

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

IQIRVO®

elafibranor film-coated tablets

1 NAME OF THE MEDICINE

elafibranor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each IQIRVO film-coated tablet contains 80 mg of elafibranor as the active ingredient.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

IQIRVO 80 mg film-coated tablets are round, orange, debossed with 'ELA 80' on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

IQIRVO is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended dose is 80 mg once daily with or without food.

Missed doses

If a dose of elafibranor is missed, the patient should not take the missed dose and instead take their subsequent dose at the next scheduled time point. The patient should not take a double dose to make up for the missed dose.

Special Populations

Elderly patients

No dose adjustment is necessary in patients older than 65 years of age (see section 5.2 PHARMACOKINETIC PROPERTIES).

Patients with renal impairment

No dose adjustment is necessary in patients with renal impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

The safety and efficacy of elafibranor have not been established in patients with PBC with severe hepatic impairment. Use in patients with severe hepatic impairment (Child-Pugh C) is not recommended (see section 5.2 PHARMACOKINETIC PROPERTIES).

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

Method of administration

For oral use. Take one tablet once daily.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Liver related events

Increases in liver biochemical tests including transaminases and bilirubin increase have been reported in 3.7% of participants receiving elafibranor compared to 5.7% of participants receiving placebo.

Clinical and laboratory assessment of liver function should be done prior to initiation of elafibranor treatment and thereafter according to routine patient management.

If increases in liver biochemical tests and/or liver dysfunction are observed, prompt investigation of the cause is recommended and interruption of elafibranor treatment should be considered.

Myalgia, Myopathy, and Rhabdomyolysis

Increases in blood creatine phosphokinase (CPK) have been reported in participants receiving elafibranor (3.7% in elafibranor group compared to 0% in placebo group). In addition to these reported CPK increases, there was one case of rhabdomyolysis which occurred in the pivotal phase 3 ELATIVE study in a participant with cirrhosis and ongoing treatment with an HMG-CoA reductase inhibitor. CPK should be evaluated prior to initiation of elafibranor treatment and thereafter according to routine patient management. Periodic CPK measurements may be considered in patients starting elafibranor treatment, especially those on concomitant HMG-CoA reductase inhibitors. Patients on elafibranor treatment should be advised to report any unexplained muscle symptoms such as pain, soreness, or weakness to their treating physician.

If increases in CPK or unexplained signs and symptoms of muscle injury are observed, prompt investigation of the cause is recommended and interruption of elafibranor treatment should be considered (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Embryo-Foetal Toxicity

Based on data from animal studies, elafibranor may cause foetal harm when administered to a pregnant woman. Patients should be informed of the potential risk to the foetus if elafibranor is taken during pregnancy (see section 4.6 FERTILITY, PREGNANCY AND LACTATION).

The use of elafibranor is not recommended during pregnancy and in women of childbearing potential not using effective contraception (see section 4.6 FERTILITY, PREGNANCY AND LACTATION). The pregnancy status of women of childbearing potential should be checked prior to initiation of elafibranor treatment.

Women of childbearing potential should be advised to use effective contraception during treatment and for 3 weeks following the final dose of elafibranor.

Use in the elderly

No data available.

Paediatric use

No data available. There is no relevant use of elafibranor in the paediatric population (below 18 years of age) for the indication of PBC.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Based on *in vitro* and *in vivo* studies, no clinically relevant drug-drug interaction is expected by co-administering elafibranor with any other medicinal products.

Based on *in vitro* studies, CYP and UGT enzymes were shown not to play a major role in elafibranor metabolism. Drug-drug interactions (DDI) are expected to be limited with drugs that significantly alter CYP or UGT activity.

Clinical studies

Warfarin (CYP2C9 substrate):

Concomitant administration of elafibranor with warfarin resulted in no increase in exposure (AUC, C_{max}) of warfarin, and no difference in international normalized ratio (INR) compared to warfarin alone.

Simvastatin and atorvastatin (CYP3A, organic anion transporting polypeptides 1B1 (OATP1B1) and OATP1B3 substrates):

Concomitant administration of repeat doses of elafibranor with simvastatin, or atorvastatin, resulted in no increase in exposure (AUC, C_{max}) of simvastatin or its β -Hydroxyacid metabolite, or atorvastatin.

Indomethacin (PTGR1 inhibitor):

Following clinical DDI studies, no effect on the clinical PK of elafibranor was observed with co-administration of indomethacin.

Sitagliptin (dipeptidyl peptidase-IV (DPP-IV) inhibitor):

No clinically significant effects were observed when co-administering elafibranor as a DDI perpetrator with sitagliptin.

