



Summary Report of Benefit-Risk Assessment

IQIRVO® FILM-COATED TABLET 80MG

NEW DRUG APPLICATION

Active Ingredient(s)	Elafibranor
Product Registrant	Ipsen Pharma Singapore Pte. Ltd.
Product Registration Number	SIN17332P
Application Route	Abridged evaluation
Date of Approval	18 September 2025

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A INTRODUCTION

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.

The active substance, elafibranor, is a dual peroxisome proliferator-activated receptor (PPAR) α/δ agonist. Through PPAR α activation, it decreases bile acid synthesis, increases bile acid detoxification, reduces bile toxicity, and decreases injury to cholangiocytes and hepatocytes. PPAR α activation also regulates transporters that absorb and secrete bile components. Both PPAR α and PPAR δ activation provide anti-inflammatory effects through different pathways - nuclear factor kappa B (NF- κ B) and B-cell lymphoma 6 (BCL6) pathways, respectively.

IQIRVO is available as film-coated tablet containing 80 mg of elafibranor. Other ingredients in the tablet core are microcrystalline cellulose, povidone, croscarmellose sodium, anhydrous colloidal silica, and magnesium stearate. Ingredients in the film coating include polyvinyl alcohol - part hydrolysed, titanium dioxide, macrogol, talc, iron oxide yellow, and iron oxide red.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, elafibranor, is manufactured at PCAS, Gard, France. The drug product, IQIRVO film-coated tablet 80 mg, is manufactured at Delpharm Milano Srl, Segrate, Italy.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates, and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP).

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance with a re-test period of 60 months with no special storage conditions required. The packaging is double low-density polyethylene (LDPE) bags. The LDPE bags are stored in opaque high-density polyethylene (HDPE) drums.

Drug product:

The tablets are manufactured using a wet granulation approach followed by compression and film-coating which is considered a standard manufacturing process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30°C. The in-use period after opening is 30 days stored at or below 30°C. The container closure system is a high-density polyethylene (HDPE) bottle containing 30 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of elafibranor in the treatment of PBC was based primarily on one pivotal Phase III study (319-1), referred to as the ELATIVE study. This was a double-blind, randomised, placebo-controlled, multicentre study that evaluated the efficacy and safety of elafibranor 80 mg for the treatment of patients with PBC with inadequate response or intolerance to UDCA. Supporting evidence of clinical efficacy was derived from a Phase II randomised, double-blind, placebo-controlled study (216-1) evaluating elafibranor 80 mg and 120 mg against placebo in patients with PBC with inadequate response to UDCA.

In the ELATIVE study, patients were randomised in a 2:1 ratio to receive either elafibranor 80 mg or placebo once daily for 52 weeks. Where applicable, patients continued their pre-study dose of UDCA throughout the study. The use of placebo control was considered appropriate based on the chronic and slowly progressive nature of the disease, presence of UDCA background therapy, and the relatively short double-blind period.

The primary efficacy endpoint was a composite cholestasis response at Week 52, defined as alkaline phosphatase (ALP) $<1.67 \times$ upper limit of normal (ULN), total bilirubin (TB) $\leq$ ULN, and ALP decrease $\geq 15\%$. Key secondary endpoints included ALP normalisation at Week 52 and change in pruritus from baseline through Week 52 and Week 24 based on the PBC Worst Itch Numeric Rating Scale (NRS) score in patients with baseline score ≥ 4 . The statistical analysis plan included appropriate multiplicity adjustments using a fixed-sequence testing approach.

A total of 161 patients were randomised and included in the Intent-to-Treat (ITT) analysis set: 108 patients in the elafibranor group and 53 patients in the placebo group. Demographics and baseline characteristics were well-balanced between treatment groups. Most patients were aged <65 years (78.3%), with a mean age of 57.1 years. The majority were female (95.7%) and White (91.3%). Most patients were receiving concurrent UDCA treatment (95.0%) and most patients had early disease stage (96.3%) based on Rotterdam criteria (TB $\leq$ ULN and ALB $\geq$ LLN). The mean baseline ALP concentration was 321.9 U/L, with 96.3% of patients having baseline ALP $>1.67 \times$ ULN and 39.1% having baseline ALP concentration $>3 \times$ ULN.

The mean baseline TB concentration was 9.6 µmol/L and 96.3% of patients had baseline TB concentration ≤ULN.

The primary analysis demonstrated a statistically significant improvement in cholestasis response at Week 52 for patients in the elafibranor group compared to placebo (50.9% vs 3.8%; $p < 0.0001$). The result was primarily driven by the ALP component as majority of patients (96.3%) had baseline ALP $> 1.67 \times \text{ULN}$, while 96.3% had normal TB at baseline.

