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

Cenrifki 60 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 60 mg of tolebrutinib.

Excipient with known effect

Each tablet contains 140 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Orange, drop shape tablets of 12.7 mm in length, debossed with "60" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cenrifki is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) without relapses in the last 2 years (see section 5.1).

4.2 Posology and method of administration

The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis.

Posology

The recommended dose is 60 mg orally once daily with a meal. Liver monitoring should be performed before and during treatment (see sections 4.3 and 4.4).

Dose modifications for aminotransferase elevations
Table 1 summarises recommendations for dose adjustment and monitoring for patients who develop elevated transaminases during therapy (see section 4.4).

Table 1: Therapy modifications and monitoring for elevated transaminases

Laboratory abnormalities	Therapy modifications
• ALT† or AST† > 3 x and ≤ 5 x ULN† with clinical symptoms‡ OR with	• Withhold treatment. • Repeat labs every 2-3 days until ALT or AST down-trending and monitor weekly until ALT or AST less than 1.5 x ULN. • Investigate to identify probable causes.

concurrent total bilirubin > 2x ULN • ALT or AST > 5 x ULN	If an alternative cause other than drug-induced liver injury (DILI) is identified, reinitiation of treatment can be considered when ALT or AST decreases to less than 1.5 x ULN. Upon reinitiation of treatment, if ALT or AST greater than 3 x ULN, permanently discontinue treatment.
	If no alternative cause to DILI is identified: • Permanently discontinue treatment if any of the following occurred as the initial event: o ALT or AST greater than 8 x ULN o ALT or AST greater than 5 x ULN for greater than 2 weeks o ALT or AST greater than 3 x ULN and total bilirubin greater than 2 x ULN • If the above criteria are not met, continue treatment as clinically indicated.

† ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
‡ Fatigue, nausea, vomiting, abdominal pain or tenderness, fever, rash, anorexia, jaundice, and/or eosinophilia

Missed dose
If a dose is missed on the intended time of day, take the dose as soon as possible on the same day. Do not double the dose the next day to make up for a missed dose.

Special populations

Elderly
Based on descriptive statistics on observed pharmacokinetic concentrations, no dose adjustment is required for patients aged 65 years and older (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh Class A), although caution must be exercised when initiating treatment in these patients. Tolebrutinib is contraindicated in patients with moderate (Child-Pugh Class B) to severe (Child-Pugh Class C) hepatic impairment and in patients with baseline serum ALT or AST greater than 1.5 x ULN, alkaline phosphatase greater than 2 x ULN (unless explained by a stable chronic liver disorder) or total bilirubin greater than 1.5 x ULN (unless due to Gilbert syndrome or non-liver-related disorder) (see sections 4.3, 4.4. and 5.2).

Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment. There is very limited data in patients with severe renal impairment, therefore, patients with severe renal impairment (< 30 mL/min creatinine clearance) should be treated with tolebrutinib only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity. There are no data in patients on dialysis (see section 5.2).

Paediatric population
The safety and efficacy of Cenrifki in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

This medicinal product is for oral use. Cenrifki must be taken with a meal preferably at the same time each day. Swallow tablets whole with water (see section 5.2).

4.3 Contraindications

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

Patients with moderate to severe hepatic impairment. Patients with baseline serum ALT or AST greater than 1.5 x ULN, alkaline phosphatase greater than 2 x ULN (unless explained by a stable chronic liver disorder) or total bilirubin greater than 1.5 x ULN (unless due to Gilbert syndrome or non-liver-related disorder) (see sections 4.2, 4.4 and 5.2).

Patients with severe immunodeficiency (e.g. acquired immunodeficiency syndrome (AIDS), bone marrow disease, or severe, uncontrolled active infections (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Drug-induced liver injury (DILI)

Clinically significant DILI, including acute liver failure resulting in transplant and/or death, has been reported in patients treated with Bruton tyrosine kinase inhibitors, in clinical trials, including tolebrutinib (see section 4.8). Patients with pre-existing liver disease and patients taking other hepatotoxic medicinal products, herbal or dietary supplements may be at increased risk for developing DILI when taking tolebrutinib. Concomitant use of tolebrutinib with other hepatotoxic medicinal products especially during the first 12 weeks of administration should be undertaken with caution, and alternative options for those drugs should be considered if possible. The use of herbal or dietary supplements with potential hepatotoxicity should be avoided during tolebrutinib treatment. Tolebrutinib is contraindicated in patients with moderate to severe hepatic impairment (see section 4.3).

