**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

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

## 1. NAME OF THE MEDICINAL PRODUCT

WAYRILZ 400 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg rilzabrutinib.

Excipient with known effect

Each tablet contains 0.8 mg of sunset yellow FCF (E 110).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange tablet, capsule-shaped of 16.6 × 8.1 mm size, debossed with “P” on one side and “400” on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

WAYRILZ is indicated for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1).

### 4.2 Posology and method of administration

Treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Posology

The recommended dose of rilzabrutinib is 400 mg twice daily.

*Use with CYP3A inhibitors or inducers and gastric acid reducing agents*

Recommended use with cytochrome P450 enzyme 3A (CYP3A) inhibitors or inducers and gastric acid reducing agents are provided in Table 1 (see section 4.5).

**Table 1: Use with CYP3A inhibitors or inducers and gastric acid reducing agents**

| | **Co-administered medicinal product** | **Recommended use** |
|---|---|---|
| CYP3A inhibitors | Strong and moderate CYP3A inhibitor | Avoid co-administration of rilzabrutinib with moderate or strong CYP3A inhibitors. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt rilzabrutinib. |
| | | Avoid co-administration of grapefruit, starfruit and products containing these fruits, and Seville oranges with rilzabrutinib, as these are moderate or strong inhibitors of CYP3A. |
| | Weak CYP3A inhibitor | No dose adjustment. |
| CYP3A inducers | Strong and moderate CYP3A inducers | Avoid co-administration of rilzabrutinib with moderate or strong CYP3A inducers. |
| | Weak CYP3A inducer | No dose adjustment. |
| Gastric acid reducing agents | Proton pump inhibitors (PPIs) | Avoid co-administration of rilzabrutinib with PPIs. |
| | H2-receptor antagonists or antacid | If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (H2RA) or antacid. Take rilzabrutinib at least 2 hours before taking the H2RA or antacid. |

*Missed dose*

If a dose of rilzabrutinib is missed, patients should take the missed dose as soon as possible on the same day with a return to the regular schedule the following day. The missed dose and the next regular scheduled dose must be taken more than 2 hours apart. Extra tablets should not be taken to make up for the missed dose.

*Discontinuation*

Treatment with rilzabrutinib should be discontinued after 12 weeks of rilzabrutinib therapy if the platelet count does not increase to a level sufficient to avoid clinically important bleeding.

*Special population*

*Elderly*
No dose modification is required for elderly (≥ 65 years) patients (see section 5.2).

*Renal impairment*
No dose modification is required in patients with mild or moderate renal impairment. Rilzabrutinib has not been studied in clinical trials in patients with severe renal impairment (see section 5.2).

*Hepatic impairment*
No dose modification is required in patients with mild (Child-Pugh Class A) hepatic impairment. Rilzabrutinib has not been studied in clinical trials in patients with severe (Child-Pugh Class C) hepatic impairment. In patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment, rilzabrutinib should not be administered (see section 5.2).

Paediatric population

The safety and efficacy of rilzabrutinib in children and adolescents below 18 years of age with ITP have not been established. No data are available.

Method of administration

Rilzabrutinib is for oral use.

The tablets can be taken at approximately the same time each day with or without food (see section 5.2). In patients who experience gastrointestinal symptoms, taking rilzabrutinib with food may improve tolerability. Patients should be instructed to swallow the tablets whole with water. The tablets should not be split, crushed, or chewed in order to ensure the entire dose is delivered correctly.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Serious infections

Serious infections (including bacterial, viral, or fungal) have been reported during clinical studies (see section 4.8). Monitor patients for signs and symptoms of infection and treat appropriately.

Women of childbearing potential

Women of childbearing potential must use highly effective method of contraception while taking rilzabrutinib (see section 4.6). Pregnancy status of females of child-bearing potential should be verified prior to initiating treatment.

Hepatic impairment

In patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment, rilzabrutinib should not be administered (see section 5.2). Bilirubin and transaminases are to be evaluated at baseline and as clinically indicated during treatment with rilzabrutinib. For patients who develop abnormal liver tests after rilzabrutinib, continue to monitor for liver test abnormalities as well as clinical signs and symptoms as clinically indicated.

QT shortening

In the clinical trials with ITP patients, there were no clinically meaningful QTc interval changes. In a thorough QT study, rilzabrutinib produced a shortening in the QTc interval (see section 5.1). Although the underlying mechanism and safety relevance of this finding is not known, clinicians should use caution when prescribing rilzabrutinib to patients at risk for further shortening their QTc duration (e.g., Congenital Short QT Syndrome or patients with a family history of such a syndrome).

Excipients

*Sunset yellow FCF*

This medicinal product contains azo colouring agent sunset yellow FCF (E 110), which may cause allergic reactions.

*Sodium*

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Rilzabrutinib is primarily metabolized by CYP3A.

Agents that may increase rilzabrutinib plasma concentrations

Co-administration of rilzabrutinib with a moderate or strong CYP3A inhibitor increases rilzabrutinib plasma concentrations. Increased rilzabrutinib concentrations may increase the risk of rilzabrutinib adverse reactions.

*CYP3A inhibitors*

Co-administration with a strong CYP3A inhibitor (ritonavir) increased the rilzabrutinib $C_{max}$ by approximately 5-fold and AUC by 8-fold in healthy subjects.

Avoid co-administration of moderate or strong CYP3A inhibitors (e.g., ritonavir, clarithromycin, itraconazole, erythromycin, fluconazole, verapamil, diltiazem) with rilzabrutinib. If these inhibitors will be used short term (such as anti-infectives for seven days or less), interrupt rilzabrutinib (see section 4.2).

