PDL DRUG REVIEW

Proprietary Name: Iqirvo®
Common Name: elafibranor
PDL Category: Gastrointestinal Agents

Comparable Products	Preferred Drug List Status
Ocaliva (obeticholic acid)	Non-Preferred
Ursodiol	Preferred

Pharmacology/Usage: Elafibranor and its main active metabolite GFT1007, the active ingredient of Iqirvo®, are peroxisome proliferator-activated receptor (PPAR) agonists. Elafibranor and GFT1007 both activate PPAR-alpha, PPAR-gamma, and PPAR-delta in vitro. However, the mechanism of action for its approved indication is not well understood. Pharmacological activity that is potentially relevant to therapeutic effects includes inhibition of bile acid synthesis through activation of PPAR-alpha and PPAR-delta. The signaling pathway for PPAR-delta was reported to include Fibroblast Growth Factor 21 (FGF21)-dependent downregulation of CYP7A1, the main enzyme for the synthesis of bile acids from cholesterol.

Indication: For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have had an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. This indication is approved under accelerated approval based on reduction of alkaline phosphatase (ALP). Improvement in survival or prevention of liver decompensation events have not been demonstrated. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Use of Iqirvo® is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).

There is no pregnancy category for this medication; however, the risk summary indicates that based on data from animal reproduction studies, Iqirvo® may cause fetal harm when administered during pregnancy. There are insufficient data from human pregnancies exposed to Iqirvo® to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Report pregnancies to Ipsen Pharmaceuticals, Inc. Adverse Event reporting line at 1-855-463-5127. For females of reproductive potential, verify that the patient is not pregnant prior to starting Iqirvo®. In addition, advise females of reproductive potential to use effective contraception (non-hormonal) or add a barrier method of contraception when using hormonal contraceptives during treatment with Iqirvo® and for 3 weeks after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 80mg.

Recommended Dosage: Before starting treatment:

- Assess for muscle pain or myopathy.
- Verify that females of reproductive potential are not pregnant prior to starting treatment.

The recommended dosage is 80mg PO QD, with or without food. Dose adjustments are not required with renal impairment or with mild hepatic impairment. The safety and efficacy of use in patients with decompensated cirrhosis have not been established. Use of Iqirvo® is not recommended in patients who

have or develop decompensated cirrhosis. Monitor patients with cirrhosis for evidence of decompensation. Consider discontinuing Iqirvo® if the patient progresses to moderate or severe hepatic impairment.

Administer Iqirvo® at least 4 hours before or 4 hours after administering the bile acid sequestrant, or at as great an interval as possible.

Drug Interactions: Iqirvo® is a weak CYP3A4 inducer. Coadministration of Iqirvo® with hormonal contraceptives may reduce the systemic exposure of progestin and ethinyl estradiol, which may lead to contraceptive failure and/or an increase in breakthrough bleeding. Switch to effective non-hormonal contraceptives or add a barrier method when using hormonal contraceptives during Iqirvo® treatment, and for at least 3 weeks after the last dose.

Creatine phosphokinase (CPK) elevation and/or myalgia occurred in patients on Iqirvo® monotherapy. Coadministration of Iqirvo® and HMG-CoA reductase inhibitors (statins) which have a risk of myalgia, can increase the risk of myopathy. Monitor for signs and symptoms of muscle injury. Consider periodic assessment during treatment. Interrupt Iqirvo® treatment if there is new onset or worsening of muscle pain or myopathy.

The coadministration of Iqirvo® with rifampin, an inducer of metabolizing enzymes, may reduce the systemic exposure of elafibranor and its active metabolite via increased metabolism. Monitor the biochemical response (e.g., ALP and bilirubin) when patients start rifampin during Iqirvo® treatment.

Bile acid sequestrants may interfere with the action of Iqirvo® by reducing its absorption and systemic exposure, which may reduce Iqirvo® efficacy. Administer Iqirvo® at least 4 hours before or 4 hours after taking a bile acid binding sequestrant, or at as great an interval as possible.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Iqirvo®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included weight gain (14%), diarrhea (7%), abdominal pain (9%), nausea (9%), vomiting (11%), arthralgia (7%), constipation (8%), muscle pain (7%), fracture (7%), gastroesophageal reflux disease (6%), dry mouth (4%), weight loss (5%), rash (3%), creatine phosphokinase (CPK) increased (>3 X upper limit of normal [ULN]; 4%), myalgia (2%), CPK increased and myalgia (1%), and rhabdomyolysis and AKI (acute kidney injury; 1%).

Additional adverse reactions that occurred more frequently in the Iqirvo®-treated patients compared to placebo, but in less than 5% of patients included dizziness, gastroenteritis, increased blood creatinine, and anemia.

Rhabdomyolysis resulting in acute kidney injury occurred in one Iqirvo®-treated patient who had cirrhosis at baseline and was also taking a stable dose of an HMG-CoA reductase inhibitor (statin). Myalgia or myopathy, with or without CPK elevations, occurred in patients treated with Iqirvo® alone or treated concomitantly with a stable dose of an HMG-CoA reductase inhibitor. Assess for myalgia and myopathy prior to starting Iqirvo®. Consider periodic assessment during treatment, especially in those who have signs and symptoms of new onset or worsening of muscle pain or myopathy.

