Elafibranor (IQIRVO)
National Drug Monograph
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VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: 5-D, degree, duration, direction, disability, and distribution (dimensions on the 5-D itch scale); AAE, anticipated absolute effect; ALP, alkaline phosphatase; ALT, alanine transaminase; AUC, area under the time-concentration curve; BAS, bile acid sequestrant; CFB, change from baseline; DB, double-blind; ELA, elafibranor; FDA, U.S. Food and Drug Administration; FXR, farnesoid X receptor; HDL, high density lipoprotein; LDL-C, low density lipoprotein cholesterol; LTE, long-term extension; MN, multinational; NMA, network meta-analysis; OCA, obeticholic acid; PBC, primary biliary cholangitis; PC, placebo-controlled; pp, percentage points; PPAR, peroxisome proliferator-activated receptor; Q, GRADE quality of evidence; RCT, randomized clinical trial; TB, total bilirubin; TC, total cholesterol; TG, triglyceride; UDCA, ursodeoxycholic acid or ursodiol; ULN, upper limit of normal; VLDL-C, very low density lipoprotein cholesterol; WI-NRS, Worst Itch-Numerical Rating Scale

FDA Approval Information

Description / Mechanism of Action

- Elafibranor and its main active metabolite GFT1007 are peroxisome proliferator-activated receptor (PPAR) agonists of three subgroups, PPAR-alpha, PPAR-delta, and PPAR-gamma.
- Activation of PPAR-alpha and PPAR-delta inhibits bile acid synthesis.
- [1]
- Elafibranor is the first PPAR agonist approved for the treatment of primary biliary cholangitis (PBC) and the third agent approved for PBC, following ursodiol (ursodeoxycholic acid / UDCA) and obeticholic acid.
- The FDA granted breakthrough designation and accelerated approval to elafibranor.

Indication Under Review in This Document

- Treatment of PBC in combination with ursodiol in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.[1]
- 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).
- *Limitations of Use*. Use is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).

Dosage Regimen and Dosage Form Under Review

Dosage Regimen and Dosage Form

- 80 mg orally once daily with or without food.
- Tablets: 80 mg

Dosage Modifications

- Renal Impairment – No dosage modification is recommended for mild, moderate, or severe renal impairment.
- Mild Hepatic Impairment – No dosage modification
- Moderate or Severe Hepatic Impairment (Child-Pugh B or C) – Consider discontinuing therapy
- Decompensated Cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy) – Use not recommended.

Pretreatment Evaluations

- Evaluate for muscle pain or myopathy
- Verify that patients of reproductive potential are not pregnant
- Liver tests (ALT, AST, TB, ALP)

Monitoring

- Liver tests (ALT, AST, TB, ALP)
- Bone health
- Decompensation in patients with cirrhosis

Efficacy Considerations

- No active-controlled trials have been performed.
- A phase 3, placebo-controlled randomized clinical trial (RCT), ELATIVE, showed efficacy of elafibranor in improving biochemical response but not in improving pruritus.[2] Since 95% of patients were treated with UDCA concomitantly, this trial effectively compared elafibranor + UDCA with UDCA monotherapy.
- A phase 2, dose- and placebo-controlled RCT provided supportive evidence of elafibranor efficacy in terms of the relative change of ALP and a composite end point (ALP ≤ 1.67 x ULN, decrease of ALP > 15%, and TB below ULN) at Week 12 in patients with inadequate response to UDCA.[3] All patients were on stable doses of UDCA; therefore, this trial also effectively compared elafibranor + UDCA with UDCA monotherapy.

Phase 3 Randomized Clinical Trial

Table 1 Methods of Phase 3 RCT

Topic	ELATIVE
Study Design	52-week phase 3 MN DB PC RCT Randomization stratified by ALP > 3x ULN or TB above ULN; and WI-NRS score ≥ 4 (scale 0 / No Itch to 10 / Worst Itch Imaginable) Long-term Extension (LTE): All patients completing the DB period will receive elafibranor 80 mg daily for up to 5 years.
Major Entry Criteria	*Inclusion Criteria*: PBC; inadequate response or intolerance to UDCA; age 18–75 years; ALP at least 1.67 x ULN (215 U/L for men, 174 U/L for women); TB not more than 2 x ULN (41 µmol/L) *Exclusion Criteria*: Autoimmune hepatitis (AIH), PBC-AIH overlap, clinically significant hepatic decompensation including cirrhosis / portal hypertension complications (e.g., esophageal varices, ascites, history of variceal bleeds or related interventions, hepatic encephalopathy, history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma), hepatorenal syndrome type I or II.
Interventions	Elafibranor 80 mg once daily Placebo

