

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

Mupleo 3 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 3 mg of lusutrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light red, 7.0 mm round film-coated tablets debossed with the Shionogi trademark above the identifier code “551” on one side and debossed on the other side with the strength “3”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mupleo is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended dose is 3 mg lusutrombopag once daily for 7 days.

The procedure should be performed from day 9 after the start of lusutrombopag treatment. Platelet count should be measured prior to the procedure.

Missed dose

If a dose is missed it should be taken as soon as possible. A double dose should not be taken to make up for a missed dose.

Duration of treatment

Mupleo should not be taken for more than 7 days.

Special populations

Elderly patients

No dosage adjustment is necessary in patients 65 years of age or older (see section 5.2).

Renal impairment

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

Hepatic impairment

Due to limited information available, the safety and efficacy of Mulpleo in patients with severe hepatic impairment (Child-Pugh class C) have not been established (see sections 4.4 and 5.1). No dosage adjustment is expected for these patients. Lusutrombopag therapy should only be initiated in patients with severe hepatic impairment if the expected benefit outweighs the expected risks (see sections 4.4 and 5.2). No dosage adjustment is necessary for patients with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment.

Paediatric population

The safety and efficacy of lusutrombopag in children and adolescents (< 18 years of age) have not been established. No data are available.

Method of administration

Mulpleo is for oral use. The film-coated tablet is to be taken once daily with liquid, swallowed whole and should not be chewed, divided, or crushed. It can be taken with or without food.

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

Thrombotic/thromboembolic complications

Patients with chronic liver disease have a risk of portal vein thrombosis and mesenteric vein thrombosis. The risk may be increased due to an invasive procedure. Thromboembolic and thrombotic complications are known to occur with thrombopoetin (TPO) receptor agonists based upon mechanism of action associated with increases in platelets. Caution should be exercised with respect to thromboembolic events after invasive procedures as well as post-treatment regardless of platelet counts. In patients with thrombosis or thromboembolism, with a history of thrombosis or thromboembolism, with absence of hepatopetal blood flow in the main trunk of the portal vein, or patients with congenital coagulopathy the risk for thrombosis or thromboembolism may increase. These patients should be clinically monitored when treated with lusutrombopag.

Severe hepatic impairment

There is limited information on the use of lusutrombopag in patients with severe (Child-Pugh class C) hepatic impairment (see section 5.1). Lusutrombopag should only be used in such patients if the expected benefit outweighs the expected risks (see sections 4.2 and 5.2).

Due to the unstable nature of these patients, they should be supported in line with clinical practice by close monitoring for early signs of worsening or new onset hepatic encephalopathy, ascites, and thrombotic or bleeding tendency, through monitoring of liver function tests, tests used for assessing clotting status and through imaging of portal vasculature as needed. In addition, although no dose adjustment is required in these subjects, platelet count should be measured at least once approximately 5 days after the first dose and as necessary thereafter. Appropriate measures such as discontinuation of lusutrombopag should be taken, if the platelet count reaches $\geq 50,000/\mu\text{L}$ as a result of a $20,000/\mu\text{L}$ increase from baseline.

Use in patients with chronic liver disease undergoing invasive procedures

Lusutrombopag should be used when risk for bleeding is considered to be high according to clinical laboratory test values such as platelet counts and of the coagulation-fibrinolysis system, clinical symptoms and type of invasive procedure. The efficacy and safety of lusutrombopag have not been established when administered before laparotomy, thoracotomy, open-heart surgery, craniotomy or excision of organs.

Retreatment

There is limited information on the use of lusutrombopag in patients previously exposed to lusutrombopag.

Use in patients with a history of splenectomy

The efficacy and safety of lusutrombopag have not been established when administered in patients with a history of splenectomy. Platelet count should be carefully monitored in patients with a history of splenectomy treated with lusutrombopag.

Co-administration with interferon preparations

Interferon preparations have been known to reduce platelet counts, therefore, this should be considered when co-administering lusutrombopag with interferon preparations.

Patients with body weight <45 Kg

There is limited information on the use of lusutrombopag in patients with body weight <45 Kg. Platelet count should be measured at least once approximately 5 days after the first dose and as necessary thereafter. Appropriate measures such as discontinuation of lusutrombopag should be taken, if the platelet count reaches $\geq 50,000/\mu\text{L}$ as a result of a $20,000/\mu\text{L}$ increase from baseline.

