ELOPAG®
Eltrombopag olamine
Film coated tablet

COMPOSITIONS :
ELOPAG® Film coated tablet 75 mg, each film coated tablet contains : Eltrombopag olamine equivalent to Eltrombopag 75 mg.

Description of the dosage form
ELOPAG® Film coated tablet 75 mg is yellow, round shaped bevel edged, biconvex film coated tablets, debossed with "E57" on one side and "H" on the other side.
Excipients : Microcrystalline Cellulose, mannitol, povidone, sodium starch glycolate, magnesium stearate, Instacoat universal yellow (Titanium Dioxide, Yellow Iron Oxide), purified water.

PHARMACOLOGY :
Pharmacotherapeutic group, ATC
Thrombopoietin-receptor agonist, B02BX 05

Mechanism of action (MOA)
Thrombopoietin (TPO) is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-receptor. Eltrombopag interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation of megakaryocytes and bone marrow progenitor cells.

Pharmacodynamics (PD)
Eltrombopag differs from TPO with respect to the effects on platelet aggregation. Unlike TPO, Eltrombopag treatment of normal human platelets does not enhance adenosine diphosphate (ADP)-induced aggregation or induce P-selectin expression. Eltrombopag does not antagonize platelet aggregation induced by ADP or collagen.

Pharmacokinetics (PK)
The study was designed as a open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy, adult human subjects under fasting conditions.
Based on Summary of Pharmacokinetic Data for Eltrombopag, Arithmetic mean ± Std Deviation (Coeff of Variation (%)) for test product showed : C_{max} (µg/mL) values were 7.784 ±2.774 (35.639), AUC72 (µg/mL)*(hr) values were 95.680 ±38.123 (39.844) and T_{max} (hr) values were 3.000 (1.667 - 5.500).
Results from bioequivalence study for Test Drug was as following : 90.00% Confidence Intervals of geometric means ratio of the two bioavailability parameters of Eltrombopag was 86.97%; 112.14% for C_{max} and 88.01%; 109.10% for AUC72.

Conclusion : These results showed that 75 mg Eltrombopag film coated tablet was bioequivalent to the reference product.

CLINICAL STUDIES FROM INNOVATOR PRODUCT OF ELTROMBOPAG FILM COATED TABLET

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

Adults

Two phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

TRA102537 (RAISE)

RAISE: 197 patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medication at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All subjects initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28% of eltrombopag treated patients were maintained on ≤25 mg and 29 to 53% received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥3 prior ITP therapies and 36% had a prior splenectomy.

Median platelet counts at baseline were 16,000/microL for both treatment groups and in the eltrombopag group were maintained above 50,000/microL at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained <30,000/microL throughout the study.

Platelet count response between 50,000 - 400,000/microL in the absence of rescue medication was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the 6-month treatment period.

Table 1. Secondary efficacy results from RAISE

	Eltrombopag n = 135	**Placebo n = 62**
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/microL, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75 % of assessments in the target range (50,000 to 400,000/microL), n (%)	51 (38)	4 (7)

P-value[a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
P-value[a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
P-value[a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
P-value[a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)b	37 (59)	10 32)
P-value[a]	0.16	

[a] *Logistic regression model adjusted for randomisation stratification variables*

[b] *21 out of 63 (33 %) patients treated with eltrombopag who were taking an ITP medication at baseline permanently discontinued all baseline ITP medications.*

At baseline, more than 70% of patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20% reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50% from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B

In TRA100773B, the primary efficacy endpoint was the proportion of responders, defined as patients who had an increase in platelet counts to ≥50,000/microL at Day 43 from a baseline platelet count <30,000/microL; patients who withdrew prematurely due to a platelet count >200,000/microL were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomized 2:1, with 76 randomized to **Innovator product** and 38 randomized to placebo.

Table 2. Efficacy results from TRA100773B

	Eltrombopag n = 74	**Placebo n = 38**
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥50,000/microL after up to 42 days of dosing (compared to a baseline count of <30,000/microL), n (%)	43 (59)	6 (16)
P-value[a]	< 0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)

P-value[a]	0.29

a Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medication use, splenectomy status and baseline platelet count (≤15,000/microL, >15,000/microL) at randomization.

In RAISE and TRA100773B studies, in the subgroup of patients with baseline platelet count ≤15,000/microL the median platelet counts did not reach the target level (>50,000/microL), although in both studies 43 % of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42% of patients with baseline platelet count ≤15,000/microL treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60% of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 299 patients in an open-label extension study, 126 patients completed 1 year, 48 completed 18 months and 17 completed 2 years. The median baseline platelet count was 19,500/microL prior to eltrombopag administration.

Median platelet counts at 12, 18 and 24 months on study were 68,000/microL, 75,000/microL and 119,000/microL, respectively.

Open label studies

TRA108057 (REPEAT)

TRA108057 was an open-label, repeat-dose, study which evaluated the efficacy, safety and consistency of response following repeated, intermittent, short-term dosing of eltrombopag over 3 cycles of therapy in adults with previously treated chronic ITP. A cycle was defined as an up to 6-week on-therapy period followed by an up to 4-week off-therapy period. The duration of both the on-therapy and the off-therapy periods was defined by the patient's platelet count. Patients were to interrupt treatment for the cycle if they achieved a platelet count >200,000/microL, or when they reached Week 6. Patients were to begin the next cycle when their platelet counts fell below 20,000/microL, or when they reached Week 4 of the off-therapy period. The primary endpoint in REPEAT was the proportion of 854 subjects who achieved a platelet count ≥50,000/microL and at least 2x baseline in Cycle 2 or 3, given this response in Cycle 1.

Table 3. Evaluable and responding patients in TRA108057

	Innovator product 50 mg (N=66)
Evaluable in Cycle 1, n Responders in Cycle 1, n (%)	65 52 (80)

Evaluable in Cycle 2 or 3, n	52
Responders in Cycle 1 and in Cycle 2 or 3, n (%)	45 (87)
Proportion	0.87
95% CI for Proportion (Exact Methods)	(0.74, 0.94)

Of the 52 patients who responded in Cycle 1, 33 (63%) achieved a platelet count of ≥50,000 microL and at least 2x baseline on Day 8 in Cycle 1; on Day 15, 37 (79%) of 47 evaluable patients achieved this level of response.
A reduction in any bleeding (WHO Grade 1-4) and clinically significant bleeding (WHO Grade 2-4) during the treatment phases was demonstrated in each cycle. At the baseline 863 visit of Cycle 1, 50% and 19% of patients reported any bleeding and clinically significant bleeding, respectively. At the Day 43 Visit of Cycle 1, the proportion of patients bleeding was reduced; 12% and 0% of patients reported any bleeding and clinically significant 866 bleeding, respectively. Similar results were found during the subsequent treatment cycles. Eight patients successfully managed 10 hemostatic challenges without need for additional therapy to elevate platelet counts and without unexpected bleeding.

TRA105325 (EXTEND)
TRA105325 was an open label extension study which has evaluated the safety and efficacy of **Innovator product** in patients with chronic ITP at least 6 months from diagnosis who were previously enrolled in an eltrombopag study. In this study, patients were permitted to modify their dose of study medication as well as decrease or eliminate concomitant ITP medications.

Innovator product was administered to 302 ITP patients; 218 completed 1 year of treatment, 180 completed 2 years, 107 completed 3 years, 75 completed 4 years, 34 completed 5 years and 18 completed 6 year of years of therapy. The median baseline platelet count was 19,000/microL prior to **Innovator product** administration. Median platelet counts at 1, 2, 3, 4, 5, 6, and 7 years on study were 85,000/microL, 85,000/microL, 105,000/microL, 879 64,000/microL, 75,000/microL , 119,000/microL and 76,000/microL, respectively. The median daily dose of **Innovator product** following 6 months of therapy was 50 mg (n=74).
At baseline, 59% of patients had any bleeding (WHO Bleeding Grades 1–4) and 18% had clinically significant bleeding. The proportion of patients with any bleeding and clinically significant bleeding decreased from baseline by approximately 50% for the 884 majority of assessments up to 1 year.
One-hundred and one patients were taking ITP medications at baseline upon entry into EXTEND study, and 39 patients were able to permanently discontinue or achieve a sustained reduction of at least one baseline ITP medication without needing rescue medication. Sixtyfive percent of these patients maintained this discontinuation or reduction for at least 24 weeks. Sixty-one percent of patients completely discontinued at least one baseline ITP medication, and 55% of patients permanently discontinued all baseline ITP medications, without subsequent rescue treatment.

Twenty-four patients experienced at least one hemostatic challenge during the study. No patients experienced unexpected bleeding complications related to the procedure while on study.

Pediatric patients
The safety and efficacy of **Innovator product** in pediatric patients with previously treated ITP have been demonstrated in two studies.

Double-blind placebo-controlled studies
TRA115450 (PETIT2)
The primary endpoint was a sustained response, defined as the proportion of patients receiving **Innovator product**, compared to placebo, achieving platelet counts ≥50,000/microL for at least 6 out of 8 weeks (in the absence of rescue therapy), between Weeks 5 to 12 during the double-blind randomized period. Patients were refractory or relapsed to at least one prior ITP therapy or unable to continue other ITP treatments for a medical reason and had platelet count <30,000/microL. Ninety-two patients were randomized by three age cohort strata (2:1) to **Innovator product** (n = 63) or placebo (n = 29). The dose of **Innovator product** could be adjusted based on individual platelet counts.
Overall, a significantly greater proportion of **Innovator product** patients (40%) compared with placebo patients (3%) achieved the primary endpoint (OR: 18.0 [95% CI: 2.3, 140.9] p < 0.001) which was similar across the three age cohorts (Table 4).

Table 4. Sustained platelet response rates by age cohort in pediatric patients with ITP at least 12 months from diagnosis in PETIT2*

	Innovator product n/N (%) [95% CI]	Placebo n/N (%) [95% CI]
Cohort 1 (12 to 17 years)	9/23 (39%) [20%, 61%]	1/10 (10%) [0%, 45%]
Cohort 2 (6 to 11 years)	11/26 (42%) [23%, 63%]	0/13 (0%) [N/A]
Cohort 3 (1 to 5 years)	5/14 (36%) [13%, 65%]	0/6 (0%) [N/A]
* Patients aged 6 to 17 years who were enrolled into Cohort 1 and Cohort 2 received eltrombopag tablets formulation. Patients aged 1 to 5 years who were enrolled into Cohort 3 received eltrombopag Powder for Oral Suspension (PfOS) formulation. Eltrombopag with Powder for Oral Suspension (PfOS) formulation is currently not registered in Indonesia.		

A significantly greater proportion of patients treated with **Innovator product** (75%) compared with placebo (21%) had a platelet response (at least one platelet count >50,000/microL duringthe first 12 weeks of randomized treatment in absence of rescue therapy) (OR: 11.7 [95% CI: 4.0, 34.5], p < 0.001). The proportion of patients who responded to **Innovator product** in the open-label 24-week period (80%) was similar to that observed during the randomized portion of the study.

Statistically fewer **Innovator product** patients required rescue treatment during the randomized period compared to placebo patients (19% [12/63] vs. 24% [7/29] p=0.032).

At baseline, 71% of patients in the **Innovator product** group and 69% in the placebo group reported any bleeding (WHO Grades 1-4). At Week 12, the proportion of **Innovator product** patients reporting any bleeding was decreased to half of baseline (36%). In comparison, at Week 12, 55% of placebo patients reported any bleeding.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the openlabel phase of the study and 53% (8/15) of patients were able to reduce (n = 1) or discontinue (n = 7) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

TRA108062 (PETIT)

The primary endpoint was the proportion of patients achieving platelet counts ≥50,000/microL at least once between Weeks 1 and 6 of the randomized period. Patients were refractory or relapsed to at least one prior ITP therapy with a platelet count <30,000/ (n = 67). During the randomized period of the study, patients were randomized by 3 age cohort strata (2:1) to **Innovator product** (n = 45) or placebo (n = 22). The dose of **Innovator product** could be adjusted based on individual platelet counts.

Overall, a significantly greater proportion of **Innovator product** patients (62%) compared with placebo patients (32%) met the primary endpoint (OR: 4.3 [95% CI: 1.4, 13.3] p = 0.011). Table 5 shows platelet response across the three age cohorts.

Table 5. Platelet response rates in pediatric patients with ITP at least 6 months from diagnosis in PETIT*

	Innovator product n/N (%) [95% CI]	**Placebo n/N (%) [95% CI]**
Cohort 1 (12 to 17 years)	10/16 (62%) [35%, 85%]	0/8 (0%) [N/A]
Cohort 2 (6 to 11 years)	12/19 (63%) [44%, 90%]	3/9 (33%) [7%, 70%]
Cohort 3 (1 to 5 years)	6/10 (60%) [26%, 88%]	4/5 (80%) [28%, 99%]
* Patients aged 6 to 17 years who were enrolled into Cohort 1 and Cohort 2 received eltrombopag tablets formulation. Patients aged 1 to 5 years who were enrolled into Cohort 3 received eltrombopag Powder for Oral Suspension (PfOS) formulation. Eltrombopag with Powder for Oral Suspension (PfOS) formulation is currently not registered in Indonesia		

A significantly greater proportion of patients treated with **Innovator product** (36%) compared with placebo (0%) had a platelet response (platelet counts >50,000/microL for at least 60% of assessments between Weeks 2 and 6) (OR: 5.8, [95% CI: 1.2, 28.9], p = 0.002).