Topic	ELATIVE
	Note: Per protocol, patients on UDCA before the study should have continued the same dose during the trial (applied to 95% of patients).
Primary Efficacy Measure(s)	Biochemical response at Wk 52 **Biochemical response** was defined as ALP < 1.67 x ULN, with ≥ 15% reduction from baseline, and normal TB.
Baseline Patient Characteristics (N = 161)	Age 57.1 y; 4% men; 91% White; 8 y since diagnosis; mean ALP 322 U/L; 39% with ALP > 3x ULN; TB 9.6 µmol/L; concurrent UDCA 95%; mean WI-NRS 3.3; moderate to severe pruritus 41%; liver stiffness > 10.0 kPa 31%; bridging fibrosis or cirrhosis 43%; liver stiffness > 10 kPa and/or bridging fibrosis or cirrhosis 35%

Table 2 Efficacy results from ELATIVE

Outcome	ELA	PBO	Relative Risk (95% CI)	AAE per 100 or Diff (95% CI)	Q
Biochemical response, n/N (%)	55/108 (51)	2/53 (4)	13.5 (3.42, 53.22)	47 (32, 57)	L[α]
CFB in ALP, U/L [N]	−117 [94]	−5.3 [47]	—	−112 (−142, −81)	—
CFB in TB, µmol/L [N]	−0.1 [93]	1.1 [47]	—	−1.3 (−2.8, 0.2)	—

AAE, Anticipated absolute effect for achieving the outcome; **CFB**, Change from baseline; **Q**, GRADE quality of evidence (L = Low)

[α] Downgraded for indirectness (surrogate measure, not a final health outcome) and imprecision (optimal information size not met)

- Secondary efficacy results
  - Elafibranor was significantly better than placebo in rate of normalization of ALP.
  - There was no significant treatment difference in change from baseline in WI-NRS score.
  - The itch domain scores on the PBC-40 quality of life questionnaire and the 5-D itch total score numerically favored elafibranor.
  - TC, LDL-C, VLDL-C, and TG levels were numerically lower on elafibranor than placebo within 4 weeks of starting therapy.
  - HDL levels remained stable on elafibranor.
- Subgroup Analyses
  - Elafibranor was better than placebo in all subgroups analyzed except there was no significant treatment difference in patients with baseline TB > 0.6x ULN.[5]
  - In elafibranor monotherapy patients, biochemical response rates at Week 52 were 16.6% (1 of 6) and 0% (0 of 2) in the elafibranor and placebo groups, respectively (risk difference 16.7 pp; 95% CI −50.5, 56.4).

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects seemed to occur within 4 weeks.
- Duration of an adequate therapeutic trial (time to reach peak or near-peak biochemical response) was 13 weeks.

Durability of Response

- Maintained for up to 52 weeks, the duration of evaluation. Durability of response beyond 52 weeks is unknown.

