1. NAME OF THE MEDICINAL PRODUCT

IQIRVO® Film-coated Tablet 80 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablets)

The 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 adult patients with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.

4.2 Posology and method of administration

Posology

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

Special Populations

Elderly patients (65 years of age and above)
No dose adjustment is necessary in patients older than 65 years of age (see section 5.2).

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

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).

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

Missed dose
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.

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 listed in section 6.1.

4.4 Special warnings and precautions for use

Liver related events
Increases in liver biochemical tests including transaminases and bilirubin levels 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. Consider permanent discontinuation if liver tests worsen after restarting elafibranor.

Elevated blood creatine phosphokinase and muscle injury
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).

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). The use of elafibranor is not recommended during pregnancy and in women of childbearing potential not using effective contraception (see section 4.6). The pregnancy status of women of childbearing age 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.

Fractures
Fractures occurred in 6% of IQIRVO®-treated patients compared to no placebo-treated patients.
Consider the risk of fracture in the care of patients treated with IQIRVO® and monitor bone health according to current standards of care.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 5.2).

4.6 Fertility, pregnancy, and lactation

Fertility
No human data on the effect of elafibranor on fertility are available. Animal studies do not indicate any direct or indirect effects on fertility or the ability to reproduce (see section 5.3).

Women of childbearing potential/contraception
Elafibranor is not recommended in women of childbearing potential not using effective contraception because of potential harm to the foetus.
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 section 4.4 and 5.3).

Pregnancy
There is limited amount of data from the use of elafibranor in pregnant women.
Studies in pregnant animals with elafibranor indicate adverse effects (foetal loss, malformations, stillbirths and/or perinatal deaths) at clinically relevant exposure (see section 5.3).
Elafibranor is not recommended during pregnancy because of potential harm to the foetus.

Lactation
It is unknown whether elafibranor or its metabolites are excreted in human milk. When elafibranor was administered to female rats through pregnancy and lactation, there was reduced survival and growth of offspring at maternal exposures close to patient exposures and it is unclear whether excretion of elafibranor or its metabolite in milk contributed to the adverse effects on offspring (see section 5.3).
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 Undesirable effects

Summary of the safety profile
In the pivotal phase 3 ELATIVE study, 161 participants were randomized in a 2:1 ratio to receive elafibranor 80mg (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%).

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

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1 000 to <1/100)**
Nervous system disorders		Headache	

Gastrointestinal disorders	Abdominal pain[a] Diarrhoea Nausea Vomiting	Constipation	
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.

Post-marketing experience
Not applicable

Paediatric population
Not applicable

4.9 Overdose

In the event of suspected overdose, patients should be carefully observed, and appropriate symptomatic treatment and supportive care should be initiated.

Paediatric population
Not applicable

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 dual peroxisome proliferator-activated receptor (PPAR)α/δ agonists.
Activation of PPARα decreases bile acid (BA) synthesis, increases BA detoxification, and modulates PA output, resulting in decreased bile toxicity, and less injury to cholangiocytes and hepatocytes.
Activation of PPARα also regulates transporters that absorb and secrete bile components, contributing this way to decreased bile toxicity and improving cholestasis.

Activation of PPARα and PPARδ also has anti-inflammatory effects by acting on different pathways of inflammation, nuclear factor kappa B (NF-κB) 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 alpha-hydroxy-4-cholesten-3-one (C4) and Fibroblast Growth Factor-19 (FGF-19), a BA synthesis regulator, were observed with elafibranor treatment. Significant decreases om 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 PPARα and PPARδ 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-depended manner via modulation of PDGFRβ phosphorylation. Additionally, elafibranor inhibits Transforming Growth Factor Beta (TGFβ1)-induced hHSC activation at the gene level, by down-regulating, in a dose-dependent manner, the expression of several fibrosis markers, such as alpha Smooth Muscle Actin (αSMA), Collagen 1 alpha 1 (Col1α1) and Collagen 4 alpha 1 (Col4α1), but without inhibiting the kinase activity of the TGFβ1 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 efficacy

The efficacy of elafibranor was evaluated in Study GFT505B-319-1 (ELATIVE; NCT04526665), 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 randomised 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 ≥ 1.67 x ULN and total bilirubin (TB) was ≤ 2 x 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, 39% of participants had a baseline ALP concentration > 3 x ULN.