In Vitro Studies

Cytochrome P450 (CYP) inhibition and induction:

Elafibranor and GFT1007 were not considered inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. No time-dependent CYP inhibition was observed by elafibranor and GFT1007.

Elafibranor and GFT1007 did not cause induction on CYP1A2, CYP2B6, and CYP3A4.

UGT inhibition:

Based on *in vitro* data elafibranor is not expected to inhibit UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B10, and 2B15 at clinically relevant concentrations.

GFT1007 inhibited UGT1A6 but not UGT1A1, 1A3, 1A4, 1A9, 2B7, 2B10, and 2B15, however this is not expected to be clinically relevant.

Transporter Systems:

Elafibranor was an inhibitor of organic anion transporting polypeptides 1B3 (OATP1B3) and breast cancer resistance protein (BCRP) but was not an inhibitor of Permeability-glycoprotein/multidrug resistance protein 1 (P-gp/MDR1), OATP1B1, organic cation transporter 1 (OCT1), OCT2, organic anion transporter 1 (OAT1), multidrug and toxin extrusion protein 1 (MATE1), MATE2-K, OAT3 and bile salt export pump (BSEP).

GFT1007 was not considered an inhibitor of OAT3, OATP1B3, BSEP, P-gp/MDR1, BCRP, OATP1B1, OCT1, OCT2, OAT1, MATE1 and MATE2-K.

GFT3351 is an inhibitor of multidrug resistance associated protein 2 (MRP2) and MRP3. The clinical significance of MRP2 and MRP3 inhibition by GFT3351 is unknown. GFT3351 did not inhibit BCRP, P-gp, OATP1B1, OATP1B3, OAT1, OAT2, OAT3, OCT1, OCT2, MATE1, MATE2-K, and BSEP.

Elafibranor was found *in vitro* to be a substrate for intestinal transporters multidrug resistance-associated protein 2 (MRP2) and BCRP. Elafibranor and GFT1007 are not substrates of P-gp, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2. The role of active efflux transport is considered to be negligible compared to the passive, concentration-gradient driven, high permeability absorption of elafibranor.

GFT3282 was a substrate of MRP2 and MRP3.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of elafibranor on fertility are available.

In the first fertility study, following repeated oral administration in male (from 29 days prior to mating until sacrifice, i.e. for 7 weeks in total) and female (15 days prior to pairing until day 7 post-coitum) rats, no effects on oestrous cycling, mating indices, mating period and on absolute and relative weights of testes, epididymides or gravid uterus up to 100 mg/kg/day (estimated 17- and 14-times the combined AUC for elafibranor and GFT1007 estimated exposures at the Maximum Human Recommended Dose (MHRD), in male and female rats, respectively). There were no changes in sperm parameters up to 30 mg/kg/day (estimated 6.5-times the combined AUC for elafibranor and GFT1007 estimated exposures at the MHRD). In a second fertility and early embryonic development study, following repeated oral administration in male rats (from 4 weeks prior to mating until sacrifice, i.e. for 9 weeks in total), no effect on male fertility were observed up to 100 mg/kg/day (estimated 17 times the combined AUC for elafibranor and GFT1007 estimated exposures at the MHRD).

Use in pregnancy (Category D)

There is limited amount of data from the use of elafibranor in pregnant women.

Studies in pregnant animals with elafibranor indicate adverse effects (fetal loss, malformations, stillbirths and/or perinatal deaths) at clinically relevant exposure.

Elafibranor is not recommended during pregnancy because of potential harm to the fetus.

Elafibranor is not recommended in women of childbearing potential not using effective contraception because of potential harm to the fetus.

Women of childbearing potential should continue to use effective contraception for 3 weeks following the final dose of elafibranor. The pregnancy status of patients of childbearing potential should be checked prior to initiation of elafibranor treatment.

Women planning to become pregnant are recommended to consult with their physician regarding alternate treatment options (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In pregnant rats, once daily oral administration of elafibranor during the period of organogenesis resulted in no effect on embryofetal development at dose up to 300 mg/kg/day (~100-fold the combined estimated AUC for elafibranor and GFT1007 exposures at the MHRD).