Safety measures to be taken to mitigate the risk of severe liver injury.

Do not initiate tolebrutinib in patients with pre-existing acute or chronic liver disease, or those with baseline serum ALT or AST greater than 1.5 x ULN, alkaline phosphatase greater than 2 x ULN (unless explained by a stable chronic liver disorder) or total bilirubin greater than 1.5 x ULN (unless due to Gilbert syndrome or non-liver-related disorder).

To mitigate the risk of significant or irreversible DILI, perform blood testing for ALT, AST, alkaline phosphatase, and bilirubin prior to initiation then weekly in the first 12 weeks and monthly in months 4 to 12 after initiation of treatment. Between months 12 and 24, perform monitoring every 6 months. Periodic monitoring thereafter may be performed as warranted. Weekly monitoring should be restarted following treatment interruption due to elevated transaminases or due to a gap in treatment of 1 year or longer. Monitor serum transaminase and bilirubin during treatment, particularly in patients who develop symptoms suggestive of hepatic dysfunction such as fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash, anorexia, or jaundice and/or eosinophilia. Consider additional monitoring when Cenrifki is given with other potentially hepatotoxic medicinal products. If DILI is suspected to be induced by tolebrutinib, discontinue treatment. If tolebrutinib-induced liver injury is unlikely because another probable cause has been found, resumption of therapy may be considered when ALT or AST decreases to less than 1.5 x ULN. Withhold or permanently discontinue treatment if no alternative causes of DILI are identified (see section 4.2).

Health care professionals must be familiar with the educational materials prepared for the management of the DILI risk, including the monitoring of the liver function. Prescribers must provide the patient guide to each patient / caregiver and educate them on the importance of adherence with scheduled laboratory monitoring, signs and symptoms of DILI, and what to do should they experience signs of DILI. Prescribers must also inform patients that a patient card is included in the pack and that patients should carry this card with them at all times during treatment to be able to show it to any other healthcare professional involved in their care.

Infections

Tolebrutinib may cause patients to be more susceptible to infections. Patients with active acute or chronic infections, including opportunistic infections must not start treatment until the infection(s) is

resolved. Monitor patients for signs and symptoms of infection, evaluate promptly, and treat appropriately. If a patient develops any serious infection, suspending treatment with tolebrutinib should be considered and the benefits and risk should be reassessed prior to re-initiation of therapy. Tolebrutinib is contraindicated for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled active infections (see section 4.3).

Concomitant use with immunosuppressants
The safety of concomitant use of immunosuppressants with tolebrutinib has not been studied. However, higher infection rates were observed when tolebrutinib was used concomitantly with immunosuppressants including corticosteroids. Caution should be exercised when using other immunosuppressant medicinal products concomitantly with tolebrutinib. Data are inconclusive as to whether concomitant steroid use for symptomatic treatment of relapses was associated with an increased risk of infections (see section 4.5).

Immunisations

The safety of immunisation with live attenuated or live vaccines following tolebrutinib treatment has not been studied. However, the use of live attenuated or live vaccines may carry a risk of infections and must therefore be avoided. If live attenuated or live vaccines are needed, they should be administered at least 2 months before initiating tolebrutinib treatment. Due to its mechanism of action on B-cell function, tolebrutinib may interfere with the immune response of non-live vaccines. When possible, complete all age-appropriate non-live vaccinations according to current immunisation guidelines prior to initiating tolebrutinib treatment (see section 4.5).