The mean baseline TB concentration was 9.6 µmol/L and 96% of participants had a baseline TB concentration ≤ 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 (95%) of participants received treatment in combination with UDCA or as monotherapy in 5% 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 x ULN and TB ≤ ULN and ALP decrease ≥ 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

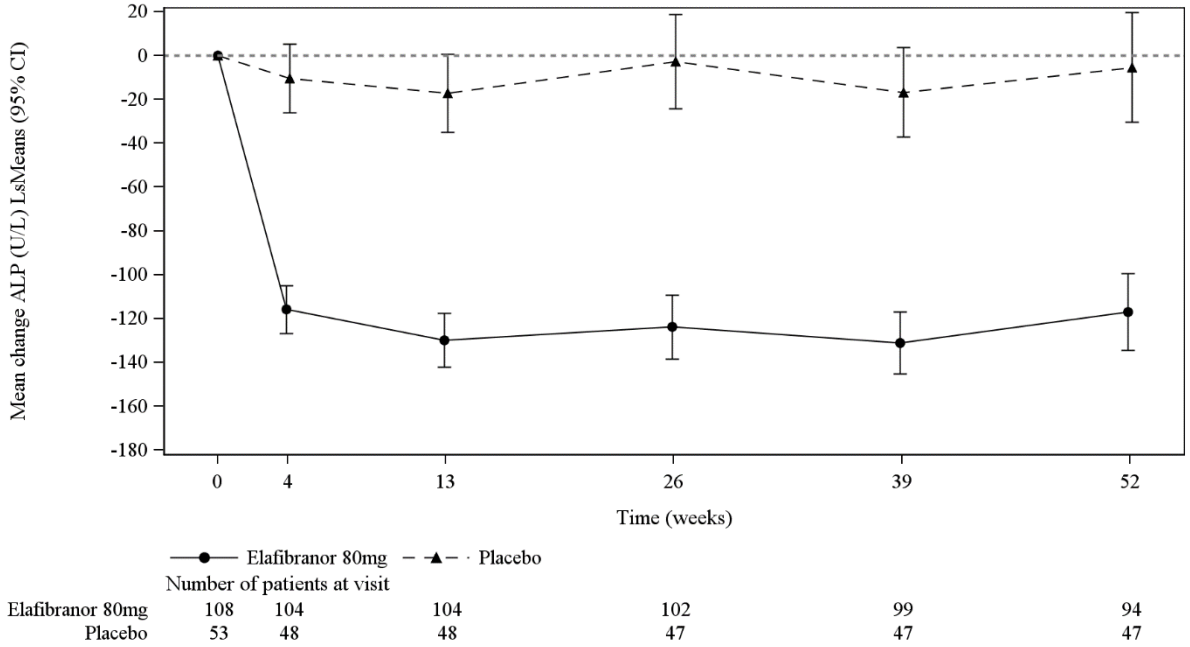
Analysis Population	Elafibranor 80 mg (N=108)	Placebo (N=53)	Treatment Difference (95% CI) [3]	Odds Ratio (95% CI) [4]	P-value [4]
Primary Composite Endpoint: Cholestasis Response [1]					
ITT	51%	4%	47% (32, 57)	37.6 (7.6, 302.2)	<0.0001
Key Secondary Endpoint: ALP normalization [2]					
ITT	15%	0	15% (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 ≤1.0× 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 was observed in participants randomised to elafibranor compared to placebo but this 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 WI-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].

Mean reduction in biomarkers of BA synthesis

The mean reduction in C4 and in FGF-19 was greater in participants treated with elafibranor compared to placebo at Week 52. The LSM means difference from placebo in C4 was -5.176 ug/L [(95% CI: 10.291, -0.062)]; p=0.0474]; and in FGF-19 it was -86.95 ug/L [(95% CI: -170.37, -3.53)]; p=0.0412].

5.2 Pharmacokinetic properties

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

Absorption

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 (Vd/F) of elafibranor in humans is 4731L, following single dose of elafibranor at 80 mg in fasted conditions.

Metabolism
In vitro, elafibranor is metabolised by 15-ketoprostaglandin 13-Δ reductase (PTGR1). In vitro neither elafibranor nor GFT1007 show major metabolism by the main cytochrome P450 (CYP) and uridine diphosphate (UDP)-glucuronosyltransferase (UGT) isoforms.
Following oral administration of 14C 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).

Transporters
Elafibranor was found in vitro to be a substrate for intestinal transporters multidrug resistance-associated protein 2 (MRP2) and breast cancer resistance protein (BCRP). The role of active efflux transport is considered to be negligible compared to the passive, concentration-gradient driven, high permeability absorption of elafibranor.

Elimination
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.

Excretion
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.

Special 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).

Drug-drug interactions
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 minimal 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 PD 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, CPT2C9, CYP2C19, CYP2D6, and CYP3A4. No time dependent CYP inhibition was observed.
Elafibranor and GFT1007 did not cause induction on CYP1A2, CYP2B6, and CYP3A4.

UGT inhibition:
Based on in vitro data elafibranor was not expected to inhibit UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 2B10, and 2B15.
GFT1007 inhibited UGT1A6 but not UGT1A1, 1A3, 1A4, 1A9, 2B7, 2B10, and 2B15.