In pregnant rabbits, once daily administration of elafibranor during the period of organogenesis at the dose of 300 mg/kg/day (3.1-fold the combined estimated AUC for elafibranor and GFT1007 exposures at MHRD), was associated with marked maternal

toxicity, increased embryo-lethality, reduced fetal weight plus a low incidence of fetal malformations. At 100 mg/kg/day (0.5-fold AUC exposure at the MHRD), despite maternal toxicity, there was no effect on embryofetal survival, or fetal weight nor fetal malformations, however, skeletal variations involving delayed and/or incomplete ossification of distal limb bones were observed. At 300 mg/kg/day (3.1-fold the combined estimated AUC for elafibranor and GFT1007 exposures at the MHRD), skeletal variations included delayed/incomplete ossification of multiple bones (metacarpal, median phalanx of hindpaw and talus), multiple visceral (absence of innominate artery) and external variations (malrotated paw, shortened tail) and malformations (cardiomegaly, absent kidney and ureter, fused/misaligned caudal vertebrae) were observed. No adverse effects were seen on embryofetal development at the low dose of 30 mg/kg/day (0.1-fold the combined estimated AUC for elafibranor and GFT1007 exposures at the MHRD). NOAEL for embryofetal toxicity was 30 mg/kg/day.

In the rat pre- and post-natal development (PPND) study, once daily oral administration of elafibranor during organogenesis through pregnancy and lactation was associated with reduced pup survival (during postnatal days 1-4 at doses 17-fold above combined maternal AUC for elafibranor and GFT1007 exposure at MHRD) and postnatal days 5-21 at 10 and 30 mg/kg/day (2.1- and 4.5-fold the combined maternal AUC for elafibranor and GFT1007 exposures at the MHRD, respectively), blue/black discolouration of the caudal section of some pups, lower pup body weights, and developmental delays (pinna unfolding) at all doses (2.1-fold the combined maternal AUC for elafibranor and GFT1007 exposures at the MHRD). Developmental delays were likely caused by the decrease in body weight. Adverse effects in the offspring occurred at maternal exposures at or above 2.5-times the combined AUC for elafibranor and GFT1007 exposures at MHRD. Increase in stillbirths were observed at 100 mg/kg/day (17-times the combined maternal AUC for elafibranor and GFT1007 exposures at MHRD). Stillbirths at 100 mg/kg/day and a single stillborn at 30 mg/kg/day (4.5-times the combined maternal AUC for elafibranor and GFT1007 exposures at MHRD) showed evidence of aortic or iliac arterial thrombosis (generally accompanied by vessel dilation, with minimal associated inflammation of the vessel wall, surrounding connective tissue, or adjacent abdominal structures). In pups sampled on postnatal day 14, elafibranor was not detected and only minimal plasma exposure to its active metabolite was detectable in pups from 100 mg/kg/day (maternal exposures were 17-fold above combined AUC for elafibranor and GFT1007 exposures at MHRD). The surviving adult offspring showed no effects of elafibranor on learning and memory, reflex development, or reproductive capability.

Use in lactation

It is unknown whether elafibranor or its metabolites are excreted in human milk. In PPND study in rats, following oral administration of elafibranor to female rats through pregnancy and lactation, there were reduced survival and growth of offspring from 10 mg/kg/day (maternal exposures 2.1-times the combined AUC for elafibranor and GFT1007 at the MHRD). Low levels of GFT1007 were detected in 2 pups at 100 mg/kg/day (maternal exposures 17 times the combined AUC for elafibranor and GFT1007 at the MHRD),

however, it is unclear whether excretion of elafibranor or its metabolite in milk contributed to the adverse effects on offspring.

Elafibranor is not recommended during breastfeeding and for at least 3 weeks following last dose of elafibranor because the risk to breastfed child cannot be excluded.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Elafibranor has no influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of safety profile

In the pivotal phase 3 ELATIVE study, 161 participants were randomized in a 2:1 ratio to receive elafibranor 80 mg (n=108) or placebo (n=53) for at least 52 weeks. At the end of the double-blind (DB) period of the study, the median duration of exposure was 63.07 and 61.00 weeks in the elafibranor and placebo groups, respectively.

The most commonly reported adverse drug reactions associated with elafibranor in more than 10% of participants (n=108) were abdominal pain (11.1%), diarrhoea (11.1%), nausea (11.1%) and vomiting (11.1%). These were non-serious and mild to moderate in severity.

The most common adverse drug reaction leading to treatment discontinuation was blood CPK increased (3.7%).

The most common adverse events with IQIRVO in the clinical study (reported in $\geq 5\%$ and higher compared to placebo) were weight gain, arthralgia, constipation, muscle injury, fracture, gastroesophageal reflux disease, dry mouth, weight loss, and rash.

