resume 500 mg daily • If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue TIBSOVO

[a]Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.
ECG, electrocardiogram.

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ORDERING AND PRODUCT INFORMATION

National Drug Code (NDC)

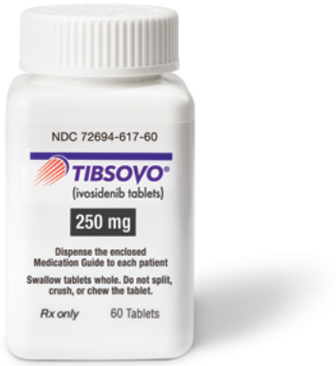
NDCs	Dosage strength	Description
10-digit code: 72694-617-60 11-digit code: 72694-0617-60	250 mg/tablet	250-mg tablet: Blue oval-shaped film-coated tablet debossed "IVO" on one side and "250" on the other side[1]

The red zero converts the 10-digit NDC to the 11-digit NDC. Some payers may require each NDC to be listed on the claim. Payer requirements regarding the use of NDCs may vary. Electronic data exchange generally requires use of the 11-digit NDC.

Product information

How TIBSOVO® is supplied: 250-mg tablets, supplied in 60-count bottles (30-day supply) with a desiccant canister[1]

Storage: Store at 20 to 25 °C (68 to 77 °F)



IMPORTANT SAFETY INFORMATION (cont'd)

LACTATION

Advise women not to breastfeed.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

DISTRIBUTION NETWORK FOR TIBSOVO®

TIBSOVO is only available through specialty distributors and specialty pharmacies.

Specialty distributors: TIBSOVO is available through specialty distributors for shipment directly to office- or hospital-based pharmacies.

McKesson Specialty Health

Multispecialty
1-855-477-9800
mscs.mckesson.com

Oncology
1-800-482-6700
mscs.mckesson.com

Cardinal Health Specialty Pharmaceutical Distribution (US)

Physician Office
1-877-453-3972
https://specialtyonline.cardinalhealth.com

Hospitals/All Other
1-866-677-4844
https://orderexpress.cardinalhealth.com

Cardinal Health (Puerto Rico)
1-787-625-4100
https://cardinalhealth.pr

ASD Healthcare Customer Service
1-800-746-6273
https://www.asdhealthcare.com

Oncology Supply
1-800-633-7555
https://www.oncologysupply.com

Network specialty pharmacies: TIBSOVO ships directly from the specialty pharmacy to your patient's home or preferred location.

Biologics by McKesson
1-800-850-4306
biologics.mckesson.com

Onco360
1-877-662-6633
Onco360.com

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ServierONE PATIENT SUPPORT SERVICES

ServierONE offers patients helpful resources and tools for navigating treatment care, costs, and education throughout their journey.

ServierONE Patient Support Services for TIBSOVO® (ivosidenib tablets) includes:

- Support with insurance coverage and reimbursement
- Financial assistance to help patients pay for TIBSOVO
- Prescription fulfillment through our network of specialty pharmacies and distributors
- Tools and resources to navigate the world of insurance

TO RECEIVE MORE INFORMATION

VISIT **ServierONE.com** **OR** CALL **1-800-813-5905**
Monday through Friday, 8 AM to 8 PM ET.

Register online for the **Commercial Copay Program** at **ServierOne-copay.com.**

FINANCIAL ASSISTANCE AND COVERAGE SUPPORT PROGRAMS

The Commercial Copay Program can lower out-of-pocket costs

- There are no income restrictions
- Available to eligible patients with commercial/private insurance
- Patients participating in government healthcare insurance are not eligible

Independent foundations[a]

- Network specialty pharmacies or ServierONE can provide more information

Patient Assistance Program

- Offers free prescriptions to eligible uninsured and underinsured patients (may apply to commercial or government insurance)

QuickStart Program

- Receive a free 30-day supply of therapy for up to two (2) dispenses for eligible patients
- For new patients with commercial or government insurance
- Must be experiencing a coverage delay of 5 or more days after submission of a completed prior authorization

Please visit **ServierONE.com** for full program details and information on how to enroll patients.

[a]Eligibility is determined by the individual foundation. Servier is not affiliated with these organizations.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

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TIBSOVO® IS THE FIRST-IN-CLASS TARGETED INHIBITOR OF mIDH1 IN CCA[1,3]

TIBSOVO delivered **significant improvements in PFS** with a 63% reduction in the risk of disease progression or death **(HR, 0.37 [95% CI, 0.25-0.54]; *P*<0.0001)**[1]

- PFS rate at 6 months: 32%[2]
- PFS rate at 12 months: 22%[2]

- Convenient, once-daily oral dosing[1]

INDICATION

TIBSOVO is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for patients with a susceptible IDH1 mutation as detected by an FDA-approved test for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome: Guillain-Barré syndrome can develop in patients treated with TIBSOVO. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information.

Visit TibsovoPro.com to learn more

References: 1. Tibsovo. Package insert. Servier Pharmaceuticals LLC; 2023. **2.** Data on File. Servier Pharmaceuticals LLC. **3.** Popovici-Muller J, Lemieux RM, Artin E, et al. Discovery of AG-120 (ivosidenib): a first-in-class mutant IDH1 inhibitor for the treatment of IDH1 mutant cancers. *ACS Med Chem Lett.* 2018;9(4):300-305. doi:10.1021/acsmedchemlett.7b00421

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