4.5 Interaction with other medicinal products and other forms of interaction

P-gp and BCRP inhibitors

Lusutrombopag is a substrate of P-gp and BCRP, but not a substrate of OATP1B1, OATP1B3, and OCT1. In the clinical drug-drug interaction study, co-administration of cyclosporine, a P-gp and BCRP dual inhibitor, increased the C_{max} and AUC_{inf} values of lusutrombopag by approximately 20% compared with lusutrombopag administration alone. Therefore, a potential interaction with either P-gp or BCRP inhibitors cannot be excluded, but no dose adjustment is necessary at the recommended clinical dosage of 3 mg in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

Mulpleo should be used with contraception (see sub-section Pregnancy and section 5.3).

Pregnancy

There are no or limited amount of data from the use of lusutrombopag in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Lusutrombopag is not recommended during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding

It is unknown whether lusutrombopag or its metabolites are excreted in human milk. Studies in animals have shown lusutrombopag is secreted in the milk of lactating rats (see section 5.3). Therefore, a risk to the breast-feeding child cannot be excluded. Mulpleo should not be administered to breast-feeding women as it was excreted in mammary milk in animals.

Fertility

Lusutrombopag did not affect male or female fertility in rats at doses up to 176 and 252 times the human clinical exposures in adults based on AUC in males and females, respectively (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were headache (4.7%, 8/171 patients in the lusutrombopag group; 3.5%, 6/170 patients in the placebo group), nausea (2.3%, 4/171 patients in the lusutrombopag group; 4.1%, 7/170 patients in the placebo group), portal vein thrombosis (1.2%, 2/171 patients in the lusutrombopag group; 1.2%, 2/170 patients in the placebo group) and rash (1.2%, 2/171 patients in the lusutrombopag group; 0%, 0/170 patients in the placebo group).

Tabulated list of adverse reactions

Adverse reactions with 3 mg of lusutrombopag once daily for up to 7 days in randomised, double-blind, placebo-controlled trials in thrombocytopenic patients with chronic liver disease undergoing an invasive procedure (M0626, M0631 and M0634; N=171) are listed in Table 1 by MedDRA System Organ Class.

Table 1 Adverse reactions

System Organ Class	Adverse reaction - Common
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea
Hepatobiliary disorders	Portal vein thrombosis
Skin and subcutaneous tissue disorders	Rash

^a Category of frequency: 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 $< 1/1,000$), and very rare ($< 1/10,000$)

Description of selected adverse reactions

Thrombotic/thromboembolic complications

Portal vein thrombosis has been reported in Phase 3 randomised, double-blind, placebo-controlled clinical studies with 3 mg of lusutrombopag once daily for up to 7 days (1.2%, 2/171 patients); the incidence was comparable to that of the placebo group (1.2%, 2/170 patients); one case of cardiac ventricular thrombosis was reported (0.6%, 1/171) in the lusutrombopag group only. In the phase 2b study one patient had portal vein thrombosis reported as a treatment-emergent adverse event (TEAE) in the lusutrombopag 2 mg and 4 mg groups. One patient had mesenteric vein thrombosis reported as a TEAE in the lusutrombopag 4 mg group; two patients had mesenteric vein thrombosis reported as a TEAE in the placebo group (see section 4.4).

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

Overdose may induce an excessive increase of platelet counts, and it may subsequently provoke a medically susceptible state to cause thrombosis and thromboembolism. There is no specific antidote for lusutrombopag overdose. Platelet counts should be measured frequently and the condition of patients should be observed closely. Since the protein-binding rate in serum of lusutrombopag is high, haemodialysis is not thought to be effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics, ATC code: B02BX07

Mechanism of action

Lusutrombopag is an orally active TPO receptor agonist. Lusutrombopag acts on the haematopoietic stem cells and on the transmembrane domain of human TPO receptors expressed in megakaryocytes, to stimulate the megakaryocyte to proliferate and differentiate via the similar signal transduction pathway for up-regulating production used by endogenous TPO, thus leading to thrombocytopoiesis.

Clinical efficacy and safety

Two Phase 3, randomised, double-blind, placebo-controlled studies were conducted to evaluate lusutrombopag versus placebo in thrombocytopenic (platelet count $< 50,000/\mu\text{L}$) subjects with chronic liver disease (Child-Pugh class A and B), undergoing elective invasive procedures (excluding laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection) in Japan (M0631 (L-PLUS 1)) and multiple countries (M0634 (L-PLUS 2)). Subjects were randomised to either of 3 mg of lusutrombopag or placebo in a 1:1 ratio. Randomisation was stratified by platelet count at screening/baseline and primary invasive procedure. Study drug was administered orally for up to 7 days. On Day 5 to Day 7, the platelet count was measured before administration of study drug. Administration of study drug was stopped if the platelet count was $\geq 50,000/\mu\text{L}$ together with an increase of $\geq 20,000/\mu\text{L}$ from baseline.