Tabulated list of adverse reactions

Within the system organ class, the adverse reactions are listed by frequency using the following categories: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/100$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Organ Class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $< 1/100$)
Nervous system disorders		Headache	
Gastrointestinal disorders	Abdominal pain ^a Diarrhoea	Constipation	

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)
	Nausea Vomiting		
Hepatobiliary disorders		Cholelithiasis	
Skin and subcutaneous tissue disorders			Rash pruritic
Musculoskeletal and connective tissue disorders		Myalgia	
Investigations		Blood CPK increased	Blood creatinine increased

^a includes abdominal pain upper and abdominal pain lower

Description of selected adverse reactions

Nine (8.3%) participants in the elafibranor group and 6 (11.3%) participants in the placebo group experienced headache. However, within the first 10 days of study treatment, more participants in the elafibranor group experienced headache compared to the placebo group (3.7% compared to 0% respectively).

Four (3.7%) participants in the elafibranor group and no participants in the placebo group had clinically significant blood CPK increase, leading to drug discontinuation. In 2 of the 4 participants, the CPK was >5 x upper limit of normal (ULN). All events were non-serious and mild to moderate in intensity. Two of the participants also experienced associated symptom of myalgia. At baseline, mean CPK values were similar between the treatment groups and within normal range; values at Week 52 remained within normal range in both groups. The mean change from baseline at Week 52 was 6.2 (38.1) U/L in the elafibranor group and 12.3 (67.0) U/L in the placebo group.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Bile and liver therapy, Other drugs for bile therapy

ATC code: A05AX06

Mechanism of action

Elafibranor and its main active metabolite GFT1007 are peroxisome proliferator-activated receptor (PPAR) agonists, both of which activate PPAR α , PPAR γ , and PPAR δ *in vitro*. *In vitro*, both elafibranor and GFT1007 demonstrated 3- to 8-fold higher activity for PPAR- α compared to PPAR- γ and PPAR- δ . Although the *in vitro* pharmacology studies detected PPAR- γ activation by elafibranor and its metabolite GFT1007, toxicology studies in rats and monkeys (species with plasma metabolite profiles comparable to human) showed none of the adverse effects that are associated with PPAR- γ activation.

PPAR α / δ are thought to be key regulators of bile acid (BA) homeostasis, inflammation and fibrosis. Activation of PPAR α decreases bile acid (BA) synthesis, increases BA detoxification, and modulates BA output, resulting in decreased bile toxicity, and less injury to cholangiocytes and hepatocytes.

Activation of PPAR δ also regulates transporters that absorb and secrete bile components, contributing this way to decreased bile toxicity and improving cholestasis.

Activation of PPAR α and PPAR δ also has anti-inflammatory effects by acting on different pathways of inflammation, nuclear factor kappa B (NF- κ B) and B-cell lymphoma 6 (BCL6) pathways, respectively.

Pharmacodynamic effects

In the pivotal phase 3 ELATIVE study, treatment with elafibranor resulted in a marked reduction from baseline in alkaline phosphatase (ALP) as early as 4 weeks which was sustained through week 52. In alignment with the observed biochemical response, greater reductions in biomarkers of BA synthesis including the BA precursor 7 α -hydroxy-4-cholesten-3-one (C4) and Fibroblast Growth Factor-19 (FGF-19), a BA synthesis regulator, were observed with elafibranor treatment. Significant decreases in Immunoglobulin M (IgM), Immunoglobulin G (IgG), and anti-inflammatory markers, were observed in participants treated with elafibranor compared to placebo in alignment with the *in vitro* demonstration of anti-inflammatory properties of elafibranor.

In vitro studies in human macrophages, monocytes and endothelial cells showed the capacity of elafibranor and/or GFT1007 to decrease the secretion of inflammatory markers such as Monocyte Chemoattractant Protein-1 (MCP-1) and Interleukin-6 (IL-6) through combined PPAR α and PPAR δ activation and parallel PPAR-independent mechanisms.

Anti-fibrotic properties of elafibranor were demonstrated in human primary hepatic stellate cells (hHSCs), pivotal for fibrogenesis in the liver. Elafibranor inhibits Platelet-Derived Growth Factor (PDGF)-stimulated hHSC proliferation in a dose-dependent manner via modulation of PDGFR β phosphorylation. Additionally, elafibranor inhibits Transforming Growth Factor Beta (TGF β 1)-induced hHSC activation at the gene level, by down-regulating, in a dose-dependent manner, the expression of several fibrosis markers, such as α Smooth Muscle Actin (α SMA), Collagen 1 α 1 (Col1 α 1) and Collagen 4 α 1 (Col4 α 1), but without inhibiting the kinase activity of the TGF β 1 receptors.

Cardiac electrophysiology

Thorough QT (TQT) analysis excluded any prolongation effect of elafibranor on QT/QTc interval at repeat doses of up to 300 mg for 14 days.