Safety Considerations

Table 3 Safety Profile from US Prescribing Information

Domain	Description
Boxed Warnings	• None
Contraindications	• None
Use Not Recommended	• Decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy)
Consider Discontinuing Therapy	• Progression to moderate or severe hepatic impairment (Child-Pugh B or C) • Worsening liver tests after restarting elafibranor in patients with DILI
Interrupt Therapy	• New onset or worsening of muscle injury or muscle pain, or myopathy, or rhabdomyolysis • Worsening of liver tests or evidence of clinical hepatitis in patients with DILI • Hypersensitivity reactions • Suspected biliary obstruction
Other Warnings / Precautions	• Myalgia, myopathy, rhabdomyolysis • Bone fractures (6% [7 of 108] elafibranor vs 0% [0 of 53] placebo) • Adverse effects on fetal and newborn development
Common Adverse Events (≥ 5%)	• Weight gain, diarrhea, abdominal pain, nausea, vomiting, arthralgia, constipation, muscle injury, fracture, gastroesophageal reflux disease, dry mouth, weight loss, rash
Drug Interactions	• Reduced effects of hormonal contraceptives – switch to nonhormonal contraceptives or add a barrier method to hormonal contraceptives during therapy and for at least 3 weeks after the last dose. • Increased risk of myopathy with concomitant HMG-CoA reductase inhibitors – monitor for signs and symptoms of muscle injury • Decreased effect of elafibranor with concomitant rifampin – monitor the therapeutic biochemical response (e.g., ALP and bilirubin) when rifampin is initiated during elafibranor therapy • Decreased effect of elafibranor with concomitant bile acid sequestrants (BASs) – administer elafibranor at least 4 hours before or 4 hours after taking a BAS, or at as great an interval as possible
Pregnancy	• May cause fetal harm based on animal studies. Insufficient human data.
Lactation	• Potential for serious adverse effects in breastfed infants. Insufficient animal and human data. Advise patients not to breastfeed during elafibranor therapy and for 3 weeks after the last dose.
Geriatric Use	• Overall, no age-related differences in effects were seen in clinical trials (25 patients ≥ 65 years; 1 patient ≥ 75 years).[1] • In pharmacokinetic studies, increased mean systemic exposure to elafibranor and its major active metabolite, GFT1007, was observed in healthy elderly subjects aged 75–80 years (AUC 23% and 52% higher, respectively, vs healthy young subjects 26–42 years of age). • No dosage adjustment is necessary for patients ≥ 65 years of age. • For patients > 75 years old, closer monitoring of adverse effects is recommended.

Table 4 Selected Safety Results from ELATIVE

Outcome	ELA	PBO
Serious adverse event, n/N (%)	11/108 (10)	7/53 (13)
Death, n/N (%)	2/108 (2)	0/53 (0)
Discontinuation due to adverse event, n/N (%)	11/108 (10)	5/53 (9)
Any treatment-related adverse event	42/108 (39)	21/53 (40)

Evidence Gaps

- Survival / Mortality

- Hospitalization or readmission
- Efficacy of elafibranor in reducing liver-related outcomes such as need for liver transplant or prevention of liver decompensation
- Long-term safety beyond 1 year including any risk of elafibranor-related decompensation in patients with cirrhosis

Network Meta-analyses

- A literature search found no well-designed NMAs.

Other Considerations

Table 5 Considerations from the FDA Integrated Review

Topic	Comments
Higher exposure to drug in men than women	After a single dose, systemic exposure to elafibranor and GFT1007 metabolite were 32% and 26% higher, respectively, in males vs females. Deemed to be not clinically significant.
Lower exposure to drug with increase in weight and BMI	Body weight in the range of 43–120 kg and BMI in the range of 14.5–54 kg/m^2 (studied in the phase 3 RCT) showed no significant impact on efficacy.

Source: 4

Other Therapeutic Options

Table 6 Therapeutic Options for PBC

Drug	Formulary	CFU Place in Therapy	FDA Place in Therapy	2018 / 2021 AASLD Guideline Place in Therapy[5]
PPAR-alpha / -delta Agonist				
Elafibranor	TBD	• TBD	• Treatment of PBC In combination with UDCA in inadequate responders to UDCA • Monotherapy in patients with UDCA intolerance • Not recommended in the presence of decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy)	• Predates drug approval
PPAR-delta Agonist				
Seladelpar	TBD	• TBD	• Same as elafibranor	• Predates drug approval
Bile Acid				
Ursodiol (UDCA)	Yes (tab)†	• NA	• Treatment of PBC; no prerequisite therapies	• UDCA 13–15 mg/kg/d is first-line therapy. • Studies have inconsistently shown improved survival • Reduces need for liver transplant and improves transplant-free survival.