For the first key secondary endpoint, ALP normalisation at Week 52 was achieved in 14.8% of elafibranor patients compared to 0% in the placebo group ($p = 0.0019$). For the second and third key secondary endpoints evaluating change in pruritus, while there were greater reductions in the elafibranor group, the differences did not reach statistical significance at either Week 52 ($p = 0.1970$) or Week 24 ($p = 0.5522$). Only patients with significant baseline itching (NRS score ≥ 4) were included in the Pruritus ITT analysis set.

Subgroup analyses showed consistent treatment effects but with diminished response rates in patients with more advanced disease markers. Patients with baseline ALP $> 3 \times \text{ULN}$ showed a smaller treatment difference for elafibranor vs placebo (20.9% vs 0.0%) compared to those with ALP $< 3 \times \text{ULN}$ (70.8% vs 6.1%). Similarly, patients with progression risk markers (TB $> 0.6 \times \text{ULN}$) showed a smaller effect size (29.6% vs 7.7%) compared to lower-risk patients (58.0% vs 2.5%). Patients with cirrhosis also demonstrated lower response rates (11.1% vs 0.0%) compared to non-cirrhotic patients (54.5% vs 4.3%). Notwithstanding the smaller treatment effect in patients with more advanced disease, a consistent trend towards benefit was observed across subgroups.

Among the subgroup of UDCA-intolerant patients (6 elafibranor, 2 placebo), one elafibranor patient (16.7%) achieved the primary composite response at Week 52; of the 4 elafibranor monotherapy patients with end-of-study data, 3 showed ALP reductions ranging from -90 to -182 U/L, while one placebo patient showed increases in both ALP and TB. Given the unmet medical need in this rare disease population with UDCA intolerance affecting 3-5% of PBC patients, and the observed ALP reductions in the limited dataset, the use of elafibranor as a monotherapy option in UDCA-intolerant PBC patients was considered acceptable.

Summary of key efficacy results

	Elafibranor (N=108)	Placebo (N=53)	Risk difference (95% CI)	p-value
<u>Primary efficacy endpoint</u> Cholestasis composite response at Week 52, n (%)	55 (50.9)	2 (3.8)	47.2 (32.0, 56.9)	< 0.0001
<u>Secondary efficacy endpoint</u> ALP normalisation at Week 52, n (%)	16 (14.8)	0 (0.0)	14.8 (6.1, 22.7)	0.0019
	Elafibranor (N=44)	Placebo (N=22)	LS Mean difference (95% CI)	p-value
<u>Secondary efficacy endpoint</u>				

LS mean change in pruritus from baseline through Week 24	-1.60	-1.26	-0.34 (-1.49, 0.80)	0.5522
<u>Secondary efficacy endpoint</u> LS mean change in pruritus from baseline through Week 52, LS means	-1.93	-1.15	-0.78 (-1.99, 0.42)	0.1970

The Phase II study (216-1) supported the findings of the pivotal study, demonstrating significant reductions in ALP levels with both 80 mg and 120 mg doses of elafibranor compared to placebo after 12 weeks of treatment. The 80 mg dose showed a 52.0% reduction ($p < 0.001$) and the 120 mg dose a 43.9% reduction ($p < 0.001$) in ALP levels from baseline.

The efficacy of elafibranor has been demonstrated consistently across both clinical studies. In the pivotal Phase III trial, elafibranor 80 mg showed statistically significant improvements compared to placebo in composite cholestasis response and ALP normalisation, with a trend toward improvement in pruritus. These findings were supported by results from the Phase II study, where both 80 mg and 120 mg doses demonstrated significant improvements in ALP levels and other markers of cholestasis.

While the magnitude of the treatment effect in terms of changes in biomarkers (ALP and TB) was considered meaningful, uncertainty remains on whether these surrogate endpoints would translate into favourable long-term clinical outcomes. The ongoing confirmatory Phase III, randomised, double-blind, placebo-controlled study (CLIN-60190-454; ELFIDENCE) to evaluate elafibranor on long-term clinical outcomes (including hepatic decompensation, liver transplant, and death) in adult patients with PBC would be required to confirm the long-term clinical benefit of elafibranor in the treatment of PBC.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of elafibranor was based primarily on data from the pivotal Phase III ELATIVE study (Study 319-1) comprising 161 patients (108 elafibranor, 53 placebo). The mean exposure was 66.2 weeks for elafibranor 80 mg and 62.2 weeks for placebo.