Invasive procedure was performed between Days 9 and 14.

In Study M0631, 96 subjects received lusutrombopag or placebo once daily: 48 subjects in the lusutrombopag group and 48 subjects in the placebo group. Eight lusutrombopag-treated subjects and 2 placebo-treated subjects received less than 7 days of treatment as they met the criterion for a responder prior to Day 7. Among the 48 subjects in the lusutrombopag group, 40 subjects received lusutrombopag for 7 days, 4 subjects for 6 days, 1 subject for 5 days, and 3 subjects for 4 days. Among the 48 subjects in the placebo group, 46 were treated for 7 days and 2 were treated for 4 days.

In Study M0634, 215 subjects were randomised in the study: 108 in the lusutrombopag 3 mg group and 107 in the placebo group. One subject in the lusutrombopag group withdrew from the study prior to administration of study drug. In the lusutrombopag group, 73/107 subjects (68.2%) received the study drug for 7 days. Of the remaining subjects in the lusutrombopag group, 15, 8, and 11 subjects received study drug for 4, 5, and 6 days, respectively. In the placebo group, 94/107 subjects (87.9%) received the study drug for 7 days. Of the remaining subjects in the placebo group, 5, 4, and 4 subjects received study drug for 4, 5, and 6 days, respectively.

The primary endpoint in Study M0631 was the proportion of subjects who required no platelet transfusion (i.e. achieved platelet count $>50,000/\mu\text{L}$) before the primary invasive procedure. The primary endpoint in Study M0634 was the proportion of subjects who required no platelet transfusion (i.e. achieved platelet count $>50,000/\mu\text{L}$) before the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary invasive procedure.

In order to allow an overall comparison of the results across Studies M0631 and M0634, as presented in Table 2 to Table 5, data from study M0631 was reanalysed according to the primary endpoint for study M0634. The proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary invasive procedure was statistically significantly greater in the lusutrombopag group compared with placebo group for the individual study and pooled analyses (Table 2).

Table 2 Proportion of subjects who required no platelet transfusion and no rescue therapy

	Study M0631		Study M0634		Overall	
	LUSU 3 mg N = 49	Placebo N = 48	LUSU 3 mg N = 108	Placebo N = 107	LUSU 3 mg N = 157	Placebo N = 155
Proportion of subjects [a] (number of subjects)	75.5% (37)	12.5% (6)	64.8% (70)	29.0% (31)	68.2% (107)	23.9% (37)
Comparison with placebo [b]: Difference of proportion (95% CI)	61.8 (46.4, 77.2)		36.6 (24.6, 48.5)		44.4 (34.9, 54.0)	
P value	< 0.0001		< 0.0001		< 0.0001	

LUSU = lusutrombopag

[a] Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy (including platelet transfusion) for bleeding from randomisation through 7 days after the primary invasive procedure. In addition to subjects who received platelet transfusion, subjects who did not receive an invasive procedure regardless of the reason were considered as receiving platelet transfusion.

[b] Cochran-Mantel-Haenszel test with baseline platelet count as stratum. In the analysis for pooled data, study was added as a stratum. The p value and confidence interval were calculated using the Wald method.

The key secondary endpoints in Studies M0631 and M0634 were

Proportion of subjects who required no platelet transfusion during the study (Day 1 through Day 35)

The proportion of subjects who required no platelet transfusion during the study was significantly greater in the lusutrombopag groups in the individual studies and the pooled (Studies M0631 and M0634) lusutrombopag group compared with placebo (Table 3).

Table 3 Proportion of Subjects who required no platelet transfusion during the study (Day 1 through Day 35)

	Study M0631		Study M0634		Overall	
	LUSU 3 mg N = 49	Placebo N = 48	LUSU 3 mg N = 108	Placebo N = 107	LUSU 3 mg N = 157	Placebo N = 155
Proportion of subjects [a] (number of subjects)	77.6% (38)	12.5% (6)	63.0% (68)	29.0% (31)	67.5% (106)	23.9% (37)
Comparison with placebo [b]: Difference of proportion (95% CI)	63.8 (48.7, 78.9)		34.7 (22.6, 46.8)		43.8 (34.2, 53.4)	
P value	< 0.0001		< 0.0001		< 0.0001	

[a] Proportion of subjects who required no platelet transfusion during the study (i.e., from Day 1 through Day 35). In addition to subjects who received platelet transfusion, subjects who did not receive an invasive procedure regardless of the reason were considered as receiving platelet transfusion.