Avoid co-administration of grapefruit, starfruit and products containing these fruits, and Seville oranges with rilzabrutinib, as these are moderate or strong inhibitors of CYP3A.

*P-glycoprotein (P-gp) inhibitors*

After co-administration of rilzabrutinib with a strong P-gp inhibitor (quinidine), a modest increase in exposure to rilzabrutinib, considered not to be clinically meaningful, was observed by 12.7% for AUC, relative to rilzabrutinib alone.

Agents that may decrease rilzabrutinib plasma concentrations

Co-administration of rilzabrutinib with moderate or strong CYP3A inducers decreases rilzabrutinib plasma concentrations. Co-administration with a PPI decreases the plasma concentrations of rilzabrutinib. Decreased rilzabrutinib plasma concentrations may reduce rilzabrutinib efficacy.

*CYP3A inducers*

Co-administration with a strong CYP3A inducer (rifampicin) decreased rilzabrutinib $C_{max}$ and AUC by about 80% in healthy subjects.

Avoid co-administration of rilzabrutinib with moderate or strong CYP3A inducers (e.g., carbamazepine, rifampicin, phenytoin) (see section 4.2).

*Gastric acid reducing agents*

Rilzabrutinib solubility decreases with increasing pH. Co-administration with a PPI (esomeprazole) decreased rilzabrutinib AUC by 51% in healthy subjects. Co-administration of rilzabrutinib with a H2RA (famotidine) reduced rilzabrutinib AUC by approximately 36% and no significant change was

observed in rilzabrutinib exposure if rilzabrutinib was administered at least 2 hours prior to famotidine.

Avoid co-administration of rilzabrutinib with PPIs. If treatment with a gastric acid reducing agent is required, consider using a H2RA. Rilzabrutinib should be administered at least 2 hours before taking a H2RA (see section 4.2). The effect of elevating gastric pH with antacids on the pharmacokinetics of rilzabrutinib has not been studied and may be similar to that seen with famotidine (H2RA). Therefore, it is recommended to take rilzabrutinib at least 2 hours before taking the antacid.

Agents that may have their plasma concentrations altered by rilzabrutinib

*CYP3A substrates*

Rilzabrutinib is both an *in vitro* inhibitor and inducer of the CYP3A4 enzyme. Co-administration of a single 400 mg dose of rilzabrutinib with a CYP3A substrate (midazolam) increased substrate exposure by 1.7-fold in healthy subjects. When midazolam was administered 2 hours after the rilzabrutinib dose there was increase in midazolam exposure approximately by 2.2-fold. The effect of a multiple-dose regimen of rilzabrutinib on CYP3A4 activity was not assessed in clinical trials. Caution should be exercised if co-administering rilzabrutinib with CYP3A substrates with narrow therapeutic range (e.g. cyclosporin).

Transporter substrates

Rilzabrutinib has shown potential to inhibit the P-gp, BCRP, and OATP1B3 transporters *in vitro*. There is a possible risk of drug-drug interactions, therefore, caution should be exercised when co-administering rilzabrutinib with P-gp, BCRP, or OATP1B3 sensitive substrates with a narrow therapeutic range (e.g. digoxin, cyclosporin, tacrolimus) (see section 5.2).

Hormonal contraceptives

The effect of rilzabrutinib on the plasma concentrations of hormonal contraceptives is unknown. Therefore, women of childbearing potential should use an alternative non-hormonal or additional highly effective method of contraception during treatment and for at least 1 month after discontinuation of rilzabrutinib (see section 4.6).

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of child-bearing potential must use highly effective contraception during rilzabrutinib treatment and for 1 month after stopping treatment (see section 4.5 regarding potential interaction with hormonal contraceptives). Pregnancy status of females of child-bearing potential should be verified prior to initiating treatment.

Pregnancy

Rilzabrutinib should not be used during pregnancy and in women of childbearing potential not using contraception. Based on the available nonclinical animal studies, there may be a risk to the foetus (see section 5.3). There are no available data on rilzabrutinib use in pregnant women.

Breast-feeding

There are no available data on the presence of rilzabrutinib or its metabolites in human milk, effects on milk production, or the breastfed infant. No conclusions can be drawn regarding whether or not rilzabrutinib is safe for use during breastfeeding. Rilzabrutinib should be used during breastfeeding

only if the potential benefits to the mother outweigh the potential risks, including those to the breastfed child.

Fertility

There are no data on the effect of rilzabrutinib on human fertility. Effects of rilzabrutinib on male and female fertility were studied in rats at doses up to 300 mg/kg/day [Human Equivalent Dose (HED) 48 mg/kg/day]. Animal studies do not indicate any effect on fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Rilzabrutinib may have a minor influence on the ability to drive and use machines. Mild dizziness has been reported in some patients taking rilzabrutinib and should be considered when assessing a patient's ability to drive or operate machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were diarrhoea (34.5%), nausea (25.4%), headache (18.3%), abdominal pain (15.8%), COVID-19 (15.5%), nasopharyngitis (11.6%), and arthralgia (11.3%). The most frequent adverse reactions resulting in discontinuation of rilzabrutinib, which occurred each in 2 patients (0.7%), were diarrhoea, nausea, headache, and pneumonia.

Tabulated list of adverse reactions

Unless otherwise stated, the following frequencies of adverse reactions are based on the 284 ITP patients exposed to rilzabrutinib in the phase 1/2 and phase 3 clinical trials (see section 5.1). The median duration of exposure was 6.6 months (range: <1 month to 70.8 months).

Adverse reactions are organised according to primary system organ class (SOC) for each preferred term in MedDRA. The adverse reactions are ranked by frequency within each SOC, and presented in order of decreasing seriousness. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000) and not known (cannot be estimated from the available data).