Overview of treatment-emergent adverse events (AEs)

AE	Elafibranor 80 mg (N=108) n (%)	Placebo (N=53) n (%)
AE	104 (96.3)	48 (90.6)
Treatment-related AE	42 (38.9)	21 (39.6)
Serious adverse events (SAE)	11 (10.2)	7 (13.2)
Treatment-related SAE	3 (2.8)	1 (1.9)
Discontinuations due to AE	11 (10.2)	5 (9.4)
Deaths	2 (1.9)	0
Overall adverse events of special interests (AESI)	32 (29.6)	14 (26.4)

The most frequent AEs were observed in the system organ classes of infections and infestations (63.0% vs 58.5%) and gastrointestinal disorders (50.9% vs 30.2%). The types of

AEs reported with elafibranor were primarily gastrointestinal in nature, with common events ($\geq 5\%$ and $>1\%$ higher than placebo) including vomiting (11.1% vs 1.9%), diarrhoea (11.1% vs 9.4%), nausea (11.1% vs 5.7%), constipation (8.3% vs 1.9%), abdominal pain upper (7.4% vs 5.7%), and gastro-oesophageal reflux disease (6.5% vs 1.9%). These AEs were generally mild and transient, and consistent with the class effect of PPAR agonists.

The overall incidence of SAEs was slightly lower in the elafibranor group (10.2%) compared to placebo (13.2%). The most common SAEs in the elafibranor group were acute kidney injury (2.8%) and hip fracture (1.9%). Treatment-related SAEs occurred in 3 (2.8%) elafibranor patients versus 1 (1.9%) placebo patient. In the elafibranor group, these included moderate-to-severe ascites with moderate acute kidney injury and severe rhabdomyolysis, moderate Crohn's disease with severe sudden hearing loss, and moderate tremor with mild parkinsonism. In the placebo group, one case of severe cataract was reported. Two deaths occurred in the elafibranor group, due to multiple organ dysfunction syndrome in one patient and biliary sepsis with acute kidney injury in the other; none of these events were considered treatment-related by investigator.

Discontinuations due to AEs were similar between groups (10.2% elafibranor vs 9.4% placebo). The only treatment discontinuation event occurring in >1 patient in the elafibranor group was blood creatine phosphokinase (CPK) increased (4 patients, 3.7%).

The predefined adverse events of special interest (AESIs) occurred in 32 (29.6%) patients in the elafibranor group compared to 14 (26.4%) patients in the placebo group. These included CPK elevations/muscle injury, hepatic events, and renal events.

CPK elevations leading to discontinuation occurred in 4 (3.7%) patients in the elafibranor group compared to none in the placebo group. All events were non-serious, with one being moderate in intensity and the remaining 3 were mild. Three of the four cases were assessed as possibly related to study drug, with no clear trend observed in time to onset (range: 29-288 days).

For hepatic events, one case of potential drug-induced liver injury (DILI) was identified in the elafibranor group and adjudicated as 'possible' DILI, while two cases in the placebo group were adjudicated as 'probable' DILI. The case of possible DILI in the patient treated with elafibranor was assessed as possibly related. Nevertheless, confounding factors were also identified including concomitant pharmacological treatment. An additional three cases of potential DILI were identified in the elafibranor group based on laboratory values, with one patient meeting criteria for cholestatic DILI and two patients falling within Temple's corollary quadrant for hepatocellular DILI.

Renal events (acute kidney injury) occurred in 3 (2.8%) patients in the elafibranor group versus 1 (1.9%) patient in the placebo group, with all events being serious. Of the 3 patients in the elafibranor group, one case occurred with rhabdomyolysis and was assessed as possibly related to treatment, while two cases occurred in the setting of complex clinical conditions leading to death and were considered unrelated to treatment by investigator.

Overall, the safety profile of elafibranor could be managed through monitoring and treatment modifications, with gastrointestinal events being the most common treatment-related adverse reactions. The most clinically important adverse drug reaction identified was CPK elevation, while important potential risks included hepatic events. The package insert has included recommendations for periodic monitoring of CPK and liver function, and guidance for treatment interruption if increases in CPK, unexplained muscle symptoms, or liver dysfunction are observed.

E ASSESSMENT OF BENEFIT-RISK PROFILE

PBC is a rare, chronic, and progressive liver disease that primarily affects women. Despite treatment with UDCA, up to 40% of patients have an inadequate response and remain at risk of disease progression, which could result in liver-related complications, liver transplant, and death. Currently, UDCA is the only approved treatment locally.

In the pivotal Phase III study (ELATIVE, Study 319-1), elafibranor 80 mg once daily has demonstrated a statistically significant and clinically meaningful improvement in the primary composite endpoint of cholestasis response at Week 52 compared to placebo (50.9% vs 3.8%, $p < 0.0001$). Elafibranor also showed significant improvement in the key secondary endpoint, ALP normalisation at Week 52 (14.8% vs 0%, $p = 0.0019$). While not statistically significant, there was a trend towards improvement in pruritus scores, a symptom that commonly affects the quality of life of PBC patients. The efficacy of elafibranor was consistent across various subgroups, including patients with more severe disease markers even though the magnitude of effect appeared to be reduced in patients with more advanced disease.

