ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Iqirvo 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 80 mg of elafibranor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

The tablets are round, orange, approximately 8 mm diameter, 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 patients unable to tolerate UDCA.

4.2 Posology and method of administration

Posology

The recommended dose is 80 mg once daily.

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.

Elderly patients
No dose adjustment is necessary in patients older than 65 years of age (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.

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).

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known or suspected pregnancy and in women of childbearing age who do not use contraception (see section 4.6).

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 participants receiving elafibranor.

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.

Elevated blood creatine phosphokinase and muscle injury

Increases in blood creatine phosphokinase (CPK) have been reported in participants receiving elafibranor (see section 4.8). 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. 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 is suspected to cause congenital malformations and reduced foetal survival when administered to a pregnant woman (see section 4.6). Therefore, elafibranor is contra-indicated in women with a known or suspected pregnancy and in women of childbearing age who do not use contraception (see section 4.3). Women with childbearing potential should be informed about this.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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

Women of childbearing potential have to use effective contraception during and up to at least 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 (see section 4.4).

Pregnancy

There is limited amount of data from the use of elafibranor in pregnant women.
Studies in pregnant animals with elafibranor have shown reproductive toxicity (foetal loss, malformations, stillbirths and/or perinatal deaths) at clinically relevant exposure (see sections 4.4 and5.3).

Elafibranor is contraindicated during pregnancy (see section 4.3). If a patient becomes pregnant, treatment with elafibranor should be discontinued.

Lactation

It is unknown whether elafibranor or its metabolites are excreted in human milk. There is no information on the excretion of elafibranor or its metabolites in animal milk, but adverse effects were seen in offspring when elafibranor was administered to female rats during pregnancy (see section 5.3) and lactation at clinically relevant exposure.

A risk to the suckling child cannot be excluded.

Elafibranor should not be used during breastfeeding and for at least 3 weeks following last dose of elafibranor.

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

The most commonly reported adverse drug reactions associated with elafibranor treatment (n = 108) which occurred in more than 10% of participants and with a higher incidence than in the placebo group (n = 53; difference >1%) were abdominal pain (11.1% versus 5.7%), diarrhoea (11.1% versus 9.4%), nausea (11.1% versus 5.7%), and vomiting (11.1% versus 1.9%). These were non-serious, mild to moderate, occurred early in treatment and tended to resolve within days to a few weeks without any dose modification or supportive measures.

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	Common	Uncommon
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

Headache
In the pivotal phase 3 ELATIVE study, 9 (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).

Blood CPK increased
In the pivotal phase 3 ELATIVE study, 4 (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 (standard deviation) 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.*

4.9 Overdose

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

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.
PPAR α/δ are thought to be key regulators of bile acid (BA) homeostasis, inflammation and fibrosis. Activation of PPARα and PPARδ decreases bile toxicity and improve cholestasis by modulating BA synthesis, detoxification and transporters.
Activation of PPARα and PPARδ also has anti-inflammatory effects by acting on different pathways.

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.

Cardiac electrophysiology

Thorough QT (TQT) analysis excluded any prolongation effect of elafibranor on QT/corrected 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), a phase 3, randomised, double blind (DB), placebo-controlled study in 161 adults with PBC with an inadequate response or intolerance to UDCA. Participants were randomised in a 2:1 ratio stratified across two factors (ALP >3 x ULN or total bilirubin (TB) >ULN and PBC Worst Itch Numeric Rating Scale (WI-NRS) score ≥4) 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 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, and 35% of participants had advanced disease at baseline, defined as liver stiffness >10 kPa and/or bridging fibrosis or cirrhosis on histology.

The median duration of exposure was 63.07 and 61.00 weeks in the elafibranor and placebo groups, respectively.