[b] Cochran-Mantel-Haenszel test with baseline platelet count as stratum. In the analysis for pooled data, study was added as a stratum. The p value and confidence interval were calculated using the Wald method.

Proportion of responders

The proportion of subjects who met the responder criterion (defined as platelet count increase to $\geq 50,000/\mu\text{L}$ with an increase of $\geq 20,000/\mu\text{L}$ from baseline) during the study was significantly greater in the lusutrombopag groups in the individual studies and the pooled (Studies M0631 and M0634) lusutrombopag group compared with placebo (Table 4).

Table 4 Proportion of responders

	Study M0631		Study M0634		Overall	
	LUSU 3 mg N = 49	Placebo N = 48	LUSU 3 mg N = 108	Placebo N = 107	LUSU 3 mg N = 157	Placebo N = 155
Proportion of subjects [a] (number of subjects)	75.5% (37)	6.3% (3)	64.8% (70)	13.1% (14)	68.2% (107)	11.0% (17)
Comparison with placebo [b]: Difference of proportion (95% CI)	68.4 (54.4, 82.3)		51.7 (41.1, 62.4)		56.9 (48.4, 65.4)	
P value	< 0.0001		< 0.0001		< 0.0001	

[a] A responder was defined as a subject who achieved a platelet count of $\geq 50,000/\mu\text{L}$ with an increase of $\geq 20,000/\mu\text{L}$ from baseline. A subject was considered a nonresponder if the subject met the responder criterion only after platelet transfusion.

[b] Cochran-Mantel-Haenszel test with baseline platelet count as stratum. In the analysis for pooled data, study was added as a stratum. The p value and confidence interval were calculated using the Wald method.

Duration of the increase in platelet count to $\geq 50,000/\mu\text{L}$

The duration of the increase in platelet count to $\geq 50,000/\mu\text{L}$ in Studies M0631 and M0634 and the pooled (Studies M0631 and M0634) lusutrombopag group was significantly greater than compared with placebo (Table 5).

Table 5 Duration of the increase in platelet count to $\geq 50,000/\mu\text{L}$

	Study M0631		Study M0634		Overall	
	LUSU 3 mg N = 49	Placebo N = 48	LUSU 3 mg N = 108	Placebo N = 107	LUSU 3 mg N = 157	Placebo N = 155
Total						
- n	48	48	107	107	155	155
- Median (days)	21.1	3.4	15.1	1.0	17.3	1.8
- (Q1, Q3)	(13.7, 25.5)	(0.0, 11.3)	(6.6, 23.9)	(0.0, 9.2)	(9.7, 24.4)	(0.0, 9.5)
- P value [a]	0.0197		0.0002		<0.0001	

LUSU = lusutrombopag; Q1 = 25th percentile; Q3 = 75th percentile

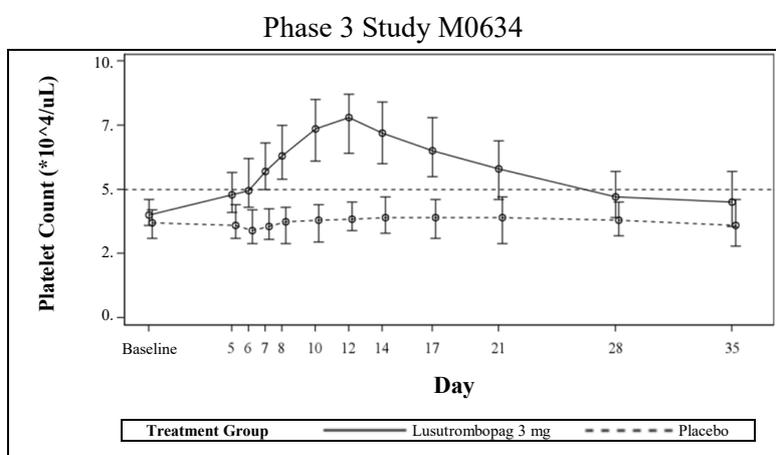
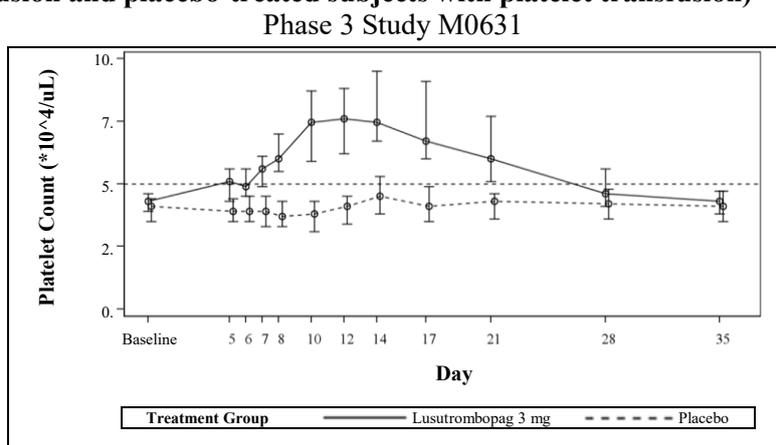
[a] P-value was calculated by the van Elteren test with platelet transfusion status as stratum. In the analysis for pooled data, study was added as a stratum.