**Table 2: Tabulated list of the adverse drug reactions**

| MedDRA system organ class | Adverse reactions | Frequency (All grades) |
|---|---|---|
| Infections and Infestations | COVID-19 | Very common |
| | Nasopharyngitis | Very common |
| | Pneumonia* | Common |
| Nervous system disorders | Headache | Very common |
| | Dizziness | Common |
| Respiratory, thoracic, and mediastinal disorders | Cough | Common |
| Gastrointestinal disorders | Diarrhoea | Very common |
| | Nausea | Very common |
| | Abdominal pain | Very common |
| | Vomiting | Common |
| | Dyspepsia | Common |
| Skin and subcutaneous tissue disorder | Rash | Common |

| | | |
|---|---|---|
| Musculoskeletal and connective tissue disorders | Arthralgia | Very common |

*Due to aspergillosis in 2 cases

*Description of selected adverse reactions*

*Infections*
Among patients exposed to rilzabrutinib, the most common infection adverse reactions were COVID-19 (15.5%) and nasopharyngitis (11.6%). The majority of infections were Grade 1 or 2 and resolved within 8 days. For those that experienced an adverse reaction of infection, the median time to onset was 2.9 months (range: 1 day; 41.7 months). In the LUNA-3 Study double blind period, Grade 2 or higher occurred in 17.3% and 14.5% in the rilzabrutinib group and placebo group, respectively. Grade 3 or higher occurred in 3.8% in the rilzabrutinib group and none in the placebo group. In the LUNA-3 Study double blind period, serious grade 3 or higher adverse reaction of infection occurred in 2 (1.5%) patients in the rilzabrutinib group, including a fatal case of pneumonia due to aspergillosis and COVID-19, and none in the placebo group.

*Gastrointestinal disorders*
Among patients exposed to rilzabrutinib, the most common GI adverse reactions were diarrhoea (34.5%), nausea (25.4%), and abdominal pain (15.8%). Majority of GI reactions were Grade 1 and resolved with median duration of 19 days for nausea, 12 days for abdominal pain, and approximately 7 days for diarrhoea. For those that experienced a GI adverse reaction, the median time to onset for GI disturbances was 4 days (range: 1 day; 12.7 months).

*Rash*
Among patients exposed to rilzabrutinib, rash (including rash maculo-papular, rash papular, rash erythematous, rash pruritic, erythema, erythema nodosum, urticaria) were all non-serious. All were Grade 1 or 2. For those that experienced an adverse reaction of rash, the median time to onset was 3.4 months (range: 6 days; 57.7 months).

*Other special population*

*Elderly*
Among the patients exposed to rilzabrutinib (n=284), 51 (17.9%) patients were 65 years of age or older. In these elderly patients, 2 (3.9%) patients experienced serious adverse reactions of pneumonia. In patients below 65 years of age, 3 (1.3%) patients had serious adverse reactions of pneumonia and COVID-19.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There is no specific antidote for overdose with rilzabrutinib. In the event of overdose, closely monitor the patient for any signs or symptoms of adverse reactions and appropriate symptomatic treatment immediately.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned, ATC code: not yet assigned

Mechanism of action

Bruton's tyrosine kinase (BTK) is an intracellular signalling molecule of the B-cell and innate immune cells. In B-cells, BTK signalling results in B-cell survival, proliferation, and maturation. In innate immune cells, BTK participates in inflammatory pathways that include, toll-like receptor signalling, Fc gamma receptor signalling, and the activation of the NLRP3 inflammasome.

Rilzabrutinib is a selective, covalent, reversible inhibitor of BTK, with a tailored residence time at BTK to reduce off-target effects. In ITP, rilzabrutinib mediates its therapeutic effect through multi-immune modulation by inhibiting B cell activation, interruption of FcγR mediated phagocytosis, and potentially amelioration of chronic inflammation associated with ITP.

Pharmacodynamic effects

*Cardiac Electrophysiology*

In the "Thorough QT Study," co-administration of 400 mg rilzabrutinib and the CYP3A inhibitor (ritonavir) resulted in plasma exposure 8 times higher than rilzabrutinib alone. Under these conditions, there was no prolongation of the mean QTc interval to any clinically relevant effect. In this same study, a concentration dependent shortening in the QTc interval was observed with a maximum shortening of -10.2 ms (90% CI: -12.24, -8.16) following the supratherapeutic dose (combination of rilzabrutinib and ritonavir 100 mg)]. The shortening was smaller [-7.3 ms (90% CI: -9.33, -5.19)] at the rilzabrutinib 400 mg twice a day dose.

Clinical efficacy and safety

The safety and efficacy of rilzabrutinib in adult patients with primary persistent or chronic immune thrombocytopenia (ITP) was evaluated in a Phase 3, randomized, double-blind (DB), placebo-controlled, parallel-group study consisting of 24 weeks of blinded treatment, followed by an open-label (OL) period of 28 weeks and long-term extension (LTE) period during both of which all patients received rilzabrutinib (LUNA 3 Study). The patients enrolled in this study did not have a sustained response to either intravenous immunoglobulin (IVIg/anti-D) or corticosteroid (CS), or had a documented intolerance or insufficient response to any appropriate course of standard-of-care ITP therapy.

Patients were randomized 2:1 to rilzabrutinib or placebo and randomization was stratified with respect to prior splenectomy and severity of thrombocytopenia.

Concomitant ITP medicinal products [oral CS and/or thrombopoietin receptor agonist (TPO-RA)] were allowed at stable doses at least 2 weeks before the start of the study and throughout the DB period. Rescue therapy was permitted.