The mean baseline TB concentration was 9.6 µmol/L and 96% of participants had a baseline TB concentration less than or equal to ULN. The mean baseline liver stiffness measurement by transient

elastography was 10.1 kPa. The baseline mean PBC WI-NRS score was 3.3 and 41% had moderate-to-severe pruritus at baseline (PBC WI-NRS score ≥4); for those with moderate-to-severe pruritus, the baseline mean PBC WI-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 WI-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

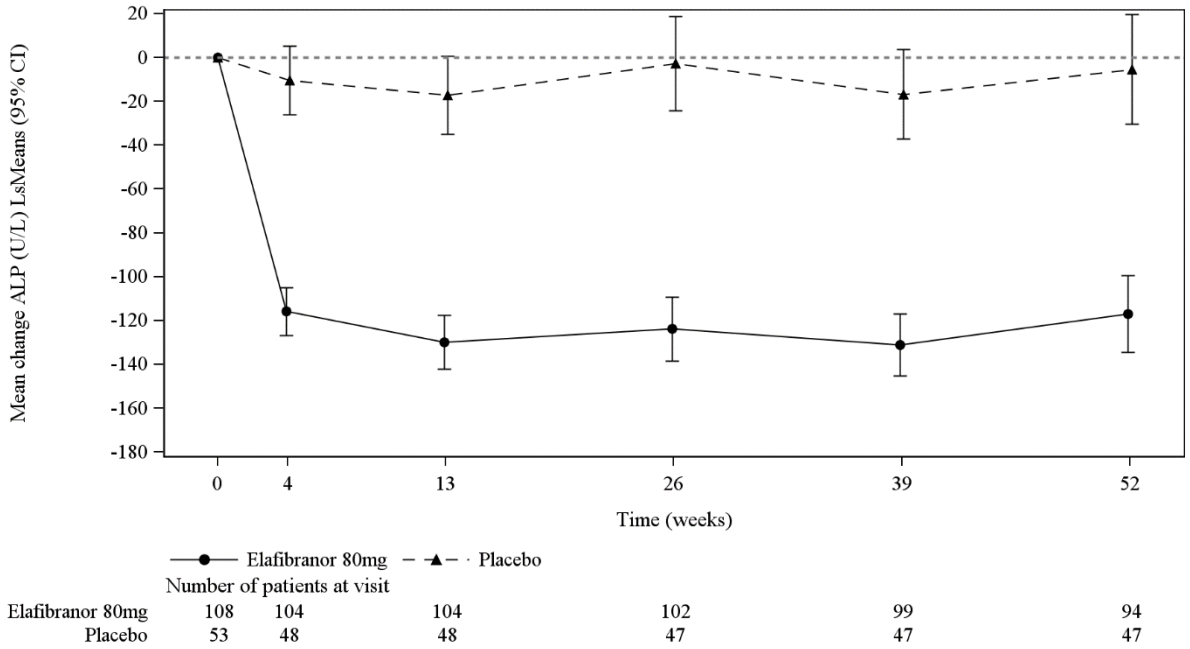
Analysis Population	Elafibranor 80 mg (N=108)	Placebo (N=53)	Treatment Difference (95% CI) [3]	Odds Ratio (95% CI) [4]	P-value [4]
Primary composite endpoint: Cholestasis response [1]					
ITT	51%	4%	47% (32, 57)	37.6 (7.6, 302.2)	<0.0001
First key secondary endpoint: ALP normalization [2]					
ITT	15%	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 in ALP 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 (Least Squares (LS) mean with 95% CI) Change from Baseline in ALP Over Time - ITT analysis set



The primary endpoint of cholestasis response in participants with a baseline ALP ≤3 x ULN or TB <ULN was achieved in 71% of participants on elafibranor versus 6% of participants on placebo, compared to those with ALP >3 x ULN or TB >ULN where cholestasis response was achieved in 21% of participants on elafibranor versus 0% on placebo.

Among the 54 participants with advanced disease, 16/35 (46%) participants on elafibranor versus 0/19 (0%) participants on placebo achieved the primary endpoint of cholestasis response. Due to the limited number of participants with advanced disease, these results should be interpreted with caution.