Transporter Systems:
Elafibranor was an inhibitor of OATP1B3 and 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 transport 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.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity and carcinogenic potential.

Carcinogenesis/mutagenesis
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. Up to the highest does tested in both species (approximately 3- and 6-fold the AUC exposure at the maximum human recommended dose (MHRD) of 80 mg/day), elafibranor administration does not result in an increased incidence of tumours that are relevant to humans.
Elafibranor, its principal active metabolite GFT1007 and the acyl glucuronide metabolite racemic GFT3351 were devoid of genotoxic potential in a comprehensive battery of in vivo and/or in vitro genotoxicity assays.

Animal toxicity and pharmacology
General toxicology has been assessed in rodent (mouse and rat) and non-rodent (monkey) species after single, and repeated dose oral administration for up to 6 months in rats and 12 months in monkeys respectively.
Elafibranor exhibited a favourable safety profile when administered as single oral doses in acute toxicity studies in rats and mice. Repeat-dose oral administration for up to 6 months in rats and 12 months in monkeys did not reveal any sign of human-relevant toxicity up to the maximum tested dose of 100 and 50 mg/kg/day, respectively (corresponding to ~15 fold the AUC exposure at the MHRD in both rat and monkey studies).

In addition, up to the highest doses tested, elafibranor did not show any relevant effects on organs and systems previously described as being of a safety concern with PPARγ agonists (weight gain, haemodilution, fluid retention leading to congestive heart failure, bladder cancer).

Reproduction and development toxicity
Elafibranor has no adverse effect on rat fertility or early embryonic development at up to 100 mg/kg/day (corresponding to approximately 17-fold the AUC exposure at the MHRD).

Elafibranor has shown evidence of developmental toxicity in both rats and rabbits.
In pregnant rats, once daily oral administration of elafibranor during the period of organogenesis from gestation day (GD) 6 to GD17 resulted in no effect on embryofoetal development at dose up to 300 mg/kg/day (~100-fold the AUC exposure at the MHRD). However, in the rat pre- and post-natal development study, once daily oral administration of elafibranor through pregnancy and lactation (from GD6 to lactation day (LD) 21) was associated with reduced pup survival (especially but not exclusively in the early perinatal period), blue/black discolouration of the caudal section of some pups, lower pup body weights and developmental delays at all doses (from material exposures of 2-fold the AUC exposure at the MHRD and above). At maternal exposures at or above 4.5-fold the AUC exposure at the MHRD, there was evidence of aortic or iliac arterial thrombosis in prematurely decedent pups. 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 the highest dose group where maternal exposures were 16-fold above AUC exposure at MHRD. The surviving adult offspring showed no effects of elafibranor on learning and memory, reflex development, or reproductive capability.

In pregnant rabbits, elafibranor administration during organogenesis at the high dose of 300 mg/kg/day (3-fold the AUC exposure at MHRD), was associated with marked maternal toxicity, increased embryo-lethality, reduced foetal weight plus a low incidence of foetal malformations. At the mid-dose of 100 mg/kg/day (0.5-fold AUC exposure at the MHRD), despite maternal toxicity, there was no effect on embryofoetal survival, or foetal weight nor foetal malformations. The only finding was foetal ossification variations in the distal limb bones. No adverse effects were seen on embryofoetal development at the low dose of 30 mg/kg/day (i.e., approximately 0.1-fold the AUC exposure at the MHRD).

Safety pharmacology
No safety issues were identified when assessing the potential effects of elafibranor on the cardiovascular, respiratory and central nervous systems.

Phototoxic potential
In the in vitro assay using 3T3 fibroblasts, elafibranor, but not GFT1007, showed phototoxic potential. From the follow-up UV-LLNA mice study, it was concluded that there is no in vivo phototoxicity risk associated with elafibranor up to the highest tested dose of 800 mg/kg/day (~46-fold the C_{max} exposure at the MHRD). Moreover, tissue distribution studies using radiolabelled elafibranor in mice, rats and monkeys showed that there was no accummulation of elafibranor in eyes and skin, which limits its phototoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content

Microcrystalline cellulose
Povidone
Croscarmellose sodium
Anhydrous colloidal silica
Magnesium stearate

Film-coating

Polyvinyl alcohol-part hydrolyzed
Titanium dioxide
Macrogol
Talc
Iron oxide yellow
Iron oxide red

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months
The in-use shelf-life after first opening is 30 days at or below 30°C.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Elafibranor 80 mg tablets are packaged in 40 mL high-density polyethylene (HDPE) bottle with a polypropylene child-resistant screw cap with integrated desiccant unit. The bottle is then packed into an outer carton.

Each bottle contains 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Delpharm Milano S.r.l.
Via Salvatore Carnevale 1,
Segrate, 20054, Italy

8. DATE OF REVISION

August 2025