In clinical studies, no clinically meaningful changes in vital signs or in electrocardiogram (ECG) (including QTc interval) were observed in participants treated with elafibranor.

Clinical trials

The efficacy of elafibranor was evaluated in Study GFT505B-319-1 (ELATIVE), a phase 3, randomised, DB, placebo-controlled study followed by an open-label long-term extension (OLE) in 161 adults with PBC with an inadequate response or intolerance to UDCA. Participants were randomized in a 2:1 ratio to receive elafibranor 80 mg or placebo once daily for at least 52 weeks. When applicable, participants continued their pre-study dose of UDCA throughout the study. Participants were included in the study if their ALP was $\geq 1.67 \times \text{ULN}$ and total bilirubin (TB) was $\leq 2 \times \text{ULN}$. Participants were excluded in case of decompensated cirrhosis or other causes of liver disease.

Overall, the mean age was 57.1 years, and the mean weight was 70.8 kg. The study population was predominately female (96%) and white (91%). The baseline mean ALP concentration was 321.9 U/L and 39% of participants had a baseline ALP concentration $> 3 \times \text{ULN}$. Mean baseline AST and ALT was 45.7 U/L and 49.6 U/L, respectively.

The mean baseline TB concentration was 9.6 $\mu\text{mol/L}$ and 96% of participants had a baseline TB concentration $\leq \text{ULN}$. The mean baseline liver stiffness measurement (LSM) by transient elastography was 10.1 kPa. The baseline mean PBC Worst Itch Numeric Rating Scale (NRS) score was 3.3 and 41% had moderate-to-severe pruritus at baseline (PBC Worst Itch NRS score ≥ 4); for those with moderate-to-severe pruritus, the baseline mean PBC Worst Itch NRS score was 6.2 for participants in the elafibranor 80 mg group and 6.3 for participants in the placebo group. The majority (n=153, 95%) of participants received treatment in combination with UDCA or as monotherapy in 5% (n=8) of participants who were unable to tolerate UDCA.

The primary endpoint was cholestasis response at week 52 as defined as the composite endpoint: ALP $< 1.67 \times \text{ULN}$ and TB $\leq \text{ULN}$ and ALP decrease $\geq 15\%$. The key secondary endpoints were ALP normalization at week 52 and the change in pruritus from baseline through week 52 and through week 24 based on the PBC Worst Itch NRS score in participants with moderate -to-severe pruritus at baseline.

Table 1 shows the primary composite endpoint of cholestasis response and the key secondary endpoint of ALP normalization.

Table 1 Percentage of Adult Participants with PBC Achieving the Primary Efficacy Composite Endpoint of Cholestasis Response and Key Secondary Efficacy Endpoint of ALP Normalization at Week 52

Analysis Population	Elafibranor 80 mg (N=108)	Placebo (N=53)	Treatment Difference (95% CI) ^[3]	Odds Ratio (95% CI) ^[4]	P-value ^[4]
Primary Composite Endpoint: Cholestasis Response ^[1]					
ITT	51%	4%	47% (32, 57)	37.6 (7.6, 302.2)	<0.0001
Key Secondary Endpoint: ALP Normalization ^[2]					
ITT	15%	0	15% (6, 23)	Infinity (2.8, infinity)	0.0019

ITT: Intention-to-treat

^[1] Cholestasis response is defined as ALP <1.67x ULN and TB ≤ULN and ALP decrease from baseline ≥ 15% at week 52. Participants who stopped prematurely the study treatment (intercurrent event 1) or used rescue therapy for PBC (intercurrent event 2) prior to week 52 assessment were considered as non-responders. In case of missing data at week 52 for participants without an intercurrent event, the closest non-missing assessment from the DB treatment period was taken into account.