Time course of platelet count

The mean (range) maximum platelet count in subjects without platelet transfusion in the lusutrombopag group in Studies M0631 and M0634 was 90,200 (59,000 to 145,000)/ μL and 86,900 (25,000 to 219,000)/ μL , respectively; and the median (range) time to reach the maximum platelet count was 14.0 (6 to 28) days and 12.0 (5 to 35) days, respectively, and platelet count is expected to decrease thereafter.

The time course of platelet counts in lusutrombopag-treated subjects without platelet transfusion and placebo-treated subjects with platelet transfusion in Studies M0631 and M0634 is presented in Figure 1.

Figure 1 Time course profiles of platelet count in the Phase 3 studies in thrombocytopenic patients with chronic liver disease (lusutrombopag-treated subjects without platelet transfusion and placebo-treated subjects with platelet transfusion)



Patients with severe hepatic impairment

In Study M0634, 3 subjects with Child-Pugh class C liver disease were erroneously enrolled (all in the lusutrombopag group). All 3 received 7 days of treatment with lusutrombopag. This limited data suggested no abnormal pattern of platelet count rise in this subpopulation.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Mulpleo in all subsets of the paediatric population for thrombocytopenia secondary to liver disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Lusutrombopag is absorbed with a peak concentration occurring 6 to 8 hours after oral administration. The accumulation ratios of the C_{max} and the AUC are approximately 2 at once-daily multiple doses and the steady-state of the plasma concentration of lusutrombopag appear to be achieved after Day 5. The pharmacokinetics of lusutrombopag was similar in both healthy subjects and the chronic liver disease population. The pharmacokinetic parameters in patients with chronic liver disease are shown in Table 6.

Table 6 Pharmacokinetic parameters of lusutrombopag after 3 mg dose once daily in thrombocytopenic patients with chronic liver disease (Study M0634)

C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-τ} (ng·hr/mL)	CL/F (L/hr)
157 (34.7)	5.95 (2.03, 7.85)	2737 (36.1)	1.10 (36.1)

n = 9.

Geometric mean (%CV) other than for T_{max}, which is median (range).

Food interaction

Neither food (including high-fat and high-calorie diet) nor co-administration with calcium has a clinically meaningful effect on the pharmacokinetics of lusutrombopag.

Distribution

Human plasma protein binding ratio is $\geq 99.9\%$. The mean (% coefficient of variation) apparent volume of distribution during the terminal phase of lusutrombopag in healthy adult subjects (n = 16) was 39.5 L (23.5%).

In rats, results indicated that lusutrombopag and its metabolites transfer to fetus via placenta.

Biotransformation

Lusutrombopag is a substrate of P-gp and BCRP, but is not a substrate of OATP1B1, OATP1B3 or OCT1. In the human mass balance study using [¹⁴C]-lusutrombopag, unchanged lusutrombopag (97% of radioactivity in plasma) was the major circulating component, and the metabolites, such as deshexyl, β -oxidated carboxylic acid, taurine conjugate of β -oxidated carboxylic acid, and acyl-glucuronide, were detected with less than 2.6% of radioactivity in plasma. In faeces, the components of radioactivity were unchanged lusutrombopag (16% of administered radioactivity) and β -oxidation-related metabolites (35% of administered radioactivity), suggesting that lusutrombopag is metabolised by ω -oxidation first, and subsequently metabolised by β -oxidation of O-hexyl side chain. *In vitro* studies revealed that CYP4 enzymes including CYP4A11 and partially CYP3A4 enzyme contributed to ω -oxidation to form 6-hydroxylated lusutrombopag. Drug interactions via inhibition and induction of any CYP4A enzymes have not been reported in clinical use. Therefore, inducers and inhibitors of CYP4A enzymes including CYP4A11 are unlikely to affect the pharmacokinetics of lusutrombopag. Lusutrombopag has low potential to inhibit CYP enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5), and to induce both CYP enzymes (CYP1A2, 2C9, and 3A4) and UGT enzymes (UGT1A2, 1A6, and 2B7). Lusutrombopag has also low potential to inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2-K, and BSEP. Lusutrombopag is not considered to affect the pharmacokinetics of co-administered medicinal products that are substrates of these enzymes or transporters.