Statistically fewer **Innovator product**-treated patients required rescue treatment during the randomized period compared to placebo treated patients (13% [6/45] vs. 50% [11/22], p = 0.002).

At baseline, 77.7% of patients in the **Innovator product** group and 81.8% in the placebo group reported any bleeding (WHO Grades 1-4). The proportion of **Innovator product** patients reporting any bleeding decreased to 22.2% at Week 6. In comparison, 72.7% of placebo patients reported any bleeding at Week 6.

Patients were permitted to reduce or discontinue baseline ITP therapy only during the openlabel phase of the study and 46% (6/13) of patients were able to reduce (n = 3) or discontinue (n = 3) baseline ITP therapy, mainly corticosteroids, without needing rescue therapy.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of **Innovator product** for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomized, double-blind, placebo- controlled studies. ENABLE 1 utilized peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b plus ribavirin. In both studies, patients with a platelet count of <75,000/microL were enrolled and stratified by platelet count (<50,000/microL and ≥50,000/microL to <75,000/microL), screening HCV RNA (<800,000 IU/mL and ≥800,000 IU/mL), and HCV genotype (genotype 2/3, and genotype 1/4/6).

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, patients received open-label **Innovator product** to increase the platelet count to ≥90,000/microL for ENABLE 1 and ≥100,000/microL for ENABLE 2. **Innovator product** was administered at an initial dose of 25 mg once daily for 2 weeks and increased in 25 mg increments over 2 to 3 week periods to achieve the required platelet count for phase 2 of the study. The maximal time patients could receive open-label **Innovator product** was 9 weeks. If sufficient platelet counts were achieved, patients were randomized (2:1) to the same dose of **Innovator product** at the end of the pre-treatment phase or to placebo. **Innovator product** was administered in combination with antiviral treatment per their respective prescribing information for up to 48 weeks.

The primary efficacy endpoint for both studies was sustained virological response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period. Approximately 70% of patients were genotype 1/4/6 and 30% were genotype 2/3. Approximately 31% of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet counts (approximately 60,000/microL) were similar among all treatment groups. The median time to achieve the target platelet count ≥90,000/microL (ENABLE 1) or ≥100,000/microL (ENABLE 2) was 2 weeks.

In both HCV studies, a significantly greater proportion of patients treated with **Innovator product** achieved SVR compared to those treated with placebo (see Table 4). Significantly fewer patients treated with **Innovator product** had any antiviral dose reductions compared to placebo. The proportion of patients with no antiviral dose reductions was 45% for **Innovator product** compared to 27% for placebo. Significantly fewer patients treated with **Innovator product** prematurely discontinued antiviral therapy compared to placebo (45% vs. 60%, p = < 0.0001). The majority of patients treated with **Innovator product** (76 %) had minimum platelet counts that were ≥50,000/vL compared to 19% for placebo. A greater proportion of subjects in the placebo group (20%) had minimum platelet counts fall below 25,000/microL during treatment compared to the **Innovator product** group (3%). In the **Innovator product** group, SVR rates in patients with high viral loads (>800,000) were 18% as compared to 8% in the placebo group. Significantly more patients reached the later antiviral milestones of early virologic response (EVR), complete early virologic response (cEVR), end of treatment response (ETR) and sustained virologic response at 12-week follow-up (SVR12) when treated with **Innovator product**.

Table 6. ENABLE 1 and ENABLE 2 virologic response

Pre-antiviral Treatment Phase % Achieving target platelet counts and initiating antiviral therapy[c]	**ENABLE 1[a]** N = 715 95%		**ENABLE 2[b]** N = 805 94%	
	Innovator product n = 450	Placebo n = 232	**Innovator product** n = 506	Placebo n = 25
Antiviral Treatment Phase	%	%	%	%
Overall SVR[d]	23	14	19	13
Overall EVR[d]	66	50	62	41

[a] **Innovator product** *given in combination with peginterferon alfa-2a (180 microg once weekly for 48 weeks for genotypes 1 or 4; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)*

[b] **Innovator product** *given in combination with peginterferon alfa-2b (1.5 microg/kg once weekly for 48 weeks for genotype 1; 24 weeks for genotype 2 or 3) plus ribavirin (800 to 1400 mg orally)*

[c] *Target platelet count was ≥90,000/microL for ENABLE 1 and ≥100,000/microL for ENABLE 2 d*

[d] *P value <0.05 for* **Innovator product** *versus placebo*

Severe Aplastic Anaemia

CETB115AUS28T

Innovator product was studied in a single-arm, single-center open-label study in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count ≤30,000/microL.

Innovator product was administered at an initial dose of 50 mg once daily for 2 weeks and increased over 2 week periods up to a maximum dose of 150 mg once daily. The primary endpoint was hematological response assessed after 12 weeks of **Innovator product** treatment.

Innovator product was discontinued after 16 weeks if no hematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study.

Hematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/microL above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase by >1.5 g/dL (for patients with pre-treatment hemoglobin <9 g/dL), or a reduction in the volume of RBC transfusions of at least 4 units for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100% (for patients with pre-treatment ANC <500/microL) or an ANC increase 500/microL.

The treated population had median age of 45 years (range 17 to 77 years) and 56% of patients were male. At baseline the median platelet count was 20,000/microL, hemoglobin was 8.4 g/dL, and ANC was 580/microL. Eighty-six percent of patients were RBC transfusion dependent, and 91% were platelet transfusion dependent. The majority of patients (84%) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

A total of 17 patients (40%) met the hematologic response criteria in at least 1 lineage at the Primary Response Assessment (95% CI: 25, 56).

Multi-lineage responses were observed in 4/17 responders (24%) at the initial response assessment and in 9/17 responders (53%) at last assessment. Of the five patients who met protocol specified 'tri-lineage hematopoiesis' criteria for at least eight weeks and were tapered off **Innovator product**, all five patients have maintained tri-lineage hematopoiesis since discontinuing treatment for a median follow up period of 20.6 months (range 5.7 to 22.5 months).

The majority of responders met platelet response criteria (65%), followed by neutrophil and hemoglobin response criteria (47% and 18% respectively). The 15 responders who had at least 2 response assessments were evaluable for assessment of response duration and had a median duration of response of 12.0 months.

Nine of the 17 responders had a multi-lineage best response. Of the 14 patients who entered the extension, seven had improvement in more than one lineage following continuation of treatment: five patients with uni-lineage response improved to multi-lineage response (bi- or tri-lineage) and two patients with bi-lineage response improved to tri-lineage response. Three of the four bi-lineage responders also had meaningful improvements in hemoglobin (>1.5 g/dL); however, as their baseline hemoglobin was above 9 g/dL they are not counted as having an erythroid response.

The longest platelet transfusion free period in responders ranged from 8 to 1,190 days with a median of approximately 287 days. The longest RBC transfusion free period in responders ranged from 15 to 1,190 days with a median of approximately 266 days. Of the five patients who met protocol specified 'tri-lineage hematopoiesis' criteria for at least eight weeks and were tapered off **Innovator product**, all five patients have maintained tri-lineage hematopoiesis since discontinuing treatment for a median follow up period of 20.6 months (range 5.7 to 22.5 months).

PHARMACOKINETICS INTERACTIONS FROM INNOVATOR PRODUCT OF ELTROMBOPAG FILM COATED TABLET

Pharmacokinetics (PK)

The plasma eltrombopag concentration-time data collected in 88 subjects with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag AUC(0-τ) and Cmax estimates for ITP subjects are presented (Table 7).

Table 7. Geometric mean (95 % confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	AUC(0-τ)[a], microgram.h/mL	Cmax[a], microgram/mL
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

[a] *AUC(0-τ) and Cmax based on population PK post-hoc estimates.*

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from subjects with HCV enrolled in the Phase II study TPL102357 and healthy adult patients in a population PK analysis. Plasma eltrombopag Cmax and AUC(0-τ) estimates for patients with HCV enrolled in the Phase III studies are presented for each dose studied in Table 8. A higher eltrombopag exposure was observed in patients with HCV at a given **Innovator product** dose.

Table 8. Geometric mean (95% CI) steady-state plasma Eltrombopag pharmacokinetic parameters in patients with chronic HCV

Innovator product dose (once daily)	N	Cmax (microgram/mL)	AUC(0-τ) (microgram.h/mL)
25 mg	330	6.40 (5.97, 6.86)	118 (109, 128)
50 mg	119	9.08 (7.96, 10.35)	166 (143, 192)
75 mg	45	16.71 (14.26, 19.58)	301 (250, 363)
100 mg	96	19.19 (16.81, 21.91)	354 (304, 411)

Data presented as geometric mean (95%CI). AUC(0-τ) and Cmax based on population PK post-hoc estimates at the highest dose in the data for each subject.

Absorption

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see Dosage regimen and administration). The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52%.

Distribution

Eltrombopag is highly bound to human plasma proteins (>99.9%), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation/metabolism

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64% of plasma radiocarbon AUCinf. Minor metabolites due to glucuronidation and oxidation were also detected. Based on a human study with radiolabel eltrombopag, it is estimated that approximately 20% of a dose is metabolized by oxidation.

Elimination
Absorbed eltrombopag is extensively metabolized. The predominant route of eltrombopag excretion is via feces (59%) with 31% of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in feces accounts for approximately 20% of the dose. The plasma elimination halflife of eltrombopag is approximately 21-32 hours.

In Vitro evaluation of drug interaction potential
Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21% of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see **DRUG INTERACTIONS**).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section Interactions). In clinical studies with eltrombopag, a dose reduction of statins by 50% was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see section Dosage regimen and administrations and section Interactions). *In vitro* studies identified CYP1A2 and CYP2C8 as the isoenzymes responsible for oxidative metabolism, uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 as the isozymes responsible for glucuronidation and that bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathways.

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter (IC50 value of 2.7 microM (1.2 microgram/mL). *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor (IC50 value of 2.7 microM (1.2 microgram/mL)).

Special populations
Renal impairment
The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the AUCinf of eltrombopag was 32% to 36% lower in subjects with mild to moderate renal impairment, and

60 % lower in subjects with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see **DOSAGE AND ADMINISTRATIONS**).

Hepatic impairment

The pharmacokinetics of eltrombopag have been studied after administration of eltrombopag to adult subjects with hepatic impairment. Following the administration of a single 50 mg dose, the AUC_{inf} of eltrombopag was 41% higher in subjects with mild hepatic impairment and 80% to 93% higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 subjects with hepatic impairment (673 subjects with HCV and 41 subjects with chronic liver disease of other aetiology). Of the 714 subjects, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with sever hepatic impairment. Compared to healthly volunteers, subjects with mild hepatic impairment had approximately 111% (85% CI: 45% to 283%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and subjects with moderate hepatic impairment had approximately 183% (95% CI: 90% to 459%) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (ChildPugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section Dosage regimen and administration and section Warning and precautions). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see **DOSAGE AND ADMINISTRATIONS**).

Race/Ethnicity

The influence of East-Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population PK analysis in 111 healthy adults (31 East-Asians) and 88 subjects with ITP (18 East-Asians). Based on estimates from the population PK analysis, East-Asian ITP subjects had approximately 87% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East-Asian subjects who were predominantly Caucasian, without adjustment for body weight differences (see **DOSAGE AND ADMINISTRATIONS**).

The influence of Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population PK analysis in 663 patients with HCV (214 East-Southeast-Asians). Based on estimates from the population PK analysis, East-Southeast-Asian patientshad similar pharmacokinetics of eltrombopag. On average, East-Southeast-Asian patientshad approximately 55% higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to subjects of other races who were predominantly Caucasian (see **DOSAGE AND ADMINISTRATIONS**).

Gender
The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population PK analysis in 111 healthy adults (14 females) and 88 subjects with ITP (57 females). Based on estimates from the population PK analysis, female ITP subjects had approximately 50% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male subjects, without adjustment for body weight differences.
The influence of gender on eltrombopag pharmacokinetics was evaluated using a population PK analysis in 663 patients with HCV (260 females). Based on model estimates, female HCV subjects had approximately 41% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male subjects.

Geriatric patients (60 years of age or above)
The age difference of eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects and 635 subjects with HCV ranging from 19 to 74 years old. Based on model estimates, elderly (>60 years) subjects had approximately 36% higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see **DOSAGE AND ADMINISTRATIONS**).

Pediatric population
The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric ITP subjects dosed once daily in two studies, TRA108062/PETIT and TRA115450/PETIT- 2. Plasma eltrombopag apparent clearance following oral administration (CL/F) increased with increasing body weight. Approximately 30% lower plasma eltrombopag CL/F was observed in subjects of East/Southeast-Asian race and 20% lower CL/F was observed in female subjects. The pharmacokinetic parameters of eltrombopag in pediatric subjects with ITP are shown in Table 9.