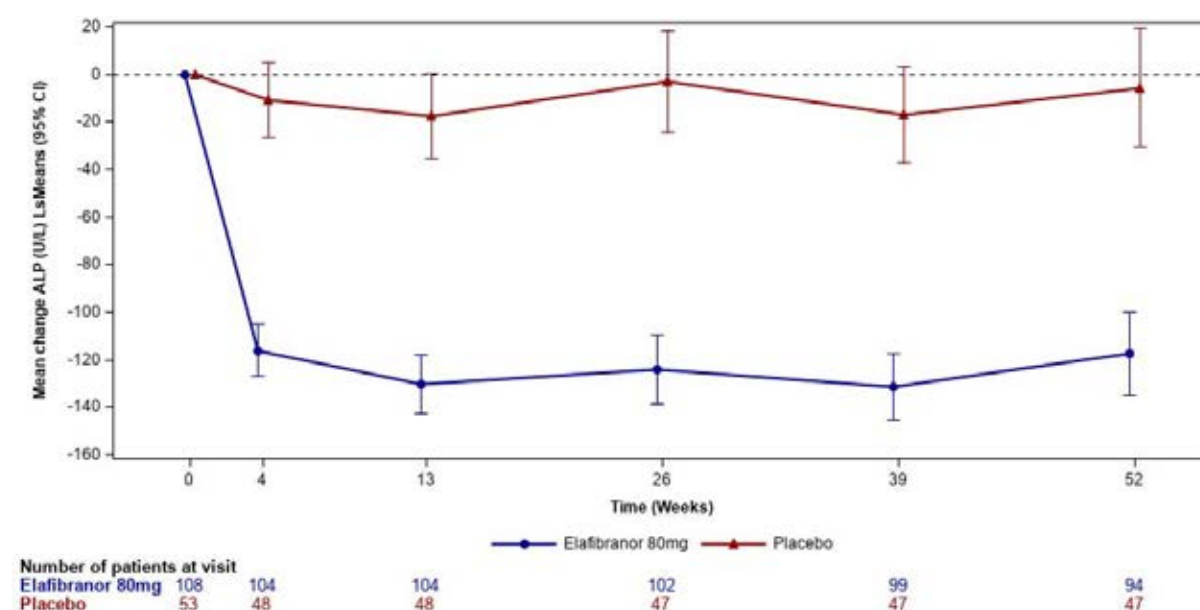
^[2] Normalization of ALP at week 52 defined as proportion of participants with ALP ≤1.0x ULN. The approach to handle intercurrent events or missing data is the same as for the primary endpoint.

^[3] The response rate differences between the treatment groups and 95% CI were calculated using the Newcombe method stratified by randomization strata for cholestasis response and unstratified for ALP normalization.

^[4] Odds ratios of response and p-values to compare treatments were from the exact Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata.

A significant decrease from baseline was seen as early as week 4 and was sustained over 52 weeks of treatment in the elafibranor group compared to placebo (Figure 1).

Figure 1 Mean Change from Baseline in ALP Over Time - ITT analysis set



Patient-reported outcomes

In participants with moderate-to-severe pruritus at baseline, the mean change from baseline in PBC Worst Itch NRS score through Week 52 and Week 24 decreased in participants randomized to elafibranor compared to placebo but did not reach statistical significance (Table 2).

Table 2 Change in Pruritus from Baseline Through Week 52 and Week 24 as Measured by PBC WI-NRS in those with Moderate-to-Severe Pruritus at Baseline

	Elafibranor 80 mg (N=44)		Placebo (N=22)	Treatment Difference	P-value
Key Secondary Endpoint: Change Through Week 52 ^[1]					
Least Squares Mean (95% CI)	-1.9 (-2.6, -1.3)		-1.1 (-2.1, -0.2)	-0.8 (-2.0, 0.4)	0.1970
Key Secondary Endpoint: Change Through Week 24 ^[1]					
Least Squares Mean (95% CI)	-1.6 (-2.2, -1.0)		-1.3 (-2.2, -0.3)	-0.3 (-1.5, 0.8)	0.5522

^[1] Analysis used the mixed model for repeated measures (MMRM) with treatment, 4-week period and treatment by 4-week period interaction as fixed factors and adjusting for baseline PBC Worst Itch NRS and the stratification factor of ALP >3 x ULN or TB >ULN. An unstructured correlation structure is used. Treatment effect through week 52 is the average of NRS score changes from baseline for the thirteen 4-week periods. Treatment effect through week 52 and week 24 is the average treatment effects of NRS score changes from baseline over the first thirteen 4-week periods and first six 4-week periods, respectively. The assessments of PBC Worst Itch NRS scores after participants stopped prematurely the study treatment or took a rescue therapy for pruritus were considered as missing.

Treatment with elafibranor was associated with an improvement in pruritus as evidenced by a reduction in the PBC-40 Itch and 5-D Itch total scores compared to placebo at Week 52 (Table 3).