Elimination

Lusutrombopag was excreted mainly via faecal route in humans (approximately 83% into faeces and 1% into urine).

Geometric mean of t_{1/2} (% coefficient of variation), was 38.3 hours (18.7%) after multiple oral dose of 3 mg lusutrombopag.

Linearity/non-linearity

Both C_{max} and AUC for lusutrombopag increase dose-proportionally over dose range of multiple oral dose of 0.25 to 4 mg once daily in patients with chronic liver disease.

Pharmacokinetics in subpopulations

Age, gender and race

A population pharmacokinetic analysis using plasma lusutrombopag concentrations from clinical studies with lusutrombopag did not identify a clinically meaningful effect of age, gender or race on the pharmacokinetics of lusutrombopag.

Paediatric population

No pharmacokinetic data have been obtained in children.

Renal impairment

Lusutrombopag is rarely excreted into urine (approximately 1%). A population pharmacokinetic analysis using plasma lusutrombopag concentrations from clinical studies with lusutrombopag did not identify a clinically meaningful effect of renal function on the pharmacokinetics of lusutrombopag.

Hepatic impairment

Mild and moderate hepatic impairment (mild, Child-Pugh class A; moderate, Child-Pugh class B) is expected to have little effect on the pharmacokinetics of lusutrombopag. The differences in pharmacokinetics of a single 0.75 mg dose of lusutrombopag were relatively small in both subjects with mild hepatic impairment and subjects with moderate hepatic impairment, compared with the healthy matched control group. Ratios of AUC relative to the healthy matched control group were 1.05 in subjects with mild hepatic impairment and 1.20 in subjects with moderate hepatic impairment.

The ranges of observed C_{max} and $AUC_{0-\tau}$ overlapped among the patients with Child-Pugh class A, B, and C. C_{max} and $AUC_{0-\tau}$ of all patients with Child-Pugh class C did not exceed the maximum values from Child-Pugh class A and class B. Due to the limited information available, lusutrombopag should not be used in Child-Pugh class C patients unless the expected benefit outweighs the expected risks.

5.3 Preclinical safety data

Lusutrombopag does not stimulate platelet production in the species used for toxicological testing because of unique human TPO receptor specificity. Thus, the data from the toxicology program in these animals do not present potential adverse effects related to exaggerated pharmacology in humans.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

In rats, lusutrombopag and its metabolites are excreted in milk, and the concentrations in milk decreased as with those in plasma.

Repeated toxicity

The principal toxicity findings associated with lusutrombopag administration included prolongation of PT and APTT (rats), increased activities of plasma ALT and AST (rats and dogs), adrenal toxicity (rats and dogs), skin and forestomach lesions (rats) and renal toxicity (rats).

High dose (10 mg/kg/day) and long-term treatment (8 weeks) of lusutrombopag has a potential risk of fibrosis in the bone marrow via human TPO receptor based on the results of study in TPOR-Ki/Shi mice with chimeric human transmembrane domain TPO receptor knocked-in to the mouse TPO receptor.

Carcinogenesis

Lusutrombopag was not carcinogenic to mice at doses up to 20 mg/kg/day in males and females (a dose at least 45 times the human clinical exposures in adults based on AUC), or rats at doses up to 20 mg/kg/day in males and 2 mg/kg/day in females (a dose 49 and 30 times, respectively, the human clinical exposures in adults based on AUC).

Mutagenesis

Lusutrombopag was not genotoxic when tested in a bacterial reverse mutation test, a chromosomal aberration test with cultured Chinese hamster lung cells, or an *in vivo* micronucleus test with mouse bone marrow cells.

Fertility

Lusutrombopag did not affect male and female fertility and early embryo development in rats at doses up to 100 mg/kg/day (176 and 252 times respectively, the human clinical exposures in adults based on AUC).