Only patients that responded during the first 12 weeks of the DB period could continue the DB treatment until Week 24 before entering the OL period. Those who did not respond could enter the OL period at Week 13 or discontinue from the study. After completing the OL period, eligible patients could continue into the LTE period.

In the LUNA 3 Study, 202 patients were randomized and treated, 133 to the rilzabrutinib group and 69 to the placebo group. At baseline, the median age was 47 years (range: 18 to 80 years), 62.9% were female, 61.9% were Caucasian, and 31.7% Asian. Of the 202 patients, 15.8% (rilzabrutinib) and 21.7% (placebo) were 65 years of age and older while 4.5% (rilzabrutinib) and 4.3% (placebo) were 75 years of age and older.

At baseline, the majority (92.6%) of patients had chronic ITP, with a median time since ITP diagnosis of 7.69 years (range: 0.3, 52.2 years), and 27.7% had undergone splenectomy. The median platelet count was 15 300/μL, with almost half (48%) less than 15 000/μL. Twenty-four (11.9%) patients had

only one prior therapy and 178 (88.1%) patients had ≥ 2 prior therapies. The median number of prior therapies, including splenectomy, was 4 (range: 1 to 15). Prior ITP treatments varied, with the most common prior therapies being CS (95.5%), TPO-RAs (68.8%), IVIg or anti-D immunoglobulins (55.4%), and anti-CD20 monoclonal antibody/rituximab (35.1%.). In addition, at baseline 65.8% of patients received both CS and TPO-RAs. Baseline characteristics were generally similar across both groups.

During the DB period, the median duration of exposure was 98 days (range: 22 to 182) and 84 days (range: 17 to 173) for the rilzabrutinib group and placebo group, respectively. The cumulative duration of treatment exposure was 44.3 participant-years and 17.9 participant years for the rilzabrutinib group and placebo group, respectively. All rilzabrutinib treated patients received 400 mg twice a day. In addition, 39.8% of patients received rilzabrutinib without CS or TPO-RA, 25.6% received rilzabrutinib and CS, 18.8% received rilzabrutinib and TPO-RA, and 15.8% received rilzabrutinib and both CS and TPO-RA.

During the first 12 weeks of the DB period, 85 (63.9%) patients and 22 (31.9%) patients in the rilzabrutinib group and placebo group, respectively, achieved platelet count response (≥ 50 000/μL or between 30 000/μL and < 50 000/μL and doubled from baseline). Among the patients who responded during the DB period, the median time to platelet response was 15 days and 50 days for the rilzabrutinib group and placebo group, respectively. Those who achieved platelet count response by week 13 were eligible to continue the DB period. Fifty-five (41.4%) and 55 (79.7%) patients in the rilzabrutinib and placebo groups, respectively, discontinued the DB period due to not achieving pre-defined criteria of platelet response and/or due to lack of response per investigator judgment. These individuals were counted as treatment failure in the primary endpoint analysis.

In the LUNA 3 Study, the primary endpoint was durable platelet response. A durable platelet response was the achievement of a weekly platelet count ≥ 50 000/μL for at least 8 out of the last 12 weeks of the 24-week DB period in the absence of rescue therapy, The proportion of patients achieving durable response was significantly higher in the rilzabrutinib group (23.3%) compared to the placebo group (0%) during the DB period (see Table 3 for study outcomes). A numerically higher percentage of patients that received rilzabrutinib with concomitant CS and/or TPO-RA had durable platelet response (27.5%) compared to those taking rilzabrutinib as monotherapy (17%).

Key secondary endpoints included persistence of platelet response, onset of clinical response, use of rescue therapy and patient reported outcome related to bleeding (see Table 3 for study outcomes).

**Table 3: LUNA 3 Study outcomes during the 24-week DB period – adult ITT population**

| **Study outcomes** | **Statistic** | **Rilzabrutinib 400 mg twice daily (N=133)** | **Placebo (N=69)** |
|---|---|---|---|
| **Durable platelet response**[1] | n (%) | 31 (23.3) | 0 (0) |
| | 95% CI | 16.12, 30.49 | 0.00, 0.00 |
| | Risk difference (95% CI) vs placebo | 23.1 (15.95, 30.31) | |
| | p-value < 0.0001 | | |
| **Number of weeks with platelet response** | | | |
| ≥ 50 000/μL or between 30 000/μL and < 50 000/μL[2] | LS[4] Mean (SE) | 7.18 (0.747) | 0.72 (0.350) |
| | LS Mean difference (SE) vs placebo | 6.46 (0.782) | |
| | 95% CI | 4.923, 7.990 | |
| | p-value < 0.0001 | | |
| ≥ 30 000/μL[3] | LS Mean (SE) | 6.95 (0.749) | 0.64 (0.337) |
| | LS Mean difference (SE) vs placebo | 6.31 (0.776) | |

| | | | |
|---|---|---|---|
| | 95% CI | 4.787, 7.831 | |
| | p-value < 0.0001 | | |
| **Time to first platelet response**[2] | Median number of days to first platelet response (95% CI) | 36 (22, 44) | NR[5] |
| | Hazard ratio (95% CI) vs placebo | 3.10 (1.948, 4.934) | |
| | p-value < 0.0001 | | |
| **Requiring rescue therapy** | n (%) | 44 (33.1) | 40 (58) |
| | Median number of days to first use of rescue therapy (95% CI) | NR[5] | 56 (36, NR[5]) |
| | Hazard ratio (95% CI) vs placebo | 0.48 (0.309, 0.733) | |
| | p-value = 0.0007 | | |
| **Change from baseline in IBLS score[6] at week 25** | LS Mean (SE) | -0.040 (0.0169) | 0.047 (0.0226) |
| | LS Mean difference (SE) vs placebo | -0.087 (0.0251) | |
| | 95% CI | -0.1358, -0.0373 | |
| | p-value = 0.0006 | | |