Haemorrhages

Haemorrhagic events were reported in patients treated with tolebrutinib (see section 4.8). The most commonly reported bleeding events were mucocutaneous manifestations including petechiae, contusions, increased tendency to bruise, and heavy menstrual bleeding. Most cases were mild. No bleeding events were associated with thrombocytopenia. Monitor patients for signs and symptoms of bleeding, including petechiae, bruising, and unusual bleeding. Exercise caution in patients with bleeding disorders, known platelet dysfunction, platelet counts below 150,000/mcL or when using tolebrutinib concomitantly with anticoagulants, antiplatelet agents, or other medicinal products that may increase bleeding risk (see section 4.5). If concurrent administration cannot be avoided, increase monitoring frequency for bleeding signs and symptoms. When planning surgical interventions, weigh the benefits and risks of withholding tolebrutinib treatment for 3 to 7 days both prior to and following the procedure, considering the nature of the surgery and the risk of bleeding. Depending on bleeding severity, interrupt or discontinue tolebrutinib and provide appropriate symptomatic treatment.

Malignancies

There does not appear to be an increased risk of malignancy with tolebrutinib in the clinical trial experience. However, second primary malignancies have been reported in oncology patients treated with BTK inhibitors, with the most frequent type being non-melanoma skin cancers.

Atrial fibrillation/flutter

Atrial fibrillation/flutter were reported in patients treated with tolebrutinib. Patients with a history of cardiac arrhythmias, particularly atrial fibrillation/flutter, and those with risk factors for developing atrial fibrillation (such as heart failure or hypertension) may be at increased risk. Monitor signs and symptoms for atrial fibrillation/flutter including palpitations, dizziness, shortness of breath, or chest discomfort, and manage as appropriate.

Suicidal ideation and behaviour

A causal association between treatment with tolebrutinib and increased risk of suicidal ideation and behaviour has not been established, however cases of suicidal ideation and behaviour were reported in

patients receiving tolebrutinib. Patients and caregivers should be advised to be alert for unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm, and to report such symptoms immediately to healthcare professionals.

Interactions with moderate or strong CYP2C8 inhibitors

Use of medicinal products that inhibit the activity of CYP2C8 would be expected to result in increased levels of tolebrutinib and decreased levels of the M2 active metabolite. As a precaution, concomitant use of moderate or strong CYP2C8 inhibitors with tolebrutinib should be avoided (see section 4.5).

Interactions with moderate or strong CYP3A/2C8 inducers

Concomitant use of tolebrutinib with moderate or strong CYP3A/2C8 inducers should be avoided. If a moderate or strong CYP3A/2C8 inducer must be used short-term (< 2 weeks), treatment with tolebrutinib can be continued. The effects of tolebrutinib may be diminished during this time (see section 4.5).

Excipient with known effect

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Tolebrutinib is metabolised mainly by CYP2C8 and to a lesser extent by CYP3A4. The active metabolite M2 is formed from tolebrutinib exclusively via CYP2C8 and is mainly metabolised by CYP3A4/5 and, to a lesser extent, by CYP2D6.

Strong or moderate CYP2C8 inhibitors

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil 600 mg twice daily) increased tolebrutinib AUC and C_{max} by 8.4-fold and 5.4-fold, while M2 AUC and C_{max} decreased by 25-fold and 50-fold, compared to single administration of tolebrutinib under fed conditions. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of strong CYP2C8 inhibitors (e.g., gemfibrozil) or moderate CYP2C8 inhibitors (e.g., deferasirox, letermovir, selpercatinib) with tolebrutinib should be avoided (see section 4.4). In case of known CYP2C8 poor metaboliser status of a patient, caution is to be exercised due to the potential changes in exposure to tolebrutinib and M2.

Strong or moderate CYP3A/2C8 inducers

Co-administration of a strong CYP3A/2C8 inducer (rifampicin 600 mg once daily) decreased both tolebrutinib AUC and C_{max} by 6.2-fold, while M2 AUC and C_{max} decreased by 2.4-fold and 1.9-fold in healthy subjects. Moderate CYP3A/2C8 inducer efavirenz may also decrease tolebrutinib and M2 metabolite exposures. Co-administration of tolebrutinib with strong CYP3A/2C8 inducers (e.g., carbamazepine, phenytoin, rifampicin, St. John's wort) or moderate CYP3A/2C8 inducers (e.g., bosentan, efavirenz, etravirine, nafcillin) should be avoided. If a moderate or strong CYP3A/2C8 inducer must be used short-term (< 2 weeks), treatment with tolebrutinib can be continued (see section 4.4).