Embryo-foetal development

Lusutrombopag showed no teratogenicity in rats and rabbits at up to 80 mg/kg/day and 1000 mg/kg/day respectively. No effects on foetal viability embryo-foetal development were noted in rabbits at doses up to 1000 mg/kg/day (161 times the human clinical exposures in adults based on AUC). In rats, there were adverse effects of lusutrombopag on foetal intrauterine growth and skeletal morphology as follows: a suppression of foetal intrauterine growth (low foetal body weight and a decrease in the number of ossified sternebrae) at 80 mg/kg/day, and an high incidence of short cervical supernumerary ribs at 40 mg/kg/day or more, and an high incidence of short thoracolumbar supernumerary rib at 4 mg/kg/day or more. A suppression of foetal intrauterine growth as well as cervical ribs occurred at doses (40 mg/kg/day or more), showing maternal toxicity. Meanwhile, the short thoracolumbar supernumerary ribs were observed at doses without maternal toxicity. The changes were also noted in F1 pups on postnatal day (PND) 4 at 12.5 mg/kg/day or more in the pre- and postnatal development study; however, F1 mature animals showed no full and short thoracolumbar supernumerary rib. On the basis of the results, the no observed adverse effect level (NOAEL) was estimated to be near 4 mg/kg/day in the embryo-foetal development study in rats (23 times the human clinical exposures in adults based on AUC).

Pre- and post-natal development

In the pre- and postnatal development study in rats at doses up to 40 mg/kg/day, there were adverse effects of lusutrombopag on postnatal development at 40 mg/kg/day as follow: prolongation of gestation period in dams, low viability before weaning, delayed postnatal growth such as delayed negative geotaxis or delayed eyelid opening, low pup body weight, low female fertility index, a tendency to low number of corpora lutea or implantations, and a tendency to increased pre-implantation loss rate and an abnormal clinical sign such as prominent annular rings on tail after weaning. There were no effects on pregnancy, parturition, lactation in F0 dams and postnatal development in F1 pups at doses up to 12.5 mg/kg/day (89 times the human clinical exposures in adults based on AUC).

Phototoxicity

Lusutrombopag has no phototoxic potential in the skin phototoxicity study in hairless mice at doses up to 500 mg/kg (96.3 µg/mL) (613 times the human clinical exposures in adults based on C_{max} [0.157 µg/mL]).

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that lusutrombopag has the potential to be very persistent, very bioaccumulative and toxic to the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Microcrystalline cellulose
Magnesium oxide
Sodium lauryl sulfate
Hydroxypropylcellulose
Carmellose calcium
Magnesium stearate

Film-coating

Hypromellose
Titanium dioxide
Triethyl citrate
Talc
Red ferric oxide (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 temperature storage conditions. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

OPA/Aluminium foil/PVC film blister with push through aluminium lidding foil, packed in a cardboard box. Each box contains 7 film-coated tablets.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).

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

7. MARKETING AUTHORISATION HOLDER

Shionogi B.V.
Kingsfordweg 151,
1043GR Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1348

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/2019

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER(S) 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**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

MPF B.V. (Manufacturing Packaging Farmaca)
Appelhof 13
8465RX Oudehaske
NETHERLANDS

Shionogi B.V.
Kingsfordweg 151,
1043GR Amsterdam
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report 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 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.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Mupleo 3 mg film-coated tablets
lusutrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 3 mg lusutrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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

Store in the original package in order to protect from moisture.

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

Shionogi B.V.
Kingsfordweg 151,
1043GR Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1348

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mupleo

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Mupleo 3 mg film-coated tablets
lusutrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shionogi

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Mulpleo 3 mg film-coated tablets lusutrombopag

▼ 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, pharmacist, or nurse.
- 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, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mulpleo is and what it is used for
2. What you need to know before you take Mulpleo
3. How to take Mulpleo
4. Possible side effects
5. How to store Mulpleo
6. Contents of the pack and other information

1. What Mulpleo is and what it is used for

Mulpleo contains the active substance lusutrombopag, which belongs to a group of medicines called thrombopoietin receptor agonists. The medicine helps to increase the number of *platelets* in your blood. Platelets are blood components that help the blood to clot and so prevent bleeding.

Mulpleo is used to **reduce the risk of bleeding during surgery and other procedures** (including tooth extractions and endoscopy). It is given to adults who have low numbers of platelets because of chronic liver disease.

2. What you need to know before you take Mulpleo

Do not take Mulpleo:

- **if you are allergic** to lusutrombopag or any of the other ingredients of this medicine (listed in section 6 under '*What Mulpleo contains*').
 - **Check with your doctor** if this applies to you before you take Mulpleo

Warnings and precautions

Talk to your doctor:

- **if you are at risk of blood clots** in your veins or arteries, or if you previously have had blood clots
- **if you have severe liver disease**
- **if your spleen has been removed**
- **if you are having interferon treatment.**

► **Talk to your doctor** before taking Mulpleo, if any of these applies.