Table 9. Geometric Mean (95% CI) Steady-State Plasma Eltrombopag Pharmacokinetic Parameters in Pediatric Subjects with ITP (50 mg Once Daily Dosing Regimen

Age	**Cmax (microgram/mL)**	**AUCtau (microgram.hr/mL)**
12 to 17 years (n=62)	6.80 (6.17, 7.50)	103 (91.1, 116)
6 to 11 years (n=68)	10.3 (9.42, 11.2)	153 (137, 170)
1 to 5 years (n=38)	11.6 (10.4, 12.9)	162 (139, 187)
Data presented as geometric mean (95%CI). AUCtau and Cmax based on population PK post-hoc estimates for a 50 mg once daily dose.		
Patients aged 6 to 17 years who were enrolled into Cohort 1 and Cohort 2 received eltrombopag tablets formulation. Patients aged 1 to 5 years who were enrolled into Cohort 3 received eltrombopag Powder for Oral Suspension (PfOS) formulation. *Eltrombopag with Powder for Oral Suspension (PfOS) formulation is currently not registered in Indonesia.*		

NON-CLINICAL SAFETY DATA FROM INNOVATOR PRODUCT OF ELTROMBOPAG FILM COATED TABLET

Safety pharmacology and repeat dose toxicity

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥6 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 3 times the human clinical exposure based on AUC in HCV patients at 100 mg/day, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥4 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2 times the human clinical exposure based on AUC in HCV patients at 100 mg/day, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. Cataracts have not been observed in dogs after 52 weeks of dosing (2 times the human clinical exposure based on AUC) (see section Warnings and precautions).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure based on AUC in HCV patients at 100 mg/day. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times respectively, the human clinical exposure based on AUC in ITP patients at 75 mg/day and 2 times and equivalent, respectively, to the human clinical exposure in HCV patients at 100 mg/day. Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) or dogs (52 weeks) at exposures up to 4 or 2 times, respectively, the human clinical exposure based on AUC.

At poorly tolerated doses in rats and dogs (>10 times maximum human clinical exposure based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times maximum human clinical exposure based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non- tolerated dose of 60 mg/kg/day (6 times maximum human clinical exposure based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times maximum human clinical exposure based on AUC.

Carcinogenicity and mutagenicity

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure based on AUC in ITP patients at

75 mg/day and 2 times the human clinical exposure based on AUC in HCV patients at 100 mg/day). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two in vivo assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure based on Cmax in ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day). In the in vitro mouse lymphoma assay, eltrombopag was marginally positive (<3-fold increase in mutation frequency). These in vitro and in vivo findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Reproductive toxicity
Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.5 times the human clinical exposure based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F1). Eltrombopag was detected in the plasma of all F1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

Juvenile animal studies
At non-tolerated doses in pre-weaning rats, ocular opacities were observed. However, at tolerated doses, no ocular opacities were observed (see section Non-clinical safety data, Safety pharmacology and repeat dose toxicity).

INDICATION :
- **ELOPAG®** is indicated for the treatment of thrombocytopenia in patients aged 6 years and above with chronic immune (idiopathic) thrombocytopenia purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- **ELOPAG®** should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding.
- **ELOPAG®** should not be used in an attempt to normalize platelet counts.
- **ELOPAG®** is indicated in adult patients with chronic hepatitis C virus (HCV) infection whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy.
- **ELOPAG®** is indicated for the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.

CONTRAINDICATIONS :
Hypersensitivity to **ELOPAG®** or to any of the excipients.

DOSAGE AND ADMINISTRATIONS :
Dosage Regimen
ELOPAG® treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.
ELOPAG® dosing requirements must be individualized based on the patient's platelet counts. The objective of treatment with **ELOPAG®** should not be to normalise platelet counts but to maintain platelet counts above the level for haemorrhagic risk (>50,000/microL). In most patients, measurable elevations in platelet counts take 1 - 2 weeks.

General target population
Chronic immune (idiopathic) thrombocytopenia (ITP)
The lowest dose of **ELOPAG®** should be used to achieve and maintain a platelet count ≥50,000/microL. Dose adjustments are based upon the platelet count response. **ELOPAG®** should not be used to normalize platelet counts. Platelet counts generally increased within 1 to 2 weeks after starting **ELOPAG®** and decreased within 1 to 2 weeks after discontinuation.

Initial dose regimen
Adults and pediatric patients aged 6 to 17 years
The recommended starting dose of **ELOPAG®** is 50 mg once daily. For patients of East-/Southeast-Asian ancestry, **ELOPAG®** should be initiated at a reduced dose of 25 mg once daily.

Monitoring and dose adjustment
After initiating **ELOPAG®**, the dose should be adjusted to achieve and maintain a platelet count ≥50,000/microL as necessary to reduce the risk for bleeding. A daily dose of 75 mg should not be exceeded.
Clinical haematology and liver tests should be monitored regularly throughout therapy with **ELOPAG®** and the dose regimen of **ELOPAG®** should be modified based on platelet counts as outlined in Table 10. During therapy with **ELOPAG®** complete blood counts (CBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥50,000/microL for at least 4 weeks) has been achieved. CBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.
The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Table 10. Dose adjustments of ELOPAG® in ITP patients

Platelet count	Dose adjustment or response
< 50,000/microL following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥ 50,000/microL to ≤ 150,000/microL	Use lowest dose of Eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/microL to ≤ 250,000/microL	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/microL	Discontinue Eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/microL, reinitiate therapy at a daily dose reduced by 25 mg.

ELOPAG® can be administered in addition to other ITP medicinal products. Modify the dose regimen of concomitant ITP medicinal products, as medically appropriate, to avoid excessive increases in platelet counts during therapy with **ELOPAG®**.

To see the effect of any dose adjustment on the patient's platelet response prior to considering another dose increase one should wait for at least 2 weeks.

The standard **ELOPAG®** dose adjustment, either decrease or increase, would be 25 mg once daily. However, in a few patients a combination of different film-coated tablet strengths on different days or less frequent dosing may be required.

Discontinuation
Treatment with **ELOPAG®** should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of **ELOPAG®** therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section **WARNINGS AND PRECAUTIONS**).

Chronic Hepatitis C (HCV) associated thrombocytopenia
When **ELOPAG®** given in combination with antiviral therapies reference should be made to the full prescribing information of the respective co-administered medicinal products for comprehensive details of administration.

The lowest dose of **ELOPAG®** to achieve and maintain a platelet count necessary to initiate and optimize antiviral therapy should be used. Dose adjustments should be based upon the platelet

count response. **ELOPAG®** should not be used to normalize platelet counts. Platelet counts generally increase within 1 week of starting **ELOPAG®**.

Initial Dose Regimen

Adults

ELOPAG® should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East-Southeast-Asian ancestry, or patients with mild hepatic impairment.

Monitoring and dose adjustment

The dose of **ELOPAG®** should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate antiviral therapy (see Table 11). Platelet counts should be monitored every week prior to starting antiviral therapy.

During antiviral therapy the dose of **ELOPAG®** should be adjusted as necessary to avoid dose reduction of peginterferon. Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved. CBC's, including platelet counts and peripheral blood smears should be obtained monthly thereafter.

A dose of 100 mg **ELOPAG®** once daily should not be exceeded.

For specific dosage instructions for Peginterferon alfa or Ribavirin, one should refer to their respective prescribing information.

Table 11. ELOPAG® dose adjustments in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
< 50,000/microL following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day
≥ 200,000/microL to ≤ 400,000/microL	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 400,000/microL	Discontinue **ELOPAG®**; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is < 150,000/microL, reinitiate therapy at a lower daily dose*.

* For patients taking 25 mg **ELOPAG®** once daily, consideration should be given to reinitiating dosing at 12.5 mg once daily or alternatively a dose of 25 mg every other day.

Discontinuation

The prescribing information for Pegylated interferon and Ribavirin include recommendations for antiviral treatment discontinuation for treatment futility. Refer to Pegylated interferon and Ribavirin prescribing information for discontinuation recommendations for antiviral treatment futility.

ELOPAG® treatment should be terminated when antiviral therapy is discontinued. Excessive platelet count responses, as outlined in Table 11 or important liver test abnormalities may also necessitate discontinuation of **ELOPAG®** (see **WARNINGS AND PRECAUTIONS**).

Children
The safety and efficacy of **ELOPAG®** in pediatric patients with chronic HCV have not been established.

Severe Aplastic Anaemia
Initial Dose Regimen
Adults
ELOPAG® should be initiated at a dose of 50 mg once daily. For SAA patients of East-/ Southeast-Asian ancestry, **ELOPAG®** should be initiated at a dose of 25 mg once daily.

Monitoring and dose adjustment
Hematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting **ELOPAG®**. Adjust the dose of **ELOPAG®** in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥50,000/microL.
Do not exceed a dose of 150 mg daily. Monitor clinical hematology and liver tests regularly throughout therapy with **ELOPAG®** and modify the dosage regimen of **ELOPAG®** based on platelet counts as outlined in Table 12.

Table 12. ELOPAG® dose adjustments in SAA patients

Platelet count	**Dose adjustment or response**
<50,000/microL following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients of East-/Southeast-Asian ancestry or those with hepatic impairment taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥200,000/microL to ≤400,000/microL at any time	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
>400,000/microL	Discontinue **ELOPAG®** for at least one week. Once the platelet count is <150,000/microL, reinitiate therapy at a dose reduced by 50 mg.
>400,000/microL after 2 weeks of therapy at lowest dose of **ELOPAG®**	Discontinue **ELOPAG®**

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders
Once platelet count >50,000/microL, hemoglobin >10 g/dL in the absence of red blood cell (RBC) transfusion, and absolute neutrophil (ANC) >1 x 109/L for more than 8 weeks, the dose of **ELOPAG®** should be reduced by up to 50%. If counts stay stable after 8 weeks at the reduced dose, then discontinue **ELOPAG®** and monitor blood counts. If platelet counts drop to

<30,000/microL, hemoglobin to <9 g/dL or ANC <0.5 x 10^9/L, **ELOPAG®** may be reinitiated at the previous dose.

Discontinuation
If no hematological response has occurred after 16 weeks of therapy with **ELOPAG®**, discontinue therapy. Consider **ELOPAG®** discontinuation if new cytogenetic abnormalities are observed (see **ADVERSE DRUG REACTIONS**). Excessive platelet count responses (as outlined in Table 12) or important liver test abnormalities also necessitate discontinuation of **ELOPAG®** (see **WARNINGS AND PRECAUTIONS**).

Children
The safety and efficacy of **ELOPAG®** in pediatric patients with SAA have not been established

Special populations (all indications)
Renal impairment
No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use **ELOPAG®** with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis.

Hepatic impairment
ELOPAG® should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see **WARNINGS AND PRECAUTIONS**). If the use of **ELOPAG®** is deemed necessary for ITP patients with hepatic impairment, the starting dose must be 25 mg once daily. After initiating the dose of **ELOPAG®** in patients with hepatic impairment, wait 3 weeks before increasing the dose.

Thrombocytopenic patients with chronic HCV with hepatic impairment and severe aplastic anaemia patients with hepatic impairment should initiate **ELOPAG®** at a dose of 25 mg once daily.

The risk of thromboembolic events (TEEs) has been found to be increased in patients with chronic liver disease treated with 75 mg Eltrombopag once daily for two weeks in preparation for invasive procedures (see **WARNINGS AND PRECAUTIONS** and **ADVERSE DRUG REACTIONS**).

Pediatric patients
ELOPAG® tablets were administered to patients aged 6 - 17 years, while **ELOPAG®** powder for oral solution (PfOS) were administered to patients aged 1 to 5 years. Since **ELOPAG®** is only available as tablet, the use in patients with ITP below the age of 6 years is not recommended as they are unable to swallow whole tablets.
The safety and efficacy of **ELOPAG®** has not been established in pediatric patients (<18 years) with chronic HCV related thrombocytopenia.

Geriatric patients (65 years of age or older)
There are limited data on the use of **ELOPAG®** in patients aged 65 years and older. Overall no clinically significant differences in safety of **ELOPAG®** were observed between subjects aged at least 65 years and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

East-/Southeast-Asian patients
For adult and pediatric patients of East-/Southeast-Asian ancestry, **ELOPAG®** should be initiated at a dose of 25 mg once daily for the treatment of ITP and HCV-associated thrombocytopenia and SAA.

Method of administration
The tablets should be administered orally. It is not recommended to split or crush the tablet. **ELOPAG®** should be taken at two hours before or four hours after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see **DRUG INTERACTIONS**). **ELOPAG®** may be taken with food containing little (<50 mg) or preferably no calcium (see **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS :

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopoenic HCV patients with advanced chronic liver disease, as defined by low albumin levels (smaller is equal to) 35 g/l or model for end stage liver disease (MELD) score (bigger is equal to) 10, when treated with Eltrombopag in combination with interferon-based therapy. IN addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin (smaller is equal to) 35 g/l) compared with the group overall. Treatment with Eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

The diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical entities presenting with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs.
The effectiveness and safety of Eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia and myelodysplastic syndromes (MDS).

Combination with direct-acting antiviral agents
Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.

Hepatotoxicity
Eltrombopag administration can cause hepatobiliary laboratory abnormalities, severe hepatotoxicity, and potentially fatal liver injury.

In clinical studies of adult and pediatric patients with chronic ITP who received Elrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see **ADVERSE DRUG REACTIONS**).