Table 3 Change in Pruritus from Baseline to Week 52 in PBC-40 Itch and 5-D Itch total scores in those with Moderate-to-Severe Pruritus at Baseline

	Elafibranor 80 mg (N=44)	Placebo (N=22)	Treatment Difference	P-value
PBC-40 Itch total score: Change at Week 52 ^[1]				
Least Squares Mean (95% CI)	-2.5 (-3.4, -1.6)	-0.1 (-1.6, 1.3)	-2.3 (-4.0, -0.7)	0.0070
5-D Itch total score: Change at Week 52 ^[1]				
Least Squares Mean (95% CI)	-4.2 (-5.6, -2.9)	-1.2 (-3.3, 0.9)	-3.0 (-5.5, -0.5)	0.0199

^[1] Analysis uses the mixed model for repeated measures (MMRM) with treatment, visits (until week 52) and treatment by visit interaction as fixed factor and adjusting for baseline score and the stratification factor of ALP > 3x ULN or TB > ULN.

Lipid parameters

Elafibranor demonstrated a favourable effect on lipid parameters. The mean reduction in very low-density lipoprotein-cholesterol (VLDL-C) and triglycerides (TG) was greater in participants treated with elafibranor compared to placebo at Week 52. The LSM means difference from placebo in VLDL-C was -0.1 mmol/L [(95% CI: -0.2, -0.1); p<0.001] and for TG was -0.3 mmol/L [(95% CI: -0.4, -0.1)]; p<0.001]. High-density lipoprotein-cholesterol (HDL-C) remained stable on treatment with elafibranor.

Mean reduction in IgM

The mean reduction in IgM was greater in participants treated with elafibranor compared to

placebo at Week 52. The LSM means difference from placebo in IgM was -0.6 g/L [(95% CI: -0.9, -0.3); $p < 0.001$].

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Elafibranor plasma exposure (AUC) increases proportionally from 50 to 360 mg (0.6 to 4.5 times the recommended dosage). Steady-state is achieved by day 14 following once daily dosing. The pharmacokinetics (PK) of elafibranor and its major active metabolite GFT1007 was found to be time-independent after 16-day repeated administration. Elafibranor and its active metabolite exposure in participants with PBC are listed in Table 4.

Table 4 Elafibranor and GFT1007 exposures in participants with PBC at steady state following 80 mg QD (once daily)

	$C_{\max,ss}$ (ng/mL)	AUC ₀₋₂₄ (ng • h/mL)	Accumulation ratio
Elafibranor	802	3758	2.9
GFT1007	2058	11985	1.3

Following repeated oral administration in participants with PBC, median peak plasma levels of elafibranor and GFT1007 at doses of 80 mg occur within 1.25 hours.

When administered with a high-fat and high-calorie meal, there was a 30-minute delay in T_{\max} for elafibranor and a 1 hour delay for GFT1007 in fed compared to fasted conditions. The plasma C_{\max} and AUC of elafibranor decreased by 50% and 15% respectively and the plasma C_{\max} of GFT1007 decreased by 30% but the AUC was not affected. Given the 2.2-5.3-fold higher circulating plasma levels of the pharmacologically active metabolite GFT1007 compared to elafibranor, food intake was deemed to have limited clinical impact based on overall exposure of parent and active metabolite.

Distribution

Plasma protein binding of both elafibranor and GFT1007 is approximately 99.7% (mainly to serum albumin). The mean apparent volume of distribution (V_d/F) of elafibranor in humans is 4731 L, following single dose of elafibranor at 80 mg in fasted conditions.

Metabolism

In vitro, elafibranor is metabolised by 15-ketoprostaglandin 13- Δ reductase (PTGR1) to form metabolite GFT1007. Other enzymes involved in the metabolism of elafibranor also included CYP2J2, and uridine diphosphate (UDP)-glucuronosyltransferase (UGT) isoforms, UGT1A3, UGT1A4, and UGT2B7. GFT1007 was further metabolised by CYP2C8 and UGT1A3 and UGT2B7.

Following oral administration of ^{14}C radiolabelled elafibranor, it was rapidly hydrolysed to the active metabolite GFT1007. Two major metabolites were identified in plasma, GFT1007 (active metabolite) and glucuronide conjugates (inactive metabolites).

Excretion

Following single 80 mg dose under fasted conditions, mean elimination half-life is 68.2 hours for elafibranor, and 15.4 hours for metabolite GFT1007. Elafibranor mean apparent total clearance (CL/F) was 50.0 L/h after a single 80 mg dose under fasted conditions.

Following a single 120 mg oral dose of ¹⁴C radiolabelled elafibranor in healthy participants, approximately 77.1% of the dose was recovered in faeces, primarily as elafibranor (56.7% of the administered dose) and its active metabolite GFT1007 (6.08% of the administered dose). Approximately 19.3% recovered in urine, primarily as glucuronide conjugates.

Pharmacokinetics in special patient populations

There was no evidence that age (from 18 to 80 years old), gender, race, Body Mass Index (BMI), and renal status, had any clinically meaningful impact on elafibranor and GFT1007 PK.