Drug	Formulary	CFU Place in Therapy	FDA Place in Therapy	2018 / 2021 AASLD Guideline Place in Therapy[5]
Farnesoid X Receptor Agonist Synthetic Bile Acid				
Obeticholic Acid (OCA)	No / CFU in PBC	• Contraindication or intolerance to UDCA or inadequate response after at least 12 months (stable dose for at least 3 months) of UDCA (13–15 mg/kg/day)	• Treatment of adults with PBC without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension either in combination with UDCA in inadequate responders to UDCA or as monotherapy in patients unable to tolerate UDCA • Contraindicated in complete biliary obstruction, decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event, and compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) • After concluding that the confirmatory COBALT trial[6] showed that OCA was ineffective in preventing liver-related complications in patients with PBC, an FDA Advisory Committee recommended against full approval for OCA.[7] OCA remains on the U.S. market as of 10/21/2024. (In September 2024, the European Commission revoked the conditional marketing authorization of OCA in the EU based on the COBALT trial results. However, the President of the General Court of the EU temporarily suspended the revocation, and OCA remains on the EU market.)[8]	• Contraindicated in advanced cirrhosis (defined as cirrhosis with current or prior evidence of liver decompensation, such as encephalopathy or coagulopathy, or evidence of portal hypertension (e.g., ascites, gastroesophageal varices, or persistent thrombocytopenia) • Recommends careful monitoring of *any* patients with cirrhosis who are on OCA
PPAR-alpha Agonist – Fibrates				
Fenofibrate‡	No (cap) Yes (tab)	• NA	• Off-label for PBC • Approved for treatment of hypertriglyceridemia, primary hypercholesterolemia, or mixed dyslipidemia	• Fibrates can be considered off-label alternatives in inadequate responders to UDCA • Use is discouraged in decompensated liver disease
PPAR-alpha, -gamma, -delta Agonist – Fibrates				
Fenofibric Acid	No (cap EC, tab)	• NA	• See fenofibrate	• See fenofibrate

Sources: FDA Multi-discipline Review,[4] UpToDate[9]
CFU, Criteria for Use
† Ursodiol capsules (e.g., RELTONE), on formulary, are not indicated for PBC.
‡ Use of fenofibrate in PBC is supported by a network meta-analysis of 5 studies: one observational study, two retrospective studies, and two meta-analyses. The NMA showed that fenofibrate + UDCA was better than UDCA and comparable to elafibranor + UDCA.[10]

Projected Place in Therapy

- **Epidemiology and Prevalence of PBC**. PBC is a rare, chronic, progressive autoimmune disease that can lead to damage and eradication of small intralobular bile ducts. Complications include chronic cholestasis and liver failure. The 5-year incidence of PBC was estimated to be 16%[5] and the prevalence is about 19–402 cases per million persons.[9]
- **Potential Place in Therapy Based on the Evidence**. Low-quality evidence from the 52-week ELATIVE phase 3 RCT showed a large benefit in terms of biochemical response rate. The results mainly support the use of elafibranor added on to UDCA over UDCA (i.e., placebo + UDCA) in patients with PBC who have had an inadequate response to UDCA alone. Although approved for use as monotherapy in patients who had intolerance to UDCA, it seems that only 5% of the study population received elafibranor without UDCA and treatment was ineffective in this subgroup, although the confidence interval for the treatment difference was wide because of the small number of patients. The effects of elafibranor on clinically outcomes, such as preventing liver-related complications, are unknown and will be evaluated in longer-term studies. There have been no trials directly comparing elafibranor with fenofibrate, obeticholic acid, or seladelpar. The drug safety profiles differ, with the main concerns being myopathy, rhabdomyolysis, cholelithiasis, increased serum creatinine, drug-induced liver injury, multiple major drug interactions with fibrates / fenofibrate, myopathy, rhabdomyolysis, and bone fractures with elafibranor; pruritus, dose-related hepatotoxicity, and cirrhotic decompensation with obeticholic acid; and bone fractures and liver test abnormalities with seladelpar. All of these agents should be avoided in decompensated liver disease.
- **Potential Place in Therapy in VHA**. Elafibranor may be used as add-on therapy to UDCA in patients with PBC without decompensated cirrhosis who have an inadequate response to UDCA, or as monotherapy in patients who have intolerance to UDCA. An adequate trial of UDCA in patients who are tolerating therapy is considered to be at least 1 year at a dosage of 13–15 mg/kg/d, with ≥ 3 months at a stable dosage.[11]

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Contact person: Francine Goodman, PharmD, BCPS, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

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