These findings were mostly mild (Grade 1 - 2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. In two placebo controlled studies in adults with chronic ITP, adverse events of ALT increase were reported in 5.7% and 4.0% of Eltrombopag and placebo treated patients, respectively. In two placebo controlled studies in pediatric subjects with chronic ITP, ALT ≥3 times the upper limit of normal (x ULN) was reported in 4.7% and 0% of the eltrombopag and placebo groups, respectively.

In two controlled clinical studies in thrombocytopenic patients with HCV, ALT or AST >3 x ULN were reported in 34% and 38% of the Eltrombopag and placebo groups, respectively. Eltrombopag administration in combination with Peginterferon/Ribavirin therapy is associated with indirect hyperbilirubinaemia. Overall, total bilirubin ≥1.5 x ULN was reported in 76% and 50% or the Eltrombopag and placebo groups, respectively.

In the single arm, monotherapy study in patients with SAA, concurrent ALT or AST >3 x ULN with total (indirect) bilirubin >1.5 x ULN were reported in 5% of patients. Total bilirubin >1.5 x ULN occurred in 14% of patients.

In patients with ITP, HCV, and SAA, serum ALT, AST and bilirubin should be measured prior to initiation of Eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, fractionation should be performed. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilize, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥3 x ULN) in patient with normal liver function or ≥3 x baseline in patients with elevations in transaminases before treatment and are :
- progressive, or
- persistent for ≥4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic 261 decompensation.

Caution should be exercised when administering Eltrombopag to patients with hepatic disease. In ITP and SAA patients, a lower starting dose of Eltrombopag should be used when administering

to patients with hepatic impairment (see **DOSAGE REGIMEN AND ADMINISTRATION**, Hepatic impairment).
Isolated cases of severe liver injury were identified in clinical studies. The elevation of liver laboratory values improved or resolved following Eltrombopag interruption or discontinuation. No cases of severe liver injury related to Eltrombopag were identified in a clinical study in patients with SAA, however, the number of exposed patients in these indications was limited. As the highest authorized dose is administered to patients in the SAA indications (150 mg/day) and due to the nature of the reaction, drug-induced liver injury might be expected in this patient population.

Hepatic decompensation (use with interferon)
Hepatic decompensation in patients with chronic hepatitis C : Monitoring is required in patients with low albumin levels (≤35g/L) or with MELD score ≥10 at baseline.

Chronic HCV patients with liver cirrhosis may be at risk for hepatic decompensation, some with fatal outcomes, when receiving alpha interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV hepatic decompensation were occurred more frequently in the Eltrombopag arm (13%) than in the placebo arm (7%). Patients with low albumin levels (<3.5 g/dL) or with a Model for End-Stage Liver Disease (MELD) score ≥10 at baseline had a greater risk of hepatic decompensation. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon prescribing information for discontinuation criteria should be referred to. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications
Platelet counts above the normal range present a theoretical risk of thrombotic/thromboembolic complications. In Eltrombopag clinical studies in ITP thromboembolic events were observed at low and normal platelet counts.
Caution should be used when administering Eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing Eltrombopag treatment if the platelet count exceeds the target levels (see **DOSAGE AND ADMINISTRATIONS**). The risk-benefit balance should be considered in patients at risk of thromboembolic events of any aetiology.
In adult ITP studies, 21 thromboembolic/thrombotic events (TEE) were observed in 42 out of 763 patients (5.5%). The TEEs included: embolism including pulmonary embolism, deep vein thrombosis, trans. The TEEs included: Embolism including pulmonary embolism, deep vein thrombosis, transient ischaemic attack, myocardial infarction, ischemic stroke, and suspected PRIND (prolonged reversible ischemic neurologic deficiency).
No cases of TEEs were identified in a clinical study in SAA patients, however, the number of exposed patients in this indication was limited. As the highest authorized dose is administered to

patients in the SAA indication (150 mg/day) and due to the nature of the reaction, TEEs might be expected in this patient population.

Eltrombopag should not be used in patients with hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering **ELOPAG®** to patients with hepatic impairment (see **DOSAGE AND ADMINISTRATIONS** and **ADVERSE DRUG REACTIONS**, Hepatic impairment).

In two controlled Phase III studies in thrombocytopenic patients with HCV receiving interferon based therapy, 31 out of 955 patients (3%) treated with Eltrombopag experienced a TEE (3%) and 5 out of 484 patients (1%) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (1% in patients treated with Eltrombopag versus < 1% for placebo). No specific temporal relationship between start of treatment and occurrence of TEE was observed. The majority of TEEs resolved and did not lead to the discontinuation of antiviral therapy.

In a controlled study in thrombocytopenic patients with chronic liver disease (n = 288, safety population) undergoing elective invasive procedures, the risk of portal vein thrombosis was increased in patients treated with 75 mg Eltrombopag once daily for 14 days. Six of 143 (4%) adult patients with chronic liver disease receiving Eltrombopag experienced TEEs (all of the portal venous system) and two out of 145 (1%) patients in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five Eltrombopag treated patients with a TEE experienced the event within 14 days of completing Eltrombopag dosing and at a platelet count above 200,000 microL
Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

Bleeding following discontinuation of Eltrombopag
Thrombocytopenia is likely to reoccur upon discontinuation of treatment with Eltrombopag. Following discontinuation of Eltrombopag, platelet counts returned to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding. This risk is increased if Eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with Eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of Eltrombopag.

Bone marrow reticulin formation and risk of bone marrow fibrosis
Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin-receptor (TPO-R) agonists, has not been established yet. Prior to initiation of Eltrombopag the peripheral blood smear

should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of Eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with Eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA
Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether Eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II refractory SAA clinical study with eltrombopag with a starting dose of 50 mg/day (escalated every 2 weeks to a maximum of 150 mg/day) (ELT112523), the incidence of new cytogenetic abnormalities was observed in 17.1% of adult patients [7/41 (where 4 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.
In the phase II refractory SAA clinical study with eltrombopag at a dose of 150 mg/day (with ethnic or age related modifications as indicated) (ELT116826), the incidence of new cytogenetic abnormalities was observed in 22.6% of adult patients [7/31 (where 3 of them had changes in chromosome 7)]. All 7 patients had normal cytogenetics at baseline. Six patients had cytogenetic abnormality at Month 3 of eltrombopag therapy and one patient had cytogenetic abnormality at Month 6.
In clinical studies with Eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of Eltrombopag treatment.
For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of Eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, it must be evaluated whether continuation of Eltrombopag is appropriate.

Malignancies and progression of malignancies
There is a theoretical concern that they may stimulate the progression of existing hematopoietic malignancies such as MDS. TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage.

The effectiveness and safety of Eltrombopag have not been established for the treatment of thrombocytopenia due to MDS. Eltrombopag should not be used outside of clinical studies for the treatment of thrombocytopenia due to MDS.

A randomized, double-blind, placebo-controlled, multicenter study in patients with International Prognostic Scoring System (IPSS) intermediate-1, intermediate-2 or high risk myelodysplastic syndrome (MDS) with thrombocytopenia, receiving azacitidine in combination with either Eltrombopag or placebo, was terminated due to futility and increased MDS progression, including

to AML. A total of 356 patients (179 on Eltrombopag, 177 on placebo) were randomized 1:1 and stratified by the International Prognostic Scoring System (IPSS): intermediate-1 (n = 64 [36%]), intermediate-2 (n = 79 [44%]), high-risk (n = 36 [20%]) in the Eltrombopag arm versus intermediate-1 (n = 65 [37%]), intermediate- 2 (n = 79 [45%]), high-risk (n = 33 [19%]) in the placebo arm. Patients were treated with either Rebo Eltrombopag zet, at a starting dose of 200 mg once daily, up to a maximum of 300 mg once daily, or placebo in combination with azacitidine for at least six cycles. Based on central review assessment, there were 76 (42%) and 67 (38%) progression-free survival events, in the Eltrombopag group and the placebo group, respectively. Twenty-one (12%) and 10 (6%) patients progressed to AML by central review assessment in the Eltrombopag group and the placebo group, respectively. In the final analysis, overall survival favored the placebo arm: a total of 57 (32%) patients died on the Eltrombopag arm versus 51 (29%) patients in the placebo arm.

Cataracts
Cataracts were observed in toxicology studies of Eltrombopag in rodents (see section Nonclinical safety data).
In controlled studies in thrombocytopenic patients with HCV receiving interferon based therapy (n = 1439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8% of the Eltrombopag group and 5% of the placebo group.
Routine monitoring of patients for cataracts is recommended.

Interference with laboratory tests
Eltrombopag is highly colored and has the potential to interfere with some laboratory tests. Serum discoloration and interference with total bilirubin and creatinine testing have been reported in patients taking Eltrombopag. If the laboratory results and clinical observations are inconsistent, evaluation of contemporaneous aminotransferase values may help in determining the validity of low total bilirubin levels in the presence of clinical jaundice and blood urea should be evaluated in the event of an unexpectedly high serum creatinine. Retesting using another method may also help in determining the validity of the result.

Loss of response to Eltrombopag
A loss of response or failure to maintain a platelet response with Eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

Note: The results based on clinical studies from Innovator drug of Eltrombopag film coated tablet.

DRUG INTERACTIONS :
Effects of other drugs on Eltrombopag
Cyclosporine
A decrease in Eltrombopag exposure was observed with co-administration of 200 mg and 600 mg Cyclosporine (a BCRP inhibitor). Administration of a single dose of Eltrombopag 50 mg with 200

mg cyclosporine decreased the Cmax and the AUCinf of eltrombopag by 25% (90% CI: 15%, 35%) and 18% (90% CI: 8%, 28%), respectively. The co-administration of 600 mg cyclosporine decreased the Cmax and the AUCinf of eltrombopag by 39% (90% CI: 30%, 47%) and 24% (90% CI: 14%, 32%), respectively. This decrease in exposure is not considered clinically meaningful. Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count (**DOSAGE AND ADMINISTRATIONS**). Platelet count should be monitored at least weekly for 2 to 3 weeks when Eltrombopag is co-administered with Cyclosporine. Eltrombopag dose may need to be increased based on these platelet counts.

Polyvalent Cations (Chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of Eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma Eltrombopag AUC_{inf} by 70% (90% CI: 64%, 76%) and C_{max} by 70% (90% CI: 62 %, 76%) (**DOSAGE AND ADMINISTRATIONS**). Eltrombopag should be taken at least two hours before or four hours after products such as Antacids, dairy products, or mineral supplements containing polyvalent cations to avoid significant reduction in Eltrombopag absorption (see **DOSAGE AND ADMINISTRATIONS**).

Lopinavir/ritonavir

Co-administration of Eltrombopag with Lopinavir/Ritonavir may cause a decrease in the concentration of Eltrombopag. A study in 40 healthy volunteers showed that the coadministration of a single 100 mg dose of Eltrombopag with repeat dose lopinavir/ritonavir 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma AUCinf by 17% (90% CI: 6.6%, 26.6%).
Therefore, caution should be used when co-administration of Eltrombopag with lopinavir/ritonavir takes place. Platelet count should be monitored at least weekly for 2 to 3 weeks in order to ensure appropriate medical management of the dose of Eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

HCV protease inhibitors

Co-administration of repeat doses of Boceprevir 800 mg every 8 hours or Telaprevir 750 mg every 8 hours with a single dose of Eltrombopag 200 mg did not alter plasma Eltrombopag exposure to a clinically significant extent.

Effects of Eltrombopag on other drugs

Rosuvastatin

Administration of Eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate Rosuvastatin 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103% (90% CI: 82%, 126%) and AUC_{inf}. 55% (90% CI: 42%, 69%).
When co-administered with Eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin side effects should be undertaken. Concomitant administration of Eltrombopag and other OATP1B1 and BCRP substrates should be undertaken with caution.

Cytochrome P450 substrates

In studies utilizing human liver microsomes, Eltrombopag (up to 100 microM) showed no in vitro inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of Eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans.

No clinically significant interactions are expected when Eltrombopag and CYP450 substrates are co-administered.

HCV Protease inhibitors

Co-administration of a single dose of Eltrombopag 200 mg with Telaprevir 750 mg every 8 hours did not alter plasma Telaprevir exposure. Co-administration of a single dose of Eltrombopag 200 mg with Boceprevir 800 mg every 8 hours did not alter plasma Boceprevir AUC_{tau}, increased C_{max}, by 19% and decreased C_{min} by 32%.

Drug-food/drink interactions

Administration of a single 50 mg-dose of Eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma Eltrombopag AUC_{inf} by 59% (90% CI: 54%, 64%) and C_{max} by 65% (90% CI: 59%, 70%). Food low in calcium [<50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma Eltrombopag exposure, regardless of calorie and fat content (see **DOSAGE AND ADMINISTRATIONS**).

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with Eltrombopag included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining Eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see **DOSAGE AND ADMINISTRATIONS**).