Hepatic impairment

The total drug exposure of the parent and active metabolite was not significantly different between participants with normal hepatic function and hepatically impaired participants (Child Pugh A, B and C). No dose adjustment is required for patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. However, the unbound fraction of elafibranor and GFT1007 increased by approximately 3-fold in the severe (Child Pugh C) hepatically impaired participants. Elafibranor is not recommended for patients with severe hepatic impairment (Child-Pugh C).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Elafibranor was negative in the *in vitro* bacterial reverse mutation (Ames) test and the *in vivo* micronucleus test. A potential clastogenic activity was observed with elafibranor at the thymidine kinase locus in mouse lymphoma cells in the *in vitro* micronucleus test. The result was not confirmed in two *in vivo* micronucleus tests in the rat bone marrow. Additionally, no genotoxic activity of elafibranor on hepatocytes was observed in two *in vivo* genotoxicity studies in the rat liver (unscheduled DNA synthesis assay and Comet assay). Together, these tests demonstrated that elafibranor has no risk of mutagenicity or genotoxicity after oral administration.

The metabolites GFT1007 and racemic GFT3351 (acyl glucuronide metabolite) were both negative in the *in vitro* bacterial reverse mutation (Ames) assay. GFT1007 tested negative in the *in vitro* micronucleus test in L5178Y tk+/- mouse lymphoma cells, and GFT3351 tested negative in the *in vitro* micronucleus assay in human lymphocytes.

Carcinogenicity

Elafibranor was assessed in two carcinogenicity studies in mice and rats, with oral gavage administration for up to two years at 1, 3, 10, or 30 mg/kg/day.

In the 2-year carcinogenicity study in mice, oral administration of elafibranor produced neoplastic findings limited to hepatocellular carcinoma, adenoma and adenoblastoma, in both sexes, present at subclinical exposures.

In the 2-year carcinogenicity study in rats, oral administration of elafibranor produced hepatocellular tumours (adenoma or carcinoma) in males and females at clinically relevant exposures. At 30 mg/kg/day (6-times the recommended dose based on combined AUC for elafibranor and GFT1007) in male rats, there was an increase in testicular Leydig cell adenomas and benign pancreatic acinar cell adenomas.

Treatment-related liver tumours identified in both the mouse and rat carcinogenicity studies may be attributed to the expected rodent-specific PPAR α -related liver toxicity and its related consequences and are not relevant to humans. Thus, up to the highest tested dose in both species (i.e. 30 mg/kg/day, approximately 3- and 6-fold the combined AUC exposure for elafibranor and GFT1007 at the maximum human recommended dose (MHRD) of 80 mg/day), elafibranor does not result in an increased incidence of tumours that are relevant to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet content

Microcrystalline cellulose
Povidone
Croscarmellose sodium
Magnesium stearate
Colloidal anhydrous silica

Film-coating

Polyvinyl alcohol
Titanium dioxide
Macrogol 3350
Purified talc
Iron oxide yellow
Iron oxide red

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

IQIRVO film-coated tablets are packaged in a HDPE bottle with a child-resistant polypropylene closure with integrated dessicant unit.

Each pack contains 30 film-coated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

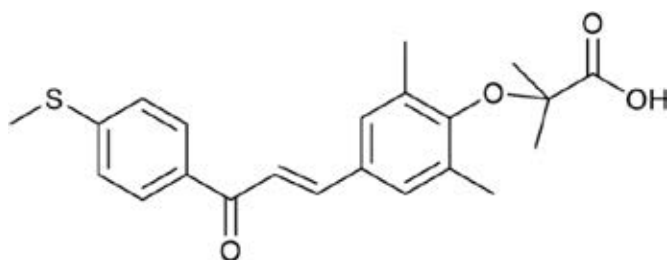
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Elafibranor is a yellow crystalline powder. It is practically insoluble in aqueous buffer and water, sparingly soluble in methanol, and freely soluble in organic solvents.

Chemical structure

The molecular formula of elafibranor is C₂₂H₂₄O₄S.



IUPAC name: 2-[2,6-dimethyl-4-[(*E*)-3-(4-methylsulfanylphenyl)-3-oxoprop-enyl]phenoxy]-2-methylpropanoic acid

Molecular weight: 384.49 g/mol

CAS number

923978-27-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Ipsen Pty Ltd
Level 5
627 Chapel Street
South Yarra Victoria 3141

Telephone: 1800 317 033

9 DATE OF FIRST APPROVAL

TBC

10 DATE OF REVISION

N/A