[1] Defined as the proportion of participants able to achieve platelet counts ≥ 50 000/μL for ≥ two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are ≥ 50 000/μL during the last 6 weeks of the 24-week blinded treatment period.
[2] Platelet count ≥ 50 000/μL or between 30 000 μL and < 50 000/μL and at least doubled from baseline in absence of rescue therapy.
[3] Platelet count ≥ 30 000/μL and at least doubled from baseline in absence of rescue therapy.
[4] LS: Least Square
[5] NR: Not Reached
[6] The ITP Bleeding Scale (IBLS) is a bleeding assessment questionnaire, with scores ranging from 0 to 2, with higher scores indicating higher presence of marked bleeding; average across anatomical sites.

After the DB period, 180 patients entered the OL period (115 patients from the rilzabrutinib group and 65 patients from the placebo group in the DB period) with a cumulative duration of treatment exposure of 75.6 participant-years. Of these 180 patients, 115 patients completed the 28-week OL period.

In the OL period, 14/65 (21.5%) patients from the placebo group achieved a durable response after being exposed to rilzabrutinib, and 10/84 (11.9%) patients in the rilzabrutinib group achieved a durable response despite not achieving durable response during the DB period.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with rilzabrutinib in one or more subsets of the paediatric population in ITP (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Mean $C_{max}$ (%CV) and AUC24h (%CV) at steady state were estimated to be 150 ng/mL (56%) and 1 540 ng.h/mL (57.5%), respectively, for the ITP population. Accumulation, as reflected by the fold change in maximum median concentrations, was 1.3-fold following dosing at 400 mg twice daily. Rilzabrutinib exhibits approximately dose proportional increases in exposure over the dose range of 300 mg to 600 mg.

Absorption

The absolute oral bioavailability of rilzabrutinib was 4.73%. The median time to peak rilzabrutinib plasma concentrations ($T_{max}$) was 0.5 to 2.5 hours.

*Effect of food*

No clinically significant differences in rilzabrutinib AUC or $C_{max}$ were observed following the administration of a single 400 mg tablet with a high-fat meal, high-calorie meal as compared to dosing under fasting conditions. Resulting $T_{max}$ was delayed by 1.5 hours.

Distribution

Volume of distribution at terminal phase (Vz) after intravenous administration is 149 L. The *in vitro* plasma protein binding of rilzabrutinib is 97.5%, mainly bound to human serum albumin, and the blood-to-plasma ratio is 0.786.

Metabolism

Rilzabrutinib is predominantly metabolized by CYP3A enzymes.

Elimination/Excretion

Rilzabrutinib is rapidly cleared from the plasma, with a $t_{1/2}$ of approximately 3 to 4 hours. Following administration of a single 400 mg 14C-labeled rilzabrutinib dose, radioactivity was predominantly excreted in feces (~86%) and to a lesser extent in urine (~5%) and bile (~6%). Approximately 0.03% of rilzabrutinib is excreted unchanged in the urine.

Special populations

Based on population PK analysis, gender, body weight (range 36-140 kg), race/ethnicity and age (range 12-80 years) had no meaningful effect on rilzabrutinib PK. The PK of rilzabrutinib in Chinese and Japanese populations is similar to the Caucasian population.

*Hepatic impairment*

Rilzabrutinib exposure increased by approximately 1.5-fold in mild hepatic impairment (Child-Pugh Class A) and approximately 4.5-fold in moderate hepatic impairment (Child-Pugh Class B). Rilzabrutinib has not been studied in patients with severe (Child-Pugh Class C) hepatic impairment.

*Renal impairment*

Patients with mild (60-90 mL/min) or moderate (30-60 mL/min) renal impairment participated in rilzabrutinib clinical trials. Population pharmacokinetic analysis suggest that mild or moderate renal impairment do not impact rilzabrutinib exposure.

Transporter inhibition

Rilzabrutinib was shown *in vitro* to be a P-gp substrate, and to a lower extent potentially a substrate of BCRP. Rilzabrutinib was not a substrate for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or BSEP. Rilzabrutinib exhibited *in vitro* a potential to inhibit P-gp, OATP1B1, OATP1B3, and BSEP. However, PBPK simulations suggest that rilzabrutinib does not have any relevant effect on P-gp, BCRP, OATP1B1, and OATP1B3 substrate (see section 4.5).

Pharmacokinetic/pharmacodynamic relationship

*Plasma exposure and BTK occupancy*

Rilzabrutinib has a short duration of systemic exposure with a long duration of action on the target due to its slow dissociation from BTK. At therapeutic doses in healthy participants, durable BTK occupancy in peripheral blood mononuclear cells was observed over a 24-hour period.

## 5.3 Preclinical safety data

General toxicity

In the 6-month repeat-dose toxicology study in rats, the oesophagus (haemorrhage), duodenum (haemorrhage), stomach (haemorrhage), brain (inflammation; neutrophilic inflammation), uterus (distended, pyometra), cervix (distended uterus), vagina (distended uterus), and ovaries (distended uterus) were identified as target organs. The no-observed-adverse-effect-level (NOAEL) was 150 mg/kg/day (AUC exposure margin of 4.5-fold) for males and 50 mg/kg/day (AUC exposure margin of 3.7-fold) for females. No rilzabrutinib-related changes, with the exception of the brain, were observed at the end of the 4-week recovery period. No evidence of neurodegeneration or cellular alteration in the brain was observed.