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk summary

There are no data or limited amount of data from of Eltrombopag in pregnant women to inform a drug-associated risk. In animal developmental and reproductive toxicology studies, oral administration of eltrombopag to pregnant rats and rabbits throughout organogenesis resulted in developmental toxicity in rats. The effect of Eltrombopag on human pregnancy is unknown. Pregnant women or women of childbearing potential should be advised of the potential risk of Eltrombopag to a fetus. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Animal data
In embryo-fetal developmental toxicity studies from Innovator drug in rats and rabbits, oral eltrombopag was administered to pregnant animals during organogenesis. In rats, a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day) resulted in decreased fetal weights and a slight increase in the incidence of the fetal variation, cervical rib. No evidence of major structural malformations was observed. In rabbits, there was no evidence of embryo- fetal toxicity or teratogenicity up to 150 mg/kg/day (0.5 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and 0.3 times the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day).
In a pre-and postnatal developmental toxicity study in pregnant rats, oral eltrombopag was administered from gestation day 6 through lactation Day 20. No adverse effects on maternal reproductive function or on the development of the offspring were observed at doses up to 20 mg/kg/day (2 times the human clinical exposure based on AUC in patients with ITP at 75 mg/day and similar to the human clinical exposure based on AUC in patients with chronic hepatitis C at 100 mg/day). Eltrombopag was detected in the plasma of offspring. The plasma concentrations in pups increased with dose following administration of drug to the F0 dams.

Lactation
Risk summary
There is no information regarding the presence of Eltrombopag or its metabolites in human milk, or their effects on the breastfed infant, or on milk production. However, Eltrombopag was detected in the pups of lactating rats 10 days postpartum suggesting the potential for transfer during lactation. A decision must be made whether to discontinue breastfeeding or to continue/abstain from Eltrombopag therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Females and males of reproductive potential
Contraception
Based on animal reproduction studies, Eltrombopag can cause fetal harm when administered to a pregnant woman (see section Pregnancy). Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using Eltrombopag during treatment and for at least 7 days after stopping treatment with Eltrombopag.

Infertility
There is no effect of Eltrombopag on fertility based on animal studies. Eltrombopag did not affect female or male fertility in rats at doses 2 and 3 times respectively the human clinical exposure based on AUC in patients with ITP at 75 mg/day and in patients with chronic Hepatitis C at 100 mg/day.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

Note: The results based on clinical studies from Innovator drug of Eltrombopag film coated tablet.

ADVERSE DRUG REACTIONS :

Summary of the safety profile

Chronic immune (idiopathic) thrombocytopenia (ITP) in adult and pediatric patients

The safety of Eltrombopag was assessed in adult patients (N=763) with previously treated ITP using data from pooled double-blind, placebo controlled studies TRA100773A and B, TRA102537 (RAISE), and TRA113765 in which patients were exposed to Eltrombopag (N=403) and to placebo (N=179), in addition to data from completed open label studies (N=360) TRA108057, TRA105325 (EXTEND), and TRA112940. Patients received study medication for up to 8 years (in EXTEND). The most important serious adverse reactions were hepatotoxicity and thrombotic/thromboembolic events. The most common adverse reactions occurring in at least 10% of patients included nausea, diarrhoea and increased alanine aminotransferase.

The safety of Eltrombopag was assessed in pediatric patients (aged 1 to 17 years) with previously treated chronic ITP using the all-treated population from two studies (N=171). PETIT2 (TRA115450) was a two-part, double-blind and open-label, randomised, placebo controlled study. Patients were randomized 2:1 and received eltrombopag (n=63) or placebo (n=29) for up to 13 weeks in the randomised period of the study. PETIT (TRA108062) was a three-part, staggered cohort, open-label and double blind, randomised, placebo controlled study. Patients were randomised 2:1 and received eltrombopag (n=44) or placebo (n=21) for up to 7 weeks. The profile of adverse reactions was comparable to that seen in adults with some additional adverse drug reactions, marked ♦ in the table below. The most common adverse drug reactions in pediatric ITP patients 1 year and older (≥3% and greater than placebo) were upper respiratory tract infection, nasopharyngitis, cough, pyrexia, abdominal pain, oropharyngeal pain, toothache and rhinorrhoea. Adverse drug reactions for the adult (N=763) and pediatric (N=171) ITP study population are shown in table 13.

Chronic Hepatitis C (HCV) associated thrombocytopenia in adult patients

ENABLE 1 (TPL103922 n = 716, 715 treated with Eltrombopag) and ENABLE 2 (TPL108390 n = 805) were randomized, double-blind, placebo-controlled, multicenter studies to assess the efficacy and safety of Eltrombopag in thrombocytopenic patients with HCV infection who were otherwise eligible to initiate antiviral therapy. In the HCV studies the safety population consisted of all randomized patients who received double- blind study drug during Part 2 of ENABLE 1 (Eltrombopag treatment n = 450, placebo treatment n = 232) and ENABLE 2 (Eltrombopag treatment n = 506, placebo treatment n = 253). Patients are analysed according to the treatment received (total safety double blind population, Eltrombopag n = 955 and placebo n = 484). Adverse drug reactions for the HCV study population (N=1520) are shown in Table 14. The most common adverse drug reactions (≥10%) for Eltrombopag were anaemia, pyrexia, fatigue, headache, nausea, influenza like illness, diarrhoea, decreased appetite, asthenia, pruritus, cough, chills, and myalgia.

Severe aplastic anemia in adult patients

The safety of Eltrombopag in severe aplastic anemia was assessed in a single-arm, open-label study (N=43) in which 11 patients (26%) were treated for >6 months and 7 patients (16%) were treated for >1 year. Adverse drug reactions for the SAA study population (N=43) are shown in Table 15.

The most common adverse drug reactions (≥10%) for Eltrombopag were nausea, fatigue, cough, headache, diarrhoea, pain in extremity, dizziness, oropharyngeal pain, pyrexia, rhinorrhoea, abdominal pain, transaminases increased, arthralgia and muscle spasms.
Most adverse drug reactions associated with Eltrombopag in ITP, HCV and SAA were mild to moderate in severity, early in onset and rarely treatment-limiting.

The adverse drug reactions identified in patients treated with Eltrombopag are presented below.
Table 13. Adverse drug reactions in the ITP study population

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Nasopharyngitis♦, upper respiratory tract infection♦
	Common	Pharyngitis, influenza, oral herpes, pneumonia, sinusitis, tonsillitis, respiratory tract infection, gingivitis
	Uncommon	Skin infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Rectosigmoid cancer
Blood and lymphatic system disorders	Common	Anaemia, eosinophilia, leukocytosis, thrombocytopenia, haemoglobin decreased, white blood cell count decreased
	Uncommon	Anisocytosis, haemolytic anaemia, myelocytosis, band neutrophil count increased, myelocyte present, platelet count increased, haemoglobin increased
Immune system disorders	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Common	Hypokalaemia, decreased appetite, blood uric acid increased
	Uncommon	Anorexia, gout, hypocalcaemia
Psychiatric disorder	Common	Sleep disorder, depression
	Uncommon	Apathy, mood altered, tearfulness
Nervous system disorders	Common	Paraesthesia, hypoaesthesia, somnolence, migraine.
	Uncommon	Tremor, balance disorder, dysaesthesia, hemiparesis, migraine with aura, neuropathy peripheral, peripheral sensory neuropathy, speech disorder, toxic neuropathy, vascular headache
Eye disorders	Common	Dry eye, vision blurred, eye pain, visual acuity reduced

	Uncommon	Lenticular opacities, astigmatism, cataract cortical, lacrimation increased, retinal haemorrhage, retinal pigment epitheliopathy, visual impairment, visual acuity tests abnormal, blepharitis, keratoconjunctivitis sicca
Ear and labyrinth disorders	Common	Ear pain, vertigo
Cardiac disorders	Uncommon	Tachycardia, acute myocardial infarction, cardiovascular disorder, cyanosis, sinus tachycardia, electrocardiogram QT prolonged
Vascular disorders	Common	Deep vein thrombosis, haematoma, hot flush
	Uncommon	Embolism, thrombophlebitis superficial, flushing
Respiratory, thoracic and mediastinal disorders	Very common	Cough♦
	Common	Oropharyngeal pain, rhinorrhoea♦
	Uncommon	Pulmonary embolism, pulmonary infarction, nasal discomfort, oropharyngeal blistering, sinus disorder, sleep apnoea syndrome
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Mouth ulceration, toothache♦, vomiting, abdominal pain*, mouth haemorrhage, flatulence * Very common in pediatric ITP
	Uncommon	Dry mouth, glossodynia, abdominal tenderness, faeces discoloured, food poisoning, frequent bowel movements, haematemesis, oral discomfort
Hepatobiliary disorders	Very common	Alanine aminotransferase increased†
	Common	Aspartate aminotransferase increased†, hyperbilirubinaemia, hepatic function abnormal
	Uncommon	Cholestasis, hepatic lesion, hepatitis, drug-induced liver injury
Skin and subcutaneous tissue disorders	Common	Rash, alopecia, hyperhidrosis, pruritus generalised, petechiae
	Uncommon	Urticaria, dermatosis, cold sweat, erythema, melanosis, pigmentation disorder, skin discolouration, skin exfoliation
Musculoskeletal and connective tissue disorders	Very common	Back pain
	Common	Myalgia, muscle spasm, musculoskeletal pain, bone pain
	Uncommon	Muscular weakness
Renal and urinary disorders	Common	Proteinuria, blood creatinine increased, thrombotic microangiopathy with renal failure‡

	Uncommon	Renal failure, leukocyturia, lupus nephritis, nocturia, blood urea increased, urine protein/creatinine ratio increased
Reproductive system and breast disorders	Common	Menorrhagia
General disorders and administration site conditions	Common	Pyrexia*, chest pain, asthenia *Very common in pediatric ITP
	Uncommon	Feeling hot, vessel puncture site haemorrhage, feeling jittery, inflammation of wound, malaise, sensation of foreign body
Investigations	Common	Blood alkaline phosphatase increased
	Uncommon	Blood albumin increased, protein total increased, blood albumin decreased, pH urine increased
Injury, poisoning and procedural complications	Uncommon	Sunburn
♦ Additional adverse reactions observed in pediatric studies (aged 1 to 17 years). † Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency. ‡ Grouped term with preferred terms acute kidney injury and renal failure		

Table 14. Adverse drug reactions in the HCV study population (Eltrombopag in combination with interferon anti-viral therapy)

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Urinary tract infection, upper respiratory tract infection, bronchitis, nasopharyngitis, influenza, oral herpes
	Uncommon	Gastroenteritis, pharyngitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Hepatic neoplasm malignant
Blood and lymphatic system disorders	Very common	Anaemia
	Common	Lymphopenia
	Uncommon	Haemolytic anaemia
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Hyperglycaemia, abnormal loss of weight
Psychiatric disorders	Common	Depression, anxiety, sleep disorder
	Uncommon	Confusional state, agitation
Nervous system disorders	Very common	Headache
	Common	Dizziness, disturbance in attention, dysgeusia, hepatic encephalopathy, lethargy, memory impairment, paraesthesia
Eye disorders	Common	Cataract, retinal exudates, dry eye, ocular icterus, retinal haemorrhage
Ear and labyrinth disorders	Common	Vertigo

Cardiac disorders	Common	Palpitations
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Dyspnoea, oropharyngeal pain, dyspnoea exertional, productive cough
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Vomiting, ascites, abdominal pain, abdominal pain upper, dyspepsia, dry mouth, constipation, abdominal distension, toothache, stomatitis, gastrooesophagal reflux disease, haemorrhoids, abdominal discomfort, varices oesophageal
	Uncommon	Oesophageal varices haemorrhage, gastritis, aphthous stomatitis
Hepatobiliary disorders	Common	Hyperbilirubinaemia, jaundice, drug-induced liver injury
	Uncommon	Portal vein thrombosis, hepatic failure
Skin and subcutaneous tissue disorders	Very common	Pruritus
	Common	Rash, dry skin, eczema, rash pruritic, erythema, hyperhidrosis, pruritus generalised, alopecia
	Uncommon	Skin lesion, skin discolouration, skin hyperpigmentation, night sweats
Musculoskeletal and connective tissue disorder	Very common	Myalgia
	Common	Arthralgia, muscle spasms, back pain, pain in extremity, musculoskeletal pain, bone pain
Renal and urinary disorders	Uncommon	Thrombotic microangiopathy with acute renal failure[†], dysuria
General disorders and administration site conditions	Very common	Pyrexia, fatigue, influenza-like illness, asthenia, chills
	Common	Irritability, pain, malaise, injection site reaction, non-cardiac chest pain, oedema, oedema peripheral
	Uncommon	Injection site pruritus, injection site rash, chest discomfort
Investigations	Common	Blood bilirubin increased, weight decreased, white blood cell count decreased, haemoglobin decreased, neutrophil count decreased, international normalised ratio increased, activated partial thromboplastin time prolonged, blood glucose increased, blood albumin decreased
	Uncommon	Electrocardiogram QT prolonged
[†] Grouped term with preferred terms oliguria, renal failure and renal impairment		

Table 15. Adverse drug reactions in the SAA study population

System organ class	Frequency	Adverse reaction
Blood and lymphatic system	Common	Neutropenia, splenic infarction
Metabolism and nutrition disorders	Common	Iron overload, decreased appetite, hypoglycaemia, increased appetite
Psychiatric disorders	Common	Anxiety, depression
Nervous system disorders	Very common	Headache, dizziness
	Common	Syncope
Eye disorders	Common	Dry eye, cataract, ocular icterus, vision blurred, visual impairment, vitreous floaters
Respiratory, thoracic and mediastinal disorders	Very common	Cough, oropharyngeal pain, rhinorrhoea
	Common	Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea, nausea, gingival bleeding, abdominal pain
	Common	Oral mucosal blistering, oral pain, vomiting, abdominal discomfort, constipation, abdominal distension, dysphagia, faeces discoloured, swollen tongue, gastrointestinal motility disorder, flatulence
Hepatobiliary disorders	Very common	Transaminases increased
	Common	Blood bilirubin increased (hyperbilirubinemia), jaundice
	Not known	Drug-induced liver injury* *Cases of drug-induced liver injury have been reported in patients with ITP and HCV
Skin and subcutaneous tissue disorders	Common	Petechiae, rash, pruritus, urticaria, skin lesion, rash macular
	Not known	Skin discolouration, skin hyperpigmentation
Musculoskeletal and connective tissue disorder	Very common	Arthralgia, pain in extremity, muscle spasms
	Common	Back pain, myalgia, bone pain
Renal and urinary disorders	Common	Chromaturia
General disorders and administration site conditions	Very common	Fatigue, pyrexia, chills
	Common	Asthenia, oedema peripheral, malaise
Investigations	Common	Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (n = 446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n = 6), pulmonary embolism (n = 6), acute myocardial infarction (n = 2), cerebral infarction (n = 2), embolism (n = 1) (see **WARNINGS AND PRECAUTIONS**).