The safety profile of elafibranor was characterised mainly by common AEs of gastrointestinal disorders, including vomiting, diarrhoea and nausea, which were mild and transient in nature. The most clinically important adverse reaction was CPK elevation, which occurred in 4 (3.7%) patients. Hepatic events were identified as an important potential risk, occurring in 3 (2.8%) patients. These risks have been described in the package insert, including recommendations for monitoring of CPK and liver function, and treatment interruption when clinically indicated.

Overall, the data supporting elafibranor's use as monotherapy in UDCA-intolerant patients was limited. Nonetheless, considering the unmet medical need, limited treatment options, the significant improvement observed with cholestasis response, the trend towards improvement in pruritus, and the manageable safety profile, the benefit-risk profile of elafibranor in the treatment of PBC patients with inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA is considered favourable.

To further characterise the efficacy and safety of elafibranor on long-term clinical outcomes in adults with PBC, a registration condition has been imposed to require data from the ongoing Phase III ELFIDENCE study to be submitted post-approval.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of IQIRVO for the treatment of PBC in combination with UDCA in adult patients with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA, was deemed favourable and approval of the product registration was granted on 18 September 2025.

The approval is subject to the submission of the final study report of Study 454 (CLIN-60190-454; ELFIDENCE) to confirm the long-term efficacy and safety of elafibranor for the approved indication.

APPROVED PACKAGE INSERT AT REGISTRATION

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$), not known (cannot be estimated from the available data).

System organ class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1\ 000$ 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 PPAR α 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 PPAR α 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 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 $\geq 1.67 \times$ ULN and total bilirubin (TB) was $\leq 2 \times$ 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 $> 3 \times$ ULN.

The mean baseline TB concentration was 9.6 μ mol/L and 96% of participants had a baseline TB concentration $\leq$ 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 $< 1.67 \times$ ULN and TB $\leq$ 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.

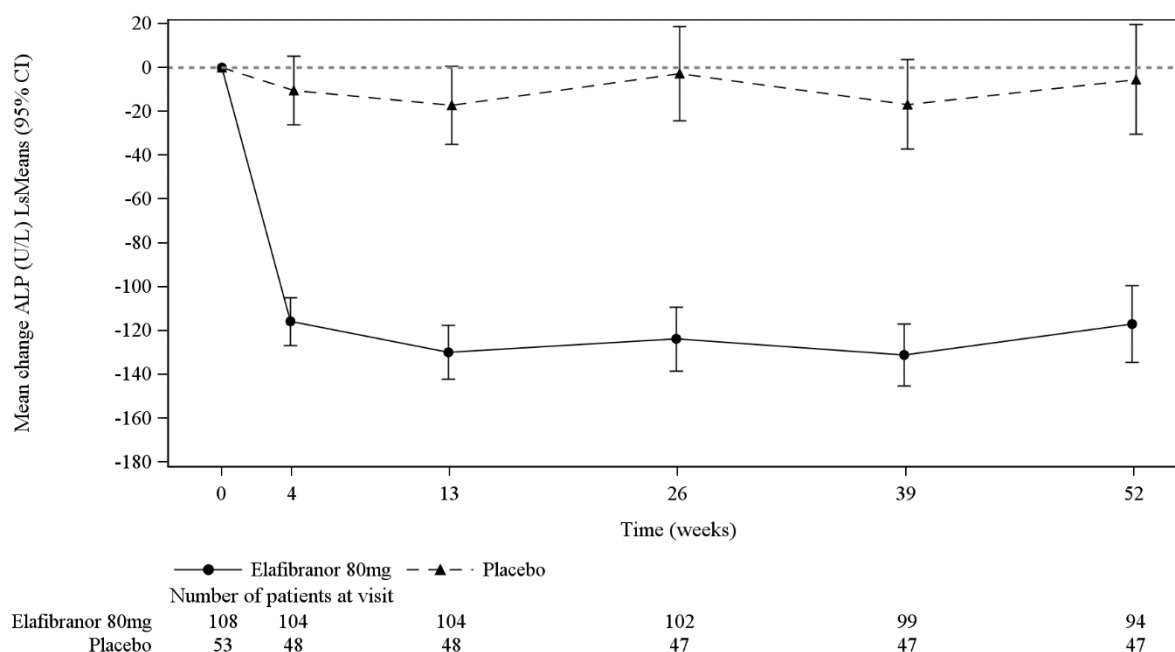
^[2] Normalization of ALP at week 52 defined as proportion of participants with ALP ≤1.0× ULN. The approach to handle intercurrent events or missing data is the same as for the primary endpoint.

^[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, CYP2C9, 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 doses 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 PPAR γ 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 accumulation 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