Immunosuppressants

Caution should be exercised when using other immunosuppressant drugs (e.g., chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) concomitantly with tolebrutinib (see section 4.4).

Immunisations

The safety of immunisation with live attenuated or live vaccines (e.g., varicella zoster, oral polio, nasal influenza vaccines) following tolebrutinib treatment has not been studied and must be avoided due to the potential risk of infections. The efficacy of non-live vaccines may be reduced during treatment with tolebrutinib (see section 4.4).

Antiplatelet or anticoagulant agents

Caution should be exercised when using tolebrutinib concomitantly with anticoagulants (e.g., warfarin, heparin, apixaban, rivaroxaban, edoxaban) or antiplatelet agents (e.g., clopidogrel, ticagrelor, prasugrel) due to the risk of bleeding events. If concurrent administration cannot be avoided, increase monitoring frequency for bleeding signs and symptoms (see section 4.4).

Transporter substrates

Tolebrutinib has shown potential to inhibit the P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, and MATE1 transporters *in vitro*. There is a possible risk of drug-drug interactions, therefore, caution should be exercised when co-administering tolebrutinib with P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, or MATE1 sensitive substrates with a narrow therapeutic range (e.g. digoxin, cyclosporin, tacrolimus).

Strong CYP3A inhibitors

No clinically significant differences in tolebrutinib pharmacokinetics were observed when co-administered with a strong CYP3A inhibitor (itraconazole 200 mg daily). Co-administration of tolebrutinib 60 mg using fed conditions with itraconazole (200 mg OD × 4 days) increased both tolebrutinib AUC and C_{max} by 1.88 and M2 AUC and C_{max} by 1.78. No dose adjustments of tolebrutinib is required during co-administration with strong CYP3A inhibitors.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data available from the use of tolebrutinib in pregnant women. Tolebrutinib and/or its metabolites crossed the placenta in rabbits. Animal studies with tolebrutinib do not indicate reproductive toxicity. However, there is insufficient information on embryo-foetal development regarding the active metabolite M2, therefore, a risk to the unborn child cannot be excluded (see section 5.3). Cenrifki is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There is insufficient information on the excretion of tolebrutinib or its metabolites in human milk. A risk to breast-fed newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to abstain/discontinue from therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

The effects of Cenrifki on fertility in humans are unknown. Animal studies with tolebrutinib and its M2 metabolite showed no adverse effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Cenrifki has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are COVID-19 (25.5%) and upper respiratory infections (16.9%) (see section 4.4). The most common serious adverse reaction is COVID-19 pneumonia (1.1%).

Tabulated list of adverse reactions

Adverse reactions reported with tolebrutinib from the clinical trials are listed below in Table 2. The adverse reactions are listed by MedDRA system organ class and categories of frequency. 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions

MedDRA System Organ Class (SOC)	Very common	Common
Infections and Infestations	COVID-19[1] Upper respiratory tract infections[1]	Influenza Lower respiratory tract and lung infections[1]
Vascular disorders		Increased tendency to bruise[2] Petechiae Contusion
Gastrointestinal disorders		Abdominal pain[1]
Reproductive system and breast disorders		Heavy menstrual bleeding[2]
Investigations		Alanine aminotransferase (ALT) elevation[3]

[1] Includes multiple preferred terms.
[2] Pooled data from clinical studies EFC16645 (HERCULES), EFC16033 (GEMINI I) and EFC16034 (GEMINI II)
[3] ALT greater than 3-fold ULN.

Description of selected adverse reactions

Drug-induced liver injury (DILI)
In the pivotal EFC16645 (HERCULES) study, ALT elevations greater than 3 x the upper limit of normal (ULN) were observed in 4.0% of patients treated with tolebrutinib and 1.6% of patients receiving placebo. Among the 754 tolebrutinib-treated patients, 0.5% experienced ALT elevations greater than 20 x ULN, and 0.3% had ALT elevations greater than 3 x ULN with concurrent bilirubin increases greater than 2 x ULN, all without alternative causes of DILI and all occurred within three months of initiating tolebrutinib treatment. In a majority of patients, patient's liver enzymes resolved spontaneously without sequelae following permanent discontinuation of tolebrutinib. One patient developed liver failure requiring a liver transplant and subsequently died due to a post-transplant complication (see section 4.4).