In a placebo-controlled study, following 2 weeks treatment in preparation for invasive procedures, 6 of 261 patients with chronic liver disease experienced 7 thromboembolic events of the portal

venous system. One additional patient developed a myocardial infarction 20 days after the last dose of study medication, which remains blinded.

Thrombocytopenia following discontinuation of treatment
In the 3 controlled clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8 % and 8 % of the eltrombopag and placebo groups, respectively (see **WARNINGS AND PRECAUTIONS**).

Increased bone marrow reticulin
Across the programme, no subjects had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In one patient, eltrombopag treatment was discontinued due to bone marrow reticulin (see **WARNINGS AND PRECAUTIONS**).

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)
The following adverse drug reactions have been reported during post-approval use of Eltrombopag. These include spontaneous case reports as well as serious adverse events from registries, investigator sponsored studies, clinical pharmacology studies and exploratory studies in unapproved indications. Because they are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA.

Table 16. Adverse drug reactions identified during post-approval use

Skin and subcutaneous tissue disorders	
Not known	Skin discolouration*
** In patients taking Eltrombopag reversible skin discolouration including hyperpigmentation and skin yellowing was observed at Eltrombopag doses higher than 100 mg per day. Skin discolouration was particularly observed in patients taking Eltrombopag for indications that require administration of high doses of Eltrombopag including severe aplastic anaemia*	

Note: The results based on clinical studies from Innovator drug of Eltrombopag film coated tablet.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 :

Pusat Farmakovigilans
c.q. Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif
Badan Pengawas Obat dan Makanan Republik Indonesia
Post: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id

Website: http://e-meso.pom.go.id/

and/or

Pharmacovigilance of PT. Amarox Pharma Global
Email : drugsafety@amaroxpharma.com
Tel: +62 8118115993

OVERDOSAGE :
Reported adverse events included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. All events were resolved without sequelae following treatment.
In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate Eltrombopag and thus limit absorption should be considered. Platelet counts should be closely monitored. Treatment with Eltrombopag should be reinitiated in accordance with dosing and administration recommendations (see **DOSAGE AND ADMINISTRATIONS**).
Because Eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, hemodialysis would not be expected to be an effective method to enhance the elimination of Eltrombopag.

STORAGE :
Store below 30°C.

PRESENTATION :
ELOPAG® Film coated tablet 75 mg
Box, 4 blisters @ 7 film coated tablets
Reg. No. :

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by :
HETERO LABS LIMITED
Unit-V, Telangana - India

Imported and marketed by :
PT. AMAROX PHARMA GLOBAL
Bekasi – Indonesia

INFORMASI PRODUK UNTUK PASIEN
ELOPAG®
Eltrombopag olamine
Tablet salut selaput

Baca semua bagian leaflet ini dengan cermat sebelum mulai menggunakan obat ini karena berisi informasi penting bagi Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, sekali pun tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter atau perawat Anda. Termasuk setiap kemungkinan efek samping yang tidak tercantum dalam leaflet ini.

Isi leaflet ini :

1. Nama obat
ELOPAG®

2. Bentuk sediaan
Tablet salut selaput

DISETUJUI OLEH BPOM : 20/1/2026 ID: EREG100425VR12600006

3. **Deskripsi obat**

ELOPAG® Tablet salut selaput 75 mg merupakan tablet salut selaput yang berwarna kuning, berbentuk bulat, bertepi miring, bikonveks, yang dicetak dengan tulisan "E57" di satu sisi dan "H" di sisi lainnya.

Zat tambahan : Microcrystalline Cellulose, mannitol, povidone, sodium starch glycolate, magnesium stearate, Instacoat universal yellow (Titanium Dioxide, Yellow Iron Oxide), purified water.

4. **Apa kandungan obat ini ?**

ELOPAG® mengandung zat aktif eltrombopag olamine, yang termasuk dalam kelompok obat yang disebut *'Thrombopoietin receptor agonists'*. **ELOPAG®** adalah obat yang dapat meningkatkan jumlah trombosit, sejenis sel darah yang membantu mengurangi atau mencegah pendarahan.

5. **Kekuatan obat**

75 mg

6. **Apa kegunaan obat ini ?**

- **ELOPAG®** diindikasikan untuk pengobatan trombositopenia pada pasien purpura trombositopenik imun/idiopatik (*immune/idiopathic thrombocytopenic purpura*, ITP) kronis usia 6 tahun ke atas yang tidak respons dengan pengobatan dengan kortikosteroid, imunoglobulin atau splenektomi.
- **ELOPAG®** digunakan hanya pada pasien ITP yang derajat trombositopenia dan kondisi klinisnya meningkatkan risiko perdarahan.
- **ELOPAG®** tidak digunakan dalam upaya menormalkan jumlah trombosit.
- **ELOPAG®** diindikasikan untuk pasien dengan infeksi virus hepatitis C (hepatitic C virus, HCV) dewasa yang derajat trombositopenianya menghambat inisiasi dari terapi berbasis interferon atau membatasi kemampuan untuk mempertahankan terapi berbasis interferon.
- **ELOPAG®** diindikasikan untuk pengobatan pasien dewasa dengan anemia aplastik berat (*severe aplastic anemia*, SAA) yang tidak memperlihatkan respons adekuat terhadap terapi imunosupresif.

Bagaimana kerja ELOPAG®

Di dalam tubuh, hormon yang disebut *'Thrombopoietin'* menstimulasi produksi trombosit dengan menempel pada reseptor tertentu di sumsum tulang. **ELOPAG®** dapat menyebabkan peningkatan produksi trombosit.

7. **Berapa banyak dan seberapa sering obat ini boleh digunakan? Apa yang harus dilakukan bila lupa minum obat ini ?**

Ikuti dengan seksama instruksi yang diberikan oleh dokter Anda. Anda harus memastikan dengan dokter atau apoteker Anda jika Anda tidak yakin.

Pengobatan dengan **ELOPAG®** harus tetap dibawah pengawasan dokter yang berpengalaman dalam perawatan penyakit hematologi.

Kebutuhan dosis **ELOPAG®** harus disesuaikan secara individual berdasarkan jumlah trombosit pasien. Tujuan pengobatan dengan **ELOPAG®** bukanlah untuk menormalkan jumlah trombosit, melainkan untuk mempertahankan jumlah trombosit diatas batas risiko perdarahan (>50.000/mikroL). Pada sebagian besar pasien, peningkatan jumlah trombosit yang terukur membutuhkan waktu 1 - 2 minggu.
Selalu gunakan obat ini sesuai dengan yang dianjurkan oleh dokter, apoteker, atau perawat kepada Anda. Konsultasikan dengan dokter, apoteker, atau perawat apabila Anda merasa tidak yakin.
Eltrombopag olamine biasanya akan diberikan kepada Anda oleh dokter atau perawat. Dewasa (usia 18 tahun ke atas).

ITP kronis
Dosis awal untuk pasien dewasa dan anak usia 6 sampai 17 tahun adalah 50 mg **ELOPAG®** sekali sehari. Dokter Anda mungkin menyesuaikan dosis dan menganjurkan dosis harian **ELOPAG®** untuk dikurangi atau ditambahkan berdasarkan respons Anda terhadap **ELOPAG®**. Pasien dengan rumpun Asia-Timur/Tenggara perlu memulai pengobatan dengan dosis yang lebih rendah (25 mg sekali sehari).

HCV
Dosis awal untuk pasien dewasa adalah 25 mg **ELOPAG®** sekali sehari. Dokter Anda mungkin menyesuaikan dosis dan menganjurkan dosis harian **ELOPAG®** untuk dikurangi atau ditambahkan berdasarkan respons Anda terhadap **ELOPAG®**. Tidak ada perbedaan dosis awal untuk pasien dengan rumpun Asia-Timur/Tenggara.
Pada awal pengobatan, jumlah trombosit Anda dan parameter darah lainnya akan dipantau secara rutin. Dokter Anda juga akan melakukan pemeriksaan darah untuk menilai fungsi hati Anda sebelum dan selama pengobatan dengan **ELOPAG®**.

Anemia aplastik berat yang tidak memperlihatkan respons adekuat terhadap terapi imunosupresif
Dosis awal untuk pasien dewasa adalah 50 mg **ELOPAG®** sekali sehari. Jika Anda tergolong rumpun Asia-Timur/Tenggara, diperlukan dosis permulaan yang lebih rendah, yaitu 25 mg sekali sehari.
Selama 1 hingga 2 minggu pertama pengobatan, pemantauan rutin akan dilakukan. Berdasarkan respons Anda terhadap **ELOPAG®**, dokter Anda dapat menganjurkan agar dosis harian Anda diubah.

Bagaimana cara mengonsumsi ELOPAG®
ELOPAG® harus ditelan sekali sehari, setiap hari, pada waktu yang sama setiap hari dengan menggunak an segelas air.

Apabila Anda lupa mengonsumsi ELOPAG®
Apabila Anda melewatkan satu dosis, minum segera setelah Anda ingat pada hari yang sama. Minumlah dosis selanjutnya sesuai jadwal. Jangan mengonsumsi dosis ganda di hari berikutnya untuk menutupi dosis yang telah Anda lewatkan. Jika Anda memiliki pertanyaan lebih lanjut terkait **ELOPAG®**, tanyakan kepada dokter atau apoteker Anda.

Berapa lama mengonsumsi ELOPAG®
Jangan berhenti mengonsumsi **ELOPAG®** sampai dokter Anda menyarankan Anda untuk melakukannya.

Apabila Anda berhenti mengonsumsi ELOPAG®
Jika dokter Anda menyarankan untuk menghentikan pengobatan dengan **ELOPAG®**, jumlah trombosit Anda akan diperiksa setiap minggu selama empat minggu.
Jika Anda mengalami masalah atau pertanyaan terkait penggunaan **ELOPAG®**, silakan berkonsultasi dengan dokter Anda.

Obat harus diresepkan oleh dokter yang berpengalaman dalam penanganannya. **ELOPAG®** akan diberikan oleh tenaga medis.

Jika Anda memiliki pertanyaan lebih lanjut seputar penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

8. Pada keadaan apa Anda tidak diperbolehkan menggunakan obat ini ?
Jangan menggunakan ELOPAG®
- Jika Anda memiliki hipersensitifitas/alergi terhadap Eltrombopag olamine atau terhadap bahan-bahan lain dalam obat ini.

9. Apa yang perlu diperhatikan bila menggunakan obat ini ?
Sampaikan kepada dokter atau perawat Anda sebelum mendapatkan eltrombopag olamine jika:
- Memiliki masalah pada hati (liver). Anda mungkin membutuhkan dosis **ELOPAG®** yang lebih rendah.
- Memiliki riwayat pembentukan gumpalan di dalam pembuluh darah yang mengganggu aliran darah (trombosis), atau Anda mengetahui riwayat trombosis dalam keluarga Anda.
- Jika Anda memiliki kondisi darah berbeda, seperti *myelodysplastic syndrome (MDS)*. Dokter Anda akan melakukan tes untuk memeriksa bahwa Anda tidak memiliki kondisi darah ini sebelum Anda menggunakan **ELOPAG®**. Jika Anda memiliki MDS dan menggunakan **ELOPAG®**, MDS Anda mungkin menjadi memburuk.
- Memiliki riwayat gangguan pada penglihatan (katarak).

Beritahukan dokter, apoteker, atau tenaga profesional kesehatan Anda segera jika Anda mendapatkan gejala-gejala ini saat mengonsumsi ELOPAG®
- Jika Anda mengalami gejala-gejala yang disebabkan oleh gumpalan darah di kaki Anda seperti pembengkakan atau nyeri/sakit satu kaki.
- Jika Anda mengalami gejala-gejala yang disebabkan oleh masalah-masalah hati seperti menguningnya kulit atau putihnya mata (sakit kuning), penggelapan urin yang tidak biasa, rasa lelah yang tidak biasa, nyeri di daerah perut kanan.