In a 9-month repeat-dose study in dogs, the stomach (increased intraepithelial lymphocytes with mucosal atrophy) and liver (Kupffer cell pigment, Kupffer cell hypertrophy and increase in ALT and AST) were identified as target organs. the NOAEL of this study was considered to be 30 mg/kg/day (AUC exposure margin of 0.4- to 0.5-fold). At the end of the 4-week recovery period, with the exception of Kupffer cell pigment, the liver and stomach findings had reversed.

Carcinogenicity/genotoxicity

Rilzabrutinib was not mutagenic in an *in vitro* bacterial reverse mutagenicity (Ames) assay, was not clastogenic in an *in vitro* human peripheral lymphocyte chromosomal aberration assay, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in rats.

Rilzabrutinib was not carcinogenic in a 6-month transgenic mouse study.
In a 2-year rat carcinogenicity study, rilzabrutinib-related thyroid adenomas and carcinomas were observed for male rats at 100 mg/kg/day (AUC exposure margin of 2.4-fold). The non-carcinogenic dose was considered to be 30 mg/kg/day (AUC exposure margin of 0.64-fold) for males and 5 mg/kg/day (AUC exposure margin of 0.13-fold) for females. Transcriptomic analysis suggests that thyroid tumours in rats derive from rilzabrutinib-mediated perturbation of thyroid hormone maintenance. This nongenotoxic effect was discovered to be specific for rats with a mechanism not considered relevant to humans, therefore, the potential for thyroid tumours in humans is considered low. In this study, the non-neoplastic observation of erythrocytosis was noted for the mesenteric lymph nodes.

Developmental and reproductive toxicity

In the combined male and female rat fertility study, no rilzabrutinib-related effects were observed for any reproductive parameters. The NOAEL for fertility, reproductive performance, and early embryonic development was considered to be 300 mg/kg/day (HED 48 mg/kg/day), the highest dose evaluated.

In definitive rat and rabbit embryo-foetal toxicity studies, no rilzabrutinib-related foetal development and foetal external, visceral, or skeletal malformations were observed. The embryo-foetal development NOAELs were 300 and 100 mg/kg/day in rats and rabbits, respectively, which were the highest doses evaluated. Exposure ratios (AUC) at the embryo-foetal NOAEL compared to human clinical exposure at 400 mg twice daily, were 11.1- and 4.5-fold, in rats and rabbits, respectively. Skeletal variations of unknown relevance were observed at the same highest dose levels. Variations consisted in a shift in

the number of thoracic and lumbar vertebrae (rats and rabbits) and an increase in the incidence of supernumerary rib pairs (rats). No such variations were observed at 150 and 30 mg/kg/day (resulting in 11.9- and 0.24-fold of clinical exposure at 400 mg twice daily, respectively) in rats and rabbits, respectively. In an exploratory rat embryo-foetal range-finding study, increased post-implantation loss and incidence of early resorption, and decreased foetal weight were observed at 500 mg/kg/day (AUC exposure margin of 21.8-fold). Foetal external, visceral and skeletal changes were observed at 500 mg/kg/day. No malformations were noted at ≤ 150 mg/kg/day (AUC exposure margin of 10-fold). In an exploratory rabbit embryo-foetal range-finding study, a slight increase in the incidence of early resorption was observed at 150 mg/kg/day (AUC exposure margin of 5.6-fold). Foetal visceral changes were observed at 150 mg/kg/day (AUC exposure margin of 5.6-fold).

In a pre-/postnatal developmental toxicity study investigating the effects of orally administered rilzabrutinib, the maternal (F0) systemic toxicity NOAEL was considered to be 50 mg/kg/day (HED 8.1 mg/kg/day). The NOAEL for F1 neonatal/developmental toxicity was considered to be 150 mg/kg/day (HED 24.2 mg/kg/day) and the NOAELs for F1 parental system toxicity, F1 reproductive toxicity, and F2 embryonic toxicity were considered to be 300 mg/kg/day (HED 48 mg/kg/day).

Other Toxicity Studies

Rilzabrutinib did not show any phototoxicity potential in the *in vitro* 3T3 neutral red uptake phototoxicity test.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core

Microcrystalline cellulose (E 460(i))
Crospovidone (Type A) (E 1202)
Sodium stearyl fumarate

Film coating

Polyvinyl alcohol (E 1203)
Macrogol (E 1521)
Titanium dioxide (E 171)
Talc (E 553b)
Sunset Yellow FCF (E 110)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

### 6.5 Nature and contents of container

White, opaque polyvinyl chloride (PVC)/polychlorotrifluoroethylene (PCTFE)-aluminium blister pack in a cardboard wallet with sun/moon symbols containing 28 film-coated tablets.

Pack sizes:

Each blister wallet contains 28 film-coated tablets.

Each pack contains:
- 28 film-coated tablets
- 56 film-coated tablets (2 blister wallets of 28)
- 196 film-coated tablets (7 blister wallets of 28).

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1974/001
EU/1/25/1974/002
EU/1/25/1974/003

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

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

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Sanofi S.r.I .
Strada Statale 17 Km 22,
Scoppito, 67019,
Italy

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where WAYRILZ is marketed, all patients who are expected to use WAYRILZ have access to/ are provided with the following educational material:

- Patient Card (included in each pack, together with the patient leaflet)

**1. Patient educational material:**

**1.1 Patient card:**

The patient card is aligned with the product labelling and includes the following key elements:

• Rilzabrutinib should not be used by pregnant women.