Infections
In the pivotal EFC16645 (HERCULES) study, 54.4% of patients receiving tolebrutinib experienced infections with 5.2% reporting severe (Grade 3 or higher) infections compared to those treated with placebo (2.9%). The most common infection adverse reactions were COVID-19 (25.5%) and upper respiratory infections (16.9%). The majority of these patients had symptom resolution without permanent discontinuation of tolebrutinib. However, one fatal case of pneumonia (bacterial) occurred

in a disabled patient in a setting of delayed care treated with tolebrutinib 60 mg for 1.8 years (see section 4.4).

Petechiae, increased tendency to bruise, heavy menstrual bleeding, contusions
In the pivotal EFC16645 (HERCULES) study, 2.7% of tolebrutinib-treated patients experienced petechiae, compared to 0.3% of those on placebo, and 3.9% of tolebrutinib-treated patients experienced contusions, compared to 1.1% of those on placebo. Across the clinical studies EFC16645 (HERCULES), EFC16033 (GEMINI I) and EFC16034 (GEMINI II), 1.5% of tolebrutinib-treated patients showed an increased tendency to bruise, compared to 0% of those on placebo and 0.3% of those on teriflunomide, and 1.7% of tolebrutinib-treated patients experienced heavy menstrual bleeding, compared to 0.3% of those on placebo and 1% of those on teriflunomide. 1% of patients with heavy menstrual bleeding also developed mild to moderate anaemia. None of the petechiae, bruising, heavy menstrual bleeding or contusions were associated with thrombocytopenia in clinical trials. Most cases were mild. Patients on anticoagulants or anti-platelet treatments, those with significant bleeding history within 6 months prior to screening, bleeding disorders, known platelet dysfunction, platelet counts below 150 000/mcL, or major surgery within 4 weeks prior to screening were excluded from the trials (see section 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose

Cenrifki 240 mg daily up to 14 days was well tolerated by healthy adult subjects. Signs and symptoms of tolebrutinib overdose have not been established and there is no specific treatment for overdose. Patients who experience overdose should be closely monitored and provided with appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA62

Mechanism of action

Tolebrutinib is primarily an inhibitor of Bruton's tyrosine kinase (BTK). Although the exact mechanism by which tolebrutinib exerts its therapeutic effect in MS is not fully understood, there is evidence to support it inhibits the activation of B cells, macrophages and microglia in the periphery and CNS.

Pharmacodynamic effects

The median steady state of BTK occupancy in peripheral blood mononuclear cells was maintained at greater than 90% over 24 hours in healthy subjects dosed with tolebrutinib 60 mg/day with a meal.

Cardiac electrophysiology

The effect of tolebrutinib and the active metabolite M2 on the QTc interval was evaluated using concentration–QTc effect modelling of data obtained during a Phase 1 study with high-quality ECG

recording. There were no effects on QTc interval or other ECG parameters at single doses up to 300 mg of tolebrutinib.

Clinical efficacy and safety

Efficacy of tolebrutinib in SPMS was evaluated in adult patients in one randomised, double-blind, 2-arm, placebo-controlled, parallel group, multicentre, event-driven pivotal study, study EFC16645 (HERCULES), with a variable treatment duration ranging from approximately 24 to 48 months.

A total of 1131 patients were randomised 2:1 to receive either tolebrutinib 60 mg daily (n=754) or a matching placebo daily (n=377). All patients (18 to 60 years of age, inclusive) had a previous diagnosis of relapsing remitting multiple sclerosis (RRMS), a current diagnosis of SPMS, documented evidence of disability progression observed during the 12 months before screening, a baseline Expanded Disability Status Scale (EDSS) of 3 to 6.5, and an absence of clinical relapses for at least 24 months. There were no exclusions based on MRI activities at baseline. Patients with ALT, AST, total bilirubin greater than 1.5 x ULN (unless due to Gilbert syndrome or non-liver related disorder) or ALP greater than 2 x ULN were excluded. Neurological evaluations were performed every