Pemantauan selama pengobatan dengan ELOPAG®
Mohon perhatian pada awal terapi, jumlah trombosit Anda dan parameter darah rutin lainnya seperti beberapa enzim hati perlu sering dipantau.
Dalam penelitian pada hewan, ditemukan bahwa **ELOPAG®** menyebabkan perkembangan katarak (kekeruhan lensa di mata). Dalam uji coba HCV pada manusia peningkatan risiko kejadian katarak juga terlihat. Dokter Anda mungkin menyarankan agar Anda diperiksa untuk katarak sebagai bagian dari pemeriksaan mata rutin.
Dokter Anda dapat merekomendasikan pemantauan fungsi hati Anda sebelum dan selama pengobatan.

Orang yang lebih tua (65 tahun ke atas)
Data terbatas tentang penggunaan **ELOPAG®** pada pasien berusia 65 tahun dan lebih tua. Perhatian harus diberikan ketika mengonsumsi **ELOPAG®** jika Anda berusia 65 tahun atau lebih.

Anak - anak
ELOPAG® dapat digunakan pada anak berusia 6 sampai 17 tahun untuk mengobati *chronic immune (idiopathic) thrombocytopenic purpura* (ITP).
ELOPAG® tidak dianjurkan pada anak-anak dengan infeksi virus hepatitis C (HCV) untuk mengobati jumlah trombosit yang rendah (trombositopenia).
Konsultasikan dengan dokter atau apoteker Anda sebelum menggunakan **ELOPAG®**.

10. Obat dan makanan apa yang harus dihindari jika menggunakan obat ini ?
Beritahukan dokter, apoteker, atau tenaga profesional kesehatan Anda segera jika Anda baru saja mengambil atau mungkin mengambil obat lain. Ini termasuk obat-obatan yang diperoleh tanpa resep dan vitamin.
Ada beberapa kelompok obat, termasuk obat resep, obat non-resep dan vitamin yang berinteraksi dengan **ELOPAG®** sehingga tidak dapat dikonsumsi bersamaan atau memerlukan penyesuaian dosis saat digunakan bersamaan dengan **ELOPAG®**. Obat-obat ini termasuk beberapa produk dalam kelompok berikut:
- Obat antasida untuk mengobati maag
- Golongan obat penurun kolesterol (statin)
- Golongan obat pengobatan HIV (lopinavir/ritonavir)
- Golongan mineral seperti aluminium, kalsium, zat besi, magnesium, selenium dan zinc yang dapat ditemukan dalam suplemen mineral,
- Obat-obatan untuk kanker seperti methotrexate dan topotecan.

Dokter Anda akan meninjau kembali obat-obatan yang sedang Anda konsumsi untuk memastikan Anda tidak sedang mengonsumsi obat-obatan yang tidak dapat digunakan bersamaan dengan **ELOPAG®**. Jika Anda membutuhkan obat-obatan ini dan tidak ada obat pengganti yang tersedia, silakan diskusikan dengan dokter Anda.
Beritahukan dokter atau apoteker Anda jika Anda sedang mengonsumsi atau pernah mengonsumsi obat-obat lain belakangan ini, termasuk obat-obat non-resep.

ELOPAG® dipengaruhi oleh asupan kalsium. Jangan minum obat **ELOPAG®** dengan makanan tinggi kalsium. **ELOPAG®** dapat dikonsumsi bersamaan dengan makanan rendah kalsium seperti:

- Buah-buahan seperti nanas, kismis dan stroberi
- Daging rendah lemak
- Jus buah yang tidak difortifikasi, susu kedelai dan biji-bijian (tidak difortifikasi maksudnya tidak ada tambahan kalsium, magnesium atau zat besi).

Silakan bicarakan dengan dokter Anda; dokter Anda akan bisa menyarankan makanan yang paling cocok dikonsumsi selama pengobatan dengan **ELOPAG®**.

Jangan mengonsumsi ELOPAG® dalam rentang **setidaknya 2 jam sebelum atau 4 jam sesudah** konsumsi:

- **Obat antasida**, yang biasa digunakan untuk mengobati gangguan pencernaan
- **Suplemen mineral**, seperti aluminium, kalsium, zat besi, magnesium, selenium atau zinc.
- **Produk olahan susu**

Jika Anda melakukannya, **ELOPAG®** tidak akan diserap dengan benar oleh tubuh Anda.
Salah satu cara untuk mencegah hal ini adalah dengan mengonsumsi obat-obatan diatas pada pagi hari dan mengonsumsi **ELOPAG®** pada malam hari. Tanyakan kepada dokter atau apoteker Anda jika Anda tidak yakin.

11. Apakah obat ini boleh digunakan pada wanita hamil dan menyusui ?

Jika Anda sedang hamil atau berencana untuk hamil, konsultasikan dulu dengan dokter sebelum menggunakan eltrombopag olamine.

ELOPAG® dianjurkan untuk dikonsumsi selama kehamilan hanya dibenarkan jika kebutuhan medis dikarenakan pengaruh **ELOPAG®** terhadap kehamilan belum diketahui. Anda harus menggunakan metode kontrasepsi yang dapat dihandalkan (untuk mencegah Anda hamil).

Jika Anda hamil, Anda mungkin hamil atau berencana untuk hamil, tanyakan kepada dokter atau perawat Anda untuk meminta saran sebelum mengonsumsi obat ini.

Jika Anda hamil saat Anda mengonsumsi **ELOPAG®**, beritahukan ke dokter Anda segera.

Tidak dianjurkan untuk menyusui selama mengonsumsi **ELOPAG®**. Belum diketahui apakah **ELOPAG®** masuk ke dalam ASI.

Mintalah saran dari dokter atau apoteker Anda sebelum mengonsumsi obat apapun jika Anda tidak yakin.

Wanita yang berpotensi untuk melahirkan dan pasien laki-laki

ELOPAG®dapat membahayakan bayi yang belum lahir. Jika Anda seorang wanita yang bisa hamil, Anda harus menggunakan kontrol kelahiran yang dapat diandalkan (kontrasepsi) saat Anda menggunakan **ELOPAG®**dan setidaknya 7 hari setelah Anda berhenti menggunakan **ELOPAG®**. Tanyakan kepada dokter Anda tentang opsi pengendalian kelahiran yang efektif

Jika Anda hamil atau menyusui, menduga bahwa diri Anda hamil, atau sedang merencanakan kehamilan, mintalah saran dari dokter atau apoteker Anda sebelum menggunakan obat ini.

12. Apakah pasien diperbolehkan mengendarai dan menjalankan mesin selama menggunakan obat ini ?

ELOPAG® dapat menyebabkan pusing dan mempunyai efek samping lain yang menyebabkan Anda menjadi kurang waspada. Jangan mengemudi atau mengoperasikan mesin kecuali Anda yakin obat ini tidak berpengaruh pada Anda.

Jika Anda merasakan hal tersebut. jangan mengendarai atau menjalankan mesin hingga gejala-gejalanya mereda. Mintalah saran dari dokter Anda.

13. Apakah efek yang tidak diinginkan yang mungkin terjadi jika menggunakan obat ini

Seperti obat pada umumnya, obat ini dapat memberikan efek samping, meskipun tidak semua orang mengalaminya.

ELOPAG® dapat menyebabkan efek samping yang serius

Masalah hati

ELOPAG® dapat menyebabkan kerusakan pada hati dan menyebabkan penyakit yang serius dan bahkan mengancam nyawa. Anda harus menjalani pemeriksaan darah untuk menilai kondisi hati Anda sebelum dan selama pengobatan dengan **ELOPAG®**. Dokter Anda akan menyarankan pemeriksaan darah ini. Pada beberapa kasus, pengobatan **ELOPAG®** dapat dihentikan.

Beritahukan segera kepada dokter Anda jika Anda mengalami tanda dan gejala masalah hati berikut ini:

- Kekuningan pada kulit atau bagian putih di mata (tanda ikterus)
- Urin berwarna gelap
- Kelelahan yang tidak biasa
- Nyeri pada perut kanan atas.

Perdarahan setelah Anda menghentikan pengobatan

Ketika Anda menghentikan pengobatan dengan **ELOPAG®**, jumlah trombosit darah Anda dapat menurun ke angka sebelum Anda mengonsumsi **ELOPAG®**. Efek ini umumnya terjadi dalam rentang waktu sekitar 4 minggu sejak Anda berhenti mengonsumsi **ELOPAG®**. Rendahnya jumlah trombosit akan meningkatkan risiko perdarahan. Dokter Anda akan memeriksa jumlah trombosit Anda sekurang-kurangnya 4 minggu sejak Anda berhenti mengonsumsi **ELOPAG®**. Beritahukan kepada dokter atau apoteker Anda jika Anda mengalami lebam atau perdarahan setelah Anda berhenti mengonsumsi **ELOPAG®**.

Masalah sumsum tulang

Pengidap penyakit seperti yang Anda alami mungkin mengalami masalah sumsum tulang. Obat seperti **ELOPAG®** dapat membuat masalah ini semakin memburuk. Tanda-tanda

perubahan pada sumsum tulang dapat berupa hasil pemeriksaan darah yang abnormal. Dokter Anda mungkin juga melakukan uji untuk memeriksa sumsum tulang Anda selama pengobatan dengan **ELOPAG®**.

Meningginya jumlah trombosit dan meningkatnya risiko penggumpalan darah (trombosis/tromboemboli)
Risiko penggumpalan darah meningkat jika jumlah trombosit terlalu tinggi selama pengobatan dengan **ELOPAG®**, namun penggumpalan darah dapat juga terjadi pada kondisi jumlah trombosit normal atau rendah. Jika Anda memiliki sirosis hati, Anda berisiko mengalami penggumpalan darah pada pembuluh darah hati (trombosis vena portal). Anda dapat pula mengalami komplikasi berat berupa terbentuknya gumpalan darah jenis tertentu, seperti gumpalan darah yang terlepas dari pembuluh darah (tromboemboli) ke paru atau yang dapat menyebabkan serangan jantung atau stroke. Dokter Anda akan memeriksa jumlah trombosit Anda dan menyesuaikan dosis atau menghentikan **ELOPAG®** jika jumlah trombosit Anda terlalu tinggi.
Segera beritahukan kepada dokter Anda jika Anda mengalami gejala penggumpalan darah di kaki, seperti pembengkakan atau nyeri pada salah satu kaki.

Efek samping di bawah ini pernah dilaporkan terkait pengobatan dengan **ELOPAG®**.
Frekuensi kejadian buruk diurutkan berdasarkan yang berikut: Paling umum (≥1/10), umum (≥1/100, <1/10), tidak umum (≥1/1000, <1/100), jarang (≥1/10000, <1/1000) dan sangat jarang (<1/10000).

Efek samping yang terlapor pada pasien ITP kronis

Klasifikasi berdasar sistem organ	**Frekuensi**	**Efek samping**
Infeksi dan infestasi	Sangat umum	Pilek dan hidung tersumbat (nasofaringitis)*, infeksi saluran pernapasan bagian atas (ISPA)*
	Umum	Sakit tenggorokan dan ketidaknyamanan saat menelan (faringitis), influenza, herpes di sekitar mulut, radang paru-paru, sinus, tonsilitis (amandel), infeksi saluran pernapasan, radang gusi
	Tidak umum	Infeksi kulit
Tumor jinak, ganas atau tidak spesifik (termasuk kista dan polip)	Tidak umum	Kanker rektosigmoid
Gangguan darah dan getah bening	Umum	Berkurangnya jumlah sel darah merah (anemia), peningkatan jumlah eosinofil dalam darah, peningkatan jumlah sel darah putih, penurunan jumlah trombosit, penurunan hemoglobin, penurunan jumlah sel darah putih

	Tidak umum	Anisositosis, anemia hemolitik, *myelocytosis*, peningkatan neutrofil batang, adanya mielosit, peningkatan jumlah trombosit, peningkatan hemoglobin
Gangguan sistem imun	Tidak umum	Hipersensitivitas
Gangguan metabolisme dan nutrisi	Umum	Penurunan kalium, penurunan nafsu makan,peningkatan asam urat darah
	Tidak umum	Anoreksia, asam urat, penurunan kalsium
Gangguan kejiwaan	Umum	Kesulitan tidur, depresi
	Tidak umum	Sikap apatis, gangguan *mood*, sedih
Gangguan sistem saraf	Umum	Kesemutan, kehilangan sensitivitas indera, mudah mengantuk, migren
	Tidak umum	Gemetar, gangguan keseimbangan, gangguan sensasi raba/sentuh, layu pada separuh badan (*hemiparesis*), migren dengan aura, gangguan pada saraf perifer, gangguan bicara, neuropati toksik, nyeri kepala tipe vaskular
Gangguan mata	Umum	Mata kering, penglihatan kabur, nyeri pada mata, penurunan ketajaman penglihatan
	Tidak umum	*Lenticular opacities*, astigmatisme, katarak kortikal, sering keluar air mata, perdarahan pada retina, gangguan pada pigmen retina, gangguan penglihatan, peradangan pada kelopak mata,*keratoconjunctivitis sicca*
Gangguan telinga dan labirin	Umum	Nyeri pada telinga, vertigo
Gangguan jantung	Tidak umum	Peningkatan denyut jantung (takikardia), infark miokardial akut, gangguan kardiovaskular, sianosis, berdebar-debar (palpitasi), takikardia sinus, pemanjangan interval QT padaelektrokardiogram
Gangguan pembuluh darah	Umum	Trombosis vena dalam *(deep vein thrombosis)*, penumpukan darah abnormal di luar pembuluh darah (hematoma), perasaan hangat yang datang tiba-tiba dan berlangsung intens di sekujur wajah, leher dan dada *(hot flush)*