• Language describing how to reduce the potential risk of exposure during pregnancy based on the following:

  o A pregnancy test should be performed before start of treatment with rilzabrutinib.

  o Women of childbearing potential have to use highly effective contraception method during treatment with rilzabrutinib and up to at least 1 month after the last dose.

  o Rilzabrutinib may reduce the efficacy of hormonal contraceptives. Therefore, a non-hormonal contraceptive method should be used or have their male partner use a barrier method.

  o If a pregnancy occurs during treatment with rilzabrutinib contact your treating physician immediately.

• Contact details of the rilzabrutinib prescriber.

• Women of childbearing potential should be instructed to talk to their healthcare professional about contraception while taking rilzabrutinib.

• Instruct patient to refer to PIL for additional information about the safety of rilzabrutinib.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON (with Blue Box)**

## 1. NAME OF THE MEDICINAL PRODUCT

WAYRILZ 400 mg film-coated tablets
rilzabrutinib

## 2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 400 mg of rilzabrutinib

## 3. LIST OF EXCIPIENTS

Contains Sunset yellow FCF (E 110).

See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
56 film-coated tablets
196 film-coated tablets

## 5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1974/001 28 film-coated tablets
EU/1/25/1974/002 56 film-coated tablets
EU/1/25/1974/003 196 film-coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

WAYRILZ 400 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING**

**OUTER WALLET (without Blue Box)**

## 1. NAME OF THE MEDICINAL PRODUCT

WAYRILZ 400 mg film-coated tablets
rilzabrutinib

## 2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 400 mg of rilzabrutinib

## 3. LIST OF EXCIPIENTS

Contains Sunset yellow FCF (E 110).

See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets

## 5. METHOD AND ROUTE OF ADMINISTRATION

Oral use

Read the package leaflet before use.

1. Press and hold here
2. Pull out blister card

Opening Instructions:
[Image for opening instructions]
Press and hold down button (1), while pulling out blister card (2).

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

WAYRILZ 400 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**INNER WALLET**

## 1. NAME OF THE MEDICINAL PRODUCT

WAYRILZ 400 mg film-coated tablets
rilzabrutinib

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Take one tablet by mouth twice a day

Day

Mon
Tue
Wed
Thur
Fri
Sat
Sun

Sun/Moon symbol

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

WAYRILZ 400 mg
rilzabrutinib

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**Patient Card**

**Important safety information for women taking WAYRILZ (rilzabrutinib)**

Treating doctor's name: _____

Treating doctor's phone number: _____

**Pregnancy**

- This medicine should not be used during pregnancy. If a pregnancy occurs during treatment with rilzabrutinib contact your treating physician immediately.
- A pregnancy test should be done before you start taking this medicine.
- Talk to your doctor before taking this medicine if you are pregnant, think you may be pregnant, or are planning on having a baby.

**Contraception**

- It is not known if rilzabrutinib interferes with how well hormonal birth control works.
- You should use an effective method of birth control during and for one month after receiving this medicine to avoid becoming pregnant while being treated with this medicine.
- Tell your doctor if you are taking a hormonal birth control.

*For additional information about the safety of rilzabrutinib, please refer to the patient information leaflet*

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**WAYRILZ 400 mg film-coated tablets**
rilzabrutinib

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

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

**What is in this leaflet**



## 1. What WAYRILZ is and what it is used for

WAYRILZ contains the active substance rilzabrutinib. It belongs to a group of medicines called Bruton's tyrosine kinase inhibitors.

WAYRILZ is used to treat adults with immune thrombocytopenia (ITP) when prior treatments for ITP have not worked well enough. ITP is an autoimmune disease, in which the body´s own immune system attacks and destroys platelets in the blood, causes fatigue, and increases risk of bleeding. Platelets are needed to help create clots and stop bleeding.

The active substance in WAYRILZ, rilzabrutinib, works by blocking Bruton´s tyrosine kinase, a protein in the body that plays a role on the immune system (the body´s defences). By blocking this protein, WAYRILZ can decrease the destruction of blood platelets and help increase the number of healthy platelets in the body. This helps reduce the risk of bleeding.

## 2. What you need to know before you take WAYRILZ

**Do not take WAYRILZ**
- if you are allergic to rilzabrutinib or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**

Talk to your doctor or pharmacist if:
- you have an infection or if you often get infections.
- If you have liver problems

- you have a heart condition known as congenital short QT syndrome or a family history of this syndrome. Taking rilzabrutinib could make this condition worse.

**Children and adolescents**

This medicine should not be used in patients less than 18 years old. The safety and effectiveness of this medicine in this age group are not known.

**Other medicines and WAYRILZ**
Tell your doctor, pharmacist, or nurse if you are taking, have recently taken or might take any other medicines, especially if you take any of the following, but not limited to. This is because rilzabrutinib may affect the way some other medicines work. Also, some other medicines can affect the way rilzabrutinib works.

- Medicines that may increase the concentration of rilzabrutinib in the blood and thus may increase side effects
    - Ritonavir, itraconazole, and fluconazole (used to treat viral and fungal infections)
    - Clarithromycin and erythromycin (used to treat bacterial infections)
    - Verapamil and diltiazem (used to treat high blood pressure)
- Medicines that may reduce the concentration of rilzabrutinib in the blood and thus may reduce efficacy
    - Rifampicin (used to treat bacterial infections)
    - Carbamazepine and phenytoin (which is an anticonvulsant and mood stabilizer)
    - Proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, and pantoprazole (used to treat acid reflux or heartburn)
        - If treatment with a gastric acid reducing agent is required, consider using an H2 blocker medicine, such as famotidine and cimetidine, or antacids (used to treat acid reflux). Take rilzabrutinib at least 2 hours before taking these medicines.
- Medicines whose concentration could be increased by rilzabrutinib and thus may increase their side effects. Caution should be taken when these medicines are taken with rilzabrutinib.
    - Midazolam (used to treat fits (seizures) or epilepsy)
    - Cyclosporin and tacrolimus (used to reduce immune reactions and prevent organ rejection)
    - Digoxin (used to treat abnormal heart rhythm or disorders)
- Medicines that may be less effective when taken with rilzabrutinib
    - Hormonal birth control. It is not known if rilzabrutinib interferes with how well hormonal contraceptives work. Alternative or additional forms of contraception should be considered.