Patient- reported outcomes

In participants with moderate-to-severe pruritus at baseline, a greater decrease from baseline in PBC WI-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
Second 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
Third 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)	-

[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 WI-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
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)
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)

[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 LS 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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Iqirvo in all subsets of the paediatric population in primary biliary cholangitis (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review any new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Elafibranor plasma exposure (AUC) increases proportionally from 50 to 360 mg (0.6 to 4.5 times the recommended dose). 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 exposure (AUC) of elafibranor decreased by 15% and the plasma AUC of GFT1007 was not affected. Given the 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.

Biotransformation

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).

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 (CYP3A, Breast Cancer Resistance Protein (BCRP), organic anion transporting polypeptides 1B1 (OATP1B1) and OATP1B3 substrates) 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.

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

No clinically significant effects on blood levels of GLP-1 were observed when co-administering 100 mg of elafibranor as a DDI perpetrator once daily for 15 days with a single oral 100 mg dose of sitagliptin during a meal test.

In Vitro Studies

Cytochrome P450 (CYP) inhibition and induction:

Elafibranor and GFT1007 were not considered inhibitors of main CYPs. 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 and GFT1007 were not expected to inhibit main UGTs at clinically significant concentrations.

Transporter systems:

Elafibranor was an inhibitor of OATP1B3 and BCRP. Based on the in vivo studies with simvastatin and atorvastatin, no clinical consequences are expected from the inhibition of OATP1B3 and BCRP.

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.

Reproduction and development toxicity

Elafibranor has shown evidence of developmental toxicity in both rats and rabbits.In rat pre- and post-natal study, maternal exposures to elafibranor (at or above 2-fold the AUC exposure at the maximum human recommended dose (MHRD)) led to reduced pup survival, developmental delay, or thrombosis. In pregnant rabbits, maternal exposure (3-fold the AUC exposure at MHRD) to elafibranor caused marked maternal toxicity, increased embryo-lethality, reduced foetal weight and a low incidence of foetal malformations.

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 hydrolysed
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

40 mL high-density polyethylene (HDPE) bottle with a polypropylene child-resistant screw cap.
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. MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai George Gorse
92100 Boulogne-Billancourt
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1855/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Delpharm Milano Srl
Via Salvatore Carnevale 1
Segrate, 20054
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of elafibranor in 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 patients unable to tolerate UDCA, the MAH shall conduct and submit the final results of the phase III randomised, parallel-group, double-blind, placebo-	

Description	Due date
controlled, two-arm study (ELFIDENCE) to evaluate the efficacy and safety of elafibranor on long-term clinical outcomes in adults with Primary Biliary Cholangitis (PBC).	May 2030

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Iqirvo 80 mg film-coated tablets
elafibranor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg of elafibranor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets

30 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1855/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

iqirvo

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Iqirvo 80 mg film-coated tablets
elafibranor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg of elafibranor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablets
30 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1855/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Iqirvo 80 mg film-coated tablets
elafibranor

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Iqirvo is and what it is used for

Iqirvo contains the active substance elafibranor which acts on 2 types of receptors (PPAR alpha and PPAR delta).

This medicine is used in adults to treat primary biliary cholangitis (PBC), a type of liver disease in which the bile ducts are slowly destroyed, making it harder for bile to flow through. Bile is a fluid that helps digest food, especially fats. When the bile cannot flow into the digestive tract, it backs up in the liver (this is called cholestasis), where it damages liver tissues. This can decrease liver function and cause inflammation. Iqirvo can be used together with ursodeoxycholic acid (UDCA), or by itself in patients who cannot use UDCA.

The active substance in Iqirvo, elafibranor, works by activating the PPAR alpha and PPAR delta receptors. These proteins are thought to regulate levels of bile acids, inflammation, and fibrosis (formation of scar tissue). This reduces the production and the build-up of bile in the liver and also reduces inflammation of the liver.