	Tidak umum	Embolisme, penggumpalan darah di vena yang terletak tepat di bawah permukaan kulit (*thrombophlebitis superficial*), kemerahan
Gangguan pernapasan, rongga dada dan mediastinum	Sangat umum	Batuk*
	Umum	Nyeri pada orofaring (*oropharyngealpain)*, hidung meler (*rhinorrhoea*)*
	Tidak umum	Emboli paru, infark paru, rasa tidak nyaman pada hidung, lepuh pada orofaring *(orophrayngeal blistering)*, gangguan sinus, sesak napas
Gangguan pencernaan	Sangat umum	Mual, diare*
	Umum	Luka pada mulut, sakit gigiC̈, muntah, sakit perut*, perdarahan pada mulut, perut kembung*sangat umum pada pediatrik ITP
	Tidak umum	Mulut kering, peradangan mulut, nyeri pada perut, perubahan warna feses, keracunan makanan, sering buang air besar, muntah darah (*haematemesis*), gangguan pada rongga mulut
Gangguan hati dan empedu	Sangat umum	Peningkatan alanin aminotransferase†
	Umum	Peningkatan aspartat aminotransferase†,peningkatan bilirubin dalam darah, fungsi hati yang tidak normal
	Tidak umum	Sumbatan empedu (kolestasis), lesi pada hati, hepatitis, hilangnya fungsi hati karena efek samping dari pengobatan (*drug-induced liver injury*)
Gangguan pada kulit dan jaringan bawah kulit	Umum	Ruam, rambut rontok atau penipisan yang tidak biasa (alopecia), keringat berlebihan (hiperhidrosis), gatal di seluruh tubuh, perdarahan bawah kulit (petekie)
	Tidak umum	Biduran (urtikaria), kelainan kulit non-radang (dermatosis), keringat dingin, munculnya bercak kemerahan pada kulit (eritema), perubahan pigmen kulit (melanosis), gangguan pigmentasi, perubahan warna kulit, pengelupasan kulit

Gangguan tulang, otot dan jaringan penyokong	Umum	Nyeri otot, kram otot, nyeri sendi, nyeri tulang, nyeri punggung
	Tidak umum	Kelemahan otot
Gangguan ginjal dan saluran kemih	Umum	Peningkatan protein dalam urin, peningkatan kadar kreatinin dalam darah, kerusakan yang terjadi di pembuluh darah terkecil di dalam ginjal yang menyebabkan hilangnya fungsi ginjal (thrombotic microangiopathy with acute renal failure)‡
	Tidak umum	Gagal ginjal, peningkatan sel darah putih dalam urin, nefritis lupus, sering buang air kecil pada malam hari, peningkatan kadar urea dalam darah, peningkatan rasio protein/kreatinin dalam urin
Sistem reproduksi dan gangguan payudara	Umum	Jumlah darah yang keluar saat haidberlebihan (menorrhagia)
Gangguan umum dan kondisi pada tempat pemberian obat	Umum	Demam*, nyeri dada, tidak berenergi *sangat umum pada pediatrik ITP
	Tidak umum	Dada terasa panas, perdarahan, tidak berenergi, gelisah, peradangan pada luka, lemas (malaise), terasa seperti ada benda asing
Abnormalitas hasil pemeriksaan	Umum	Peningkatan fosfatase alkali dalam darah
	Tidak umum	Peningkatan bilirubin dalam darah, peningkatan protein total, penurunan albumin dalam darah, peningkatan pH urin
Cedera, keracunan dan komplikasi prosedural	Tidak umum	Kulit terbakar

* Reaksi efek samping tambahan yang diamati dalam studi pediatrik (usia 1 hingga 17 tahun).
† Peningkatan alanin aminotransferase dan aspartat aminotransferase dapat terjadi secara bersamaan, meskipun pada frekuensi yang tidak begitu sering.
‡ Pengelompokan istilah yang digunakan pada ginjal akut dan gagal ginjal.

Efek samping yang terlapor pada pasien HCV kronis (ELOPAG® dikombinasikan dengan terapi anti viral interferon)

Klasifikasi berdasar sistem organ	**Frekuensi**	**Efek samping**
Infeksi dan infestasi	Umum	Infeksi saluran kemih, infeksi saluran pernapasan bagian atas (ISPA), bronkitis, pilek dan hidung tersumbat (nasofaringitis), influenza, herpes di sekitar mulut

	Tidak umum	Muntah dan diare akibat infeksi atau peradangan pada dinding saluran pencernaan (gastroenteritis), sakit tenggorokan dan ketidaknyamanan saat menelan (faringitis)
Tumor jinak, ganas atau tidak spesifik (termasuk kista dan polip)	Umum	Kanker hati ganas
	Sangat umum	Berkurangnya jumlah sel darah merah (anemia)
Gangguan darah dan getah bening	Umum	Penurunan jumlah limfosit dalam darah
	Tidak umum	Anemia hemolitik
Gangguan metabolisme dan nutrisi	Sangat umum	Kehilangan selera makan
	Umum	Kelebihan gula darah, penurunan berat badan yang abnormal
Gangguan kejiwaan	Umum	Depresi, kecemasan, gangguan tidur
	Tidak umum	Kebingungan, mudah merasa iritasi
Gangguan sistem saraf	Sangat umum	Sakit kepala
	Umum	Pusing, gangguan konsentrasi, gangguan pengecapan, sindrom neuropsikiatri yang dapat terjadi pada gagal hati, tidak antusias (letargi), gangguan ingatan, kesemutan
Gangguan mata	Umum	Kekeruhan pada lensa mata (katarak), eksudat pada retina, mata kering, mata kuning, perdarahan pada retina
Gangguan telinga dan labirin	Umum	Vertigo
Gangguan jantung	Umum	Berdebar-debar
Gangguan pernapasan, rongga dada, dan mediastinum	Sangat umum	Batuk
	Umum	Sesak napas, nyeri pada mulut dan tenggorok, sesak napas saat beraktivitas, batuk berdahak
Gangguan pencernaan	Sangat umum	Mual, diare
	Umum	Muntah, pembesaran perut, nyeri perut bagian atas, kembung, mulut kering, sembelit, perut tegang, sakit gigi, peradangan mulut, penyakit refluks gastroesofagus, wasir, rasa tidak nyaman di perut, varises pada esofagus
	Tidak umum	Perdarahan akibat varises pada esofagus, maag, peradangan dengan rasa terbakar pada jaringan lunak rongga mulut

Gangguan hati dan empedu	Umum	Meningkatnya kadar pigmen bilirubin dalam darah, yang dapat menyebabkan menguningnya kulit atau bagian putih mata (hyperbilirubinaemia), penyakit kuning (jaundice), gangguan fungsi hati karena efek samping dari pengobatan (drug induced liver injury)
	Tidak umum	Pembekuan darah (portal vein thrombosis),gangguan fungsi hati yang serius (hepatic failure)
Gangguan kulit danjaringan bawah kulit	Sangat umum	Gatal
	Umum	Ruam, kulit kering, eksim, ruam pruritus, munculnya bercak kemerahan pada kulit yang disebabkan oleh pelebaran pembuluh darah di bawah kulit (eritema), keringat berlebihan, rambut rontok atau penipisan yang tidak biasa (alopecia)
	Tidak umum	Pengelupasan kulit, perubahan warna kulit,gangguan pigmentasi, berkeringat pada malam hari
Gangguan tulang, otot, dan jaringan penyokong	Sangat umum	Nyeri otot
	Umum	Nyeri sendi, kram otot, nyeri punggung, nyeri pada tangan dan/atau kaki, nyeri otot, nyeri tulang
Gangguan ginjal dan saluran kemih	Tidak umum	Kerusakan yang terjadi di pembuluh darah kecilkecil pada ginjal yang menyebabkan penurunan fungsi ginjal *(thrombotic microangiopathy with acute renal failure)*†, rasa sakit saat buang air kecil (*dysuria*)
Gangguan umum dan kondisi pada tempat pemberian obat	Sangat umum	Demam, mudah lelah, penyakit mirip influenza, tidak berenergi, menggigil
	Umum	Mudah teriritasi, nyeri, lesu, nyeri pada tempat injeksi, nyeri dada non-kardiak, edema, kesulitan untuk menggerakkan bagian tubuh
	Tidak umum	Gatal pada tempat injeksi, ruam pada tempat injeksi, perasaan tidak nyaman pada dada
Abnormalitas hasilpemeriksaan	Umum	Peningkatan bilirubin dalam darah, penurunan berat badan, penurunan jumlah sel darah putih, penurunan hemoglobin, penurunan jumlah neutrofil, peningkatan INR *(international*

		normalised ratio), pemanjangan aPTT *(activated partial thromboplastin time)*, peningkatan kadar gula darah, penurunan albumin dalam darah
	Tidak umum	Pemanjangan interval QT pada elektrokardiogram

† Pengelompokan istilah yang digunakan pada oliguria, gagal ginjal dan gangguan ginjal

Efek samping yang terlapor pada pasien SAA

Klasifikasi berdasar sistem organ	**Frekuensi**	**Efek samping**
Gangguan darah dan getah bening	Umum	Neutropenia, infark pada limpa
Gangguan kejiwaan	Sangat umum	Insomnia
	Umum	Kecemasan, depresi
Gangguan sistem saraf	Sangat umum	Sakit kepala, pusing
	Umum	Pingsan (sinkop)
Gangguan mata	Umum	Mata kering, mata gatal, katarak, mata kuning, penglihatan kabur, gangguan penglihatan, *vitreous floaters*
Gangguan pernapasan, rongga dada, dan mediastinum	Sangat umum	Batuk, sesak napas, nyeri pada mulut dantenggorok, hidung meler
	Umum	Mimisan
Gangguan pencernaan	Sangat umum	Nyeri perut, diare, mual
	Umum	Perdarahan pada gusi, lepuh pada mukosa mulut, nyeri pada mulut, muntah, rasa tidak nyaman di perut, sakit perut, sembelit, perut kembung, gangguan menelan, feses berubah warna, lidah bengkak, gangguan motilitas saluran cerna, sering “buang gas”
Gangguan hati dan empedu	Sangat umum	Transaminase meningkat
	Umum	Peningkatan bilirubin dalam darah(hiperbilirubinemia), ikterus
Gangguan kulit dan jaringan bawah kulit	Sangat umum	Lebam (ekimosis)
	Umum	Petekie, ruam, gatal, biduran, lesi kulit, ruam makular
Gangguan otot, tulang, dan jaringan penyokong	Sangat umum	Nyeri sendi, kram otot, nyeri pada tangan dan/atau kaki
	Umum	Nyeri punggung, nyeri otot, nyeri tulang
Gangguan ginjal dan saluran kemih	Umum	Kromaturia

Gangguan umum dan kondisi pada tempat pemberian	Sangat umum	Mudah lelah, neutropenia disertai demam *(febrile neutropenia)*, demam
	Umum	Tidak berenergi, edema perifer, menggigil, lesu
Gangguan metabolisme dan nutrisi	Umum	Kelebihan zat besi, penurunan atau peningkatan nafsu makan, hipoglikemia
Abnormalitas hasil pemeriksaan	Umum	Peningkatan kadar kreatinin fosfokinase dalam darah

Jika salah satu dari efek samping yang tercantum dalam brosur ini menjadi serius, atau jika Anda mengalami efek samping apapun yang tidak tercantum dalam brosur ini, beritahukan kepada dokter atau apoteker Anda.

Apabila ada keluhan efek samping atau kondisi tidak nyaman selama dan setelah penggunaan obat, termasuk efek samping yang tidak ada dalam daftar, konsultasikan ke dokter, apoteker, atau perawat, Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

Pelaporan dugaan efek samping
Pelaporan dugaan efek samping setelah produk obat mendapatkan izin edar merupakan hal yang penting. Hal ini memungkinkan pemantauan berkelanjutan terhadap rasio manfaat/risiko dari produk obat tersebut. Setiap dugaan efek samping dapat dilaporkan melalui :
Farmakovigilans PT. Amarox Pharma Global
Email : drugsafety@amaroxpharma.com
Tel: +62 8118115993

14. Overdosis dan penanganannya

Jika Anda telah mengambil terlalu banyak **ELOPAG®**, atau jika orang lain secara tidak sengaja mengambil obat Anda, segera hubungi dokter atau rumah sakit untuk meminta saran. Tunjukkan kemasan **ELOPAG®**. Perawatan medis mungkin diperlukan.

15. Bagaimana cara menyimpan obat ini ?

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada kemasan luar dan pada label vial setelah tulisan EXP. Tanggal kedaluarsa mengacu pada hari terakhir bulan tersebut.

Simpan obat pada suhu di bawah 30°C.

Jangan membuang obat melalui saluran limbah cair atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat yang sudah tidak digunakan. Upaya-upaya ini akan membantu perlindungan lingkungan.

KEMASAN :
ELOPAG® Tablet salut selaput 75 mg
Dus, 4 blister @ 7 tablet salut selaput
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