Fractures were reported in patients treated with Iqirvo®. Consider the risk of fracture in the care of patients treated with Iqirvo® and monitor bone health per current standards of care.

Drug-induced liver injury (DILI) occurred in one patient who took Iqirvo® 80mg QD and two patients who took Iqirvo® at 1.5 times the recommended dosage. The median time to onset of elevation in liver tests was 85 days. Obtain baseline clinical and laboratory assessments at Iqirvo® treatment initiation and monitor thereafter per routine patient management. Interrupt treatment if liver tests worsen, or the patient develops signs and symptoms consistent with clinical hepatitis. Consider permanent discontinuation if liver tests worsen after restarting Iqirvo®.

Hypersensitivity reactions have occurred with Iqirvo® at 1.5 times the recommended dosage. If a severe hypersensitivity reaction occurs, permanently discontinue Iqirvo®. If a mild or moderate hypersensitivity reaction occurs, interrupt Iqirvo® and treat promptly.

Avoid use of Iqirvo® in patients with complete biliary obstruction. If biliary obstruction is suspected, interrupt Iqirvo® and treat as clinically indicated.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Ipsen Biopharmaceuticals, Inc.

Analysis: The efficacy of Iqirvo® was assessed in Study 1, a multicenter, randomized, double-blind, placebo-controlled study that included adults (N=161) with PBC with an inadequate response or intolerance to UDCA. Patients were randomized to Iqirvo® or placebo daily for at least 52 weeks. When applicable, patients continued their pre-study dose of UDCA throughout the study. Patients were included in the study if their ALP was ≥1.67-times the upper limit of normal (ULN) and total bilirubin was ≤2-times the ULN.

The mean age of included patients was 57 years (range 36 to 76), while 96% were female and 91% were white. The mean weight was 70.8kg, the mean baseline ALP concentration was 321.9 U/L, and 39% of patients had a baseline ALP concentration greater than 3 times the ULN. The mean baseline total bilirubin concentration was 0.56 mg/dL.

Most patients (95%) received study treatment in combination with UDCA. There were 6 patients (6%) in the Iqirvo® group and 2 patients (4%) in the placebo group who were unable to tolerate UDCA and received Iqirvo® as monotherapy. At baseline, 11% of the Iqirvo® group and 15% of the placebo group met at least one of the following criteria: serum albumin <3.5g/dL, INR >1.3, total bilirubin > 1-time ULN, Fibroscan >16.9 kPa, or historical biopsy suggestive of cirrhosis.

The primary endpoint was biochemical response at week 52, where biochemical response was defined as achieving ALP less than 1.67-times ULN, total bilirubin ≤ ULN, and ALP decrease ≥15% from baseline. The ULN for ALP was defined as 129 U/L for males and 104 U/L for females. The ULN for total bilirubin was defined as 1.20mg/dL. ALP normalization (i.e., ALP ≤ ULN) at week 52 was a key secondary endpoint.

Results are presented in the table below, which was adapted from the prescribing information. Iqirvo® demonstrated greater improvement on biochemical response and ALP normalization at week 52 as compared to placebo. Overall, 96% of patients had a baseline total bilirubin concentration ≤ ULN. Thus, improvement in ALP was the main contributor to the biochemical response rate results at week 52.

	Iqirvo® 80mg (N=108)	Placebo (N=53)	Treatment difference
Biochemical response rate, n (%)	55 (51%)	2 (4%)	47%
NNT per CHC	3		
Components of biochemical response			
ALP less than 1.67-times ULN, n (%)	56 (52%)	5 (9%)	42%
Decrease in ALP of at least 15%, n (%)	81 (75%)	9 (17%)	58%
Total bilirubin ≤ ULN, n (%)	92 (85%)	44 (83%)	2%

	Iqirvo® 80mg (N=108)	Placebo (N=53)	Treatment difference
ALP normalization, n (%)	16 (15%)	0	15%

Place in Therapy: Iqirvo® is a peroxisome proliferator-activated receptor (PPAR) agonist indicated for the treatment of primary biliary cholangitis (PBC) in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. This indication is approved under accelerated approval based on reduction of alkaline phosphatase. Improvement in survival or prevention of liver decompensation events have not been demonstrated. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Use of Iqirvo® is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy). Its efficacy was assessed in phase 3, double-blind, placebo-controlled study that included adults with PBC. Most patients in the study (95%) received study treatment in combination with UDCA. The primary endpoint was biochemical response at week 52. Results suggested that Iqirvo® demonstrated greater improvement on biochemical response and ALP normalization at week 52 as compared to placebo (NNT 3 for primary endpoint of biochemical response). Per the full-text study by Kowdley et al[2], the primary endpoint of biochemical response was observed in significantly more in the Iqirvo® group as compared with placebo ($p<0.001$).

Summary

There is no evidence at this time to support that Iqirvo® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Iqirvo® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Iqirvo [package insert]. Cambridge, MA: Ipsen Biopharmaceuticals, Inc; 2024.
[2] Kowdley KV, Bowlus CL, Levy C, et al. Efficacy and safety of elafibranor in primary biliary cholangitis. *NEJM.* 2024; 390(9): 795-805.