Signs of a blood clot: look out for any of the signs below:

- **swelling, pain, heat, redness, or tenderness in your leg**

- **sudden shortness of breath**, especially with sharp pain in the chest or rapid breathing
- **pain in the abdomen** (tummy), swollen abdomen, blood in your stools.
 - ▶ **Get medical help immediately** if you notice any of these.

Children and adolescents

Do not give this medicine to children or adolescents under the age of 18 years, because the medicine has not been studied in children and adolescents.

Other medicines and Mulpleo

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

Pregnancy and breast-feeding

Do not take Mulpleo if you are pregnant unless your doctor specifically recommends it. The effect of Mulpleo during pregnancy is not known.

- **Tell your doctor** if you are pregnant, think you may be pregnant, or are planning to have a baby.
- **Use reliable methods of contraception** while you are taking Mulpleo.
- **If you do become pregnant** during treatment with Mulpleo, tell your doctor **immediately**.

Do not breast-feed during treatment with Mulpleo, as it is not known if the medicine passes into milk.

→ **If you are already breast-feeding**, talk to your doctor immediately.

Driving and using machines

Mulpleo has no known effects on your ability to drive or to use machines.

Mulpleo 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 Mulpleo

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

Recommended dose: take one tablet once a day, at the same time each day, for seven days only. Take the tablet with a liquid and swallow it whole. Do not chew, break, or crush the tablet. You can take it with food or between meals.

Your treatment will start at least 8 days before your surgery or procedure. Do not change the dose or schedule for taking Mulpleo unless your doctor or pharmacist tells you to.

If you have severe liver disease, tell your doctor before taking Mulpleo.

If you take more than you should

If you have taken more Mulpleo than you should, talk to your doctor or go to the hospital. If possible, show them the pack, or this leaflet. You may be monitored for side effects associated with excessive platelets such as blood clots (see section 2, '*Warnings and precautions*', and section 4, '*Possible side effects*').

If you forget to take a tablet

If you miss a tablet of Mulpleo, take it as soon as you remember on the same day. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Mulpleo

Do not stop taking Mulpleo without talking to your doctor and do not take Mulpleo for more than 7 days.

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.

Higher risk of blood clots

Certain people may have a higher risk of blood clots, including people with liver disease, and medicines like Mulpleo could make this problem worse.

Signs of a blood clot: look out for any of the signs below:

- **swelling, pain, heat, redness,** or tenderness in **your leg**
 - **sudden shortness of breath,** especially with sharp pain in the chest or rapid breathing
 - **pain in the abdomen** (tummy), swollen abdomen, blood in your stools.
- **Get medical help immediately** if you notice any of these.

Common side effects

(may affect up to 1 in 10 people)

- Headache
- Nausea
- Blood clot in the liver (portal vein thrombosis)
- Rash.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Mulpleo

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 carton and blisters after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.

This medicine does not require any special temperature 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 Mulpleo contains

- The active substance is lusutrombopag. Each film-coated tablet contains 3 mg lusutrombopag.
- The other ingredients are:
 - **Tablet core:** mannitol, microcrystalline cellulose, magnesium oxide, sodium lauryl sulfate, hydroxypropylcellulose, carmellose calcium and magnesium stearate
 - **Film coating:** hypromellose, titanium dioxide, triethyl citrate, talc and red-ferric oxide (E172)

What Mulpleo looks like and contents of the pack

Mulpleo 3 mg film-coated tablets are light red, 7 mm, round, film-coated tablets debossed with the Shionogi trademark above the identifier code “551” on one side and debossed with the strength “3” on the other side.

Mulpleo is supplied in aluminium blisters in a carton containing 7 film-coated tablets.

Marketing Authorisation Holder

Shionogi B.V.
Kingsfordweg 151,
1043GR Amsterdam
The Netherlands

Manufacturer

Manufacturing Packaging Farmaca (MPF) B.V.
Appelhof 13
Oudehaske
8465RX
The Netherlands

Shionogi B.V.
Kingsfordweg 151,
1043GR Amsterdam
The Netherlands

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

AT, BE, BG, CY, CZ, DK, EE, IE, EL, FI, FR, HR, HU, IE, IS, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK
Shionogi B.V. Tel/Tel./Тел./Тlf/Tél/Puh/Sími/Τηλ:
+31 (0) 207038327
contact@shionogi.eu

DE
Shionogi GmbH
Tel: +49 (0)89 2109 3049
kontakt@shionogi.eu

ES
Shionogi SLU
Tel: +34 911 239 258
contacta@shionogi.eu

IT
Shionogi Srl
Tel: +39 06 94 805 118
contattaci@shionogi.eu

UK
Shionogi B.V.
Tel: +44 (0)20 3053 4190
contact@shionogi.eu

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.