2. What you need to know before you take Iqirvo

Do not take Iqirvo
- if you are allergic to elafibranor or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant, if you think you might be pregnant or if you do not use any method of contraception to prevent pregnancy

Warnings and precautions
Iqirvo can increase blood levels of liver enzymes and bilirubin (a breakdown product of red blood cells). Your doctor may carry out blood tests to check your liver before and during treatment. If there are abnormal results from these liver tests, your doctor may temporarily stop treatment until they return to normal. Tell your doctor immediately if your develop symptoms of liver dysfunction including yellowing of the skin and eyes (jaundice), belly (abdominal) pain, feeling sick, vomiting, tiredness, loss of appetite and dark urine.

Iqirvo may increase blood levels of creatine phosphokinase (an enzyme released into the blood when muscle is damaged). Your doctor may run blood tests to check your levels of creatine phosphokinase before and during treatment, particularly if your are taking medicines known as HMG-CoA reductase inhibitors, such as atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin. Talk to your doctor immediately if you experience unexplained muscle pain, soreness or weakness whilst taking this medicine.

Children and adolescents
This medicine should not be used in children and adolescents below 18 years of age.

Other medicines and Iqirvo
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy
Do not take Iqirvo if you are pregnant, if you think you might be pregnant or if you do not use any method of contraception to prevent pregnancy. Iqirvo may harm the unborn child.

Your doctor may ask you to take a pregnancy test before starting treatment with Iqirvo to ensure you are not pregnant prior starting treatment.

If you are a woman of childbearing potential, you should use effective contraception (birth control) whilst taking this medicine and for at least 3 weeks after stopping treatment to avoid any harm to the unborn child. Your doctor will advise you on the best contraception for you.

Breast-feeding
It is unknown if Iqirvo passes into human milk. A risk to the nursing child cannot be excluded.
You should not breast-feed your baby during treatment and for 3 weeks after the last dose.

Iqirvo contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Iqirvo

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 80 mg tablet, once a day. Swallow the tablets whole with water.
Ask your doctor before taking Iqirvo if you have advanced cirrhosis (a type of chronic, progressive liver disease in which liver cells are replaced by scar tissue) with severely reduced liver function (Child-Pugh C).

If you take more Iqirvo than you should
If you have taken more of this medicine than you have been instructed to, talk to a doctor or go to the hospital straight away. Take the tablets and this leaflet with you.

If you forget to take Iqirvo
If you forget to take Iqirvo, skip the dose and take your next dose when it is due.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Iqirvo
Do not stop taking this medicine unless you have discussed this with your doctor.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible side effects are:

Very common side effects (may affect more than 1 in 10 people):
- Belly (abdominal) pain
- Diarrhoea
- Feeling sick (nausea)
- Vomiting

Common side effects (may affect up to 1 in 10 people):
- Headache
- Constipation
- Gallstones (cholelithiasis) that can block the flow of bile causing abdominal pain, nausea or vomiting
- An increase in creatine phosphokinase, as measured in blood tests
- Muscle pain (myalgia)

Uncommon (may affect 1 in 100 people)
- Itchy rash (pruritic rash)
- Increase in creatinine, as measured in blood tests. Blood levels of creatinine are measured to monitor kidney function

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.* By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Iqirvo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Iqirvo contains
- The active substance is elafibranor.
- Each film-coated tablet contains 80 mg of elafibranor.

The other ingredients are:
- **Tablet contents:** microcrystalline cellulose, povidone, croscarmellose sodium (see section 2 'Iqirvo contains sodium'), anhydrous colloidal silica, magnesium stearate.
- **Film-coating:** polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172), iron oxide red (E172).

What Iqirvo looks like and contents of the pack
Iqirvo 80 mg film-coated tablets are orange, round, approximately 8 mm diameter, and identified with 'ELA 80' on one side.
Iqirvo is available in child-resistant bottles of 30 film-coated tablets.

Marketing Authorisation Holder
Ipsen Pharma
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92100 Boulogne-Billancourt
France

Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Annex IV

Conclusions on the granting of the conditional marketing authorisation presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.