**WAYRILZ with food**
Do not take this medicine with grapefruit, starfruit and products containing these fruits, and with Seville oranges (bitter oranges). This is because they can increase the amount of this medicine in your blood.

**Pregnancy and breast-feeding**

<u>Pregnancy</u>

There is no human information about the safety of this medicine in pregnancy. A pregnancy test should be done before you start taking this medicine. Talk to your doctor before taking this medicine if you are pregnant, think you may be pregnant, or are planning on having a baby.

This medicine should not be used during pregnancy and in women who are able to have children not using birth control. If a pregnancy occurs during treatment with rilzabrutinib contact your treating physician immediately.

It is not known if rilzabrutinib interferes with how well hormonal birth control works. You should use an effective method of birth control during and for one month after receiving this medicine to avoid becoming pregnant while being treated with this medicine. Please tell your doctor if you are taking a hormonal birth control.

Breast-feeding

It is not known whether this medicine passes into breast milk. If you are breastfeeding or planning to breastfeed, talk to your doctor before using this medicine; you and your doctor must decide if you should breastfeed or if you will be given this medicine, taking into account the benefit of breast feeding for the child and the benefit of this medicine for the mother.

**Driving and using machines**
If you feel dizzy after taking this medicine, you should avoid driving or using machines.

**WAYRILZ contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

**WAYRILZ contains sunset yellow FCF (E 110)**
Sunset yellow FCF aluminium lake is a colouring agent which may cause allergic reactions.

## 3. How to take WAYRILZ

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

**How much to take**
The recommended dose is 400 mg twice daily (one tablet of 400 mg two times per day).

Do not change your dose or stop taking this medicine unless your doctor or pharmacist tells you to.

**Taking this medicine**
- You can take this medicine with or without food. If you experience diarrhoea, nausea, or stomach area (abdominal) pain during treatment, taking it with food may reduce these side effects.
- Take tablets at about the same time each day.
- Swallow tablets whole with a glass of water. Do not cut, crush, or chew the tablets.

**If you take more WAYRILZ than you should**
If you take more than you should, talk to a doctor or pharmacist. You may experience possible side effects (see section 4).

**If you forget to take WAYRILZ**
- If you miss a dose, take it as soon as you remember on the same day and return to the regular schedule the following day.
- The missed dose and the next regular scheduled dose must be taken more than 2 hours apart.
- Do not take a double dose to make up for a forgotten dose.

If you are not sure, talk to your doctor, pharmacist or nurse about when to take your next dose.

**If you stop taking WAYRILZ**
Do not stop taking this medicine unless your doctor tells you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

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

**Serious side effects –** uncommon (may affect up to 1 in 100 people)
Tell your doctor immediately if you have any of the following serious side effects:
- COVID-19. Symptoms include fever, chills, cough, difficulty breathing, sore throat, or new loss of taste or smell.
- infection of the lungs (pneumonia). Symptoms include feeling short of breath, chest pain and cough producing discoloured mucus.

**Other side effects**
**Very common** (may affect more than 1 in 10 people)
- Frequent loose stools (diarrhoea)
- Infections of the nose and throat (nasopharyngitis)
- Feeling sick to your stomach (nausea)
- Headache
- Stomach (abdominal) pain
- COVID-19
- Joint pain (arthralgia)

**Common** (may affect up to 1 in 10 people)
- Infection of the lungs (pneumonia)
- Feeling dizzy
- Vomiting
- Indigestion (dyspepsia)
- Cough
- Skin rash

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

## 5. How to store WAYRILZ

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

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

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

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

## 6. Contents of the pack and other information

**What WAYRILZ contains**
The active substance is rilzabrutinib. Each film-coated tablet contains 400 mg of rilzabrutinib.
The other ingredients are:

- Tablet core: microcrystalline cellulose (E 460(i)), crospovidone (type A) (E 1202), sodium stearyl fumarate.
- Tablet coating: polyvinyl alcohol (E 1203), macrogol (E 1521), titanium dioxide (E 171), talc (E 553b), sunset yellow FCF (E 110) (see section 2 WAYRILZ contains sunset yellow FCF (E110)).

**What WAYRILZ looks like and contents of the pack**
WAYRILZ is an orange film-coated tablet, capsule-shaped of 16.6 x 8.1 mm size, marked with "P" on one side and "400" on the other side.

WAYRILZ is supplied in a blister pack containing 28 film-coated tablets in a cardboard wallet. On each blister there are sun/moon symbols to help you take your dose at the right time – the sun for the morning dose and the moon for the evening dose. Both the sun and the moon blisters contain the same medicine.

Each carton contains 28 film-coated tablets in 1 wallet, 56 film-coated tablets in 2 wallets, or 196 film-coated tablets in 7 wallets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Sanofi B.V.
Paasheuvelweg 25
1105 BP
Amsterdam
The Netherlands

**Manufacturer**
Sanofi S.r.I .
Strada Statale 17 Km 22
Scoppito, 67019
Italy

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

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**This leaflet was last revised in** .

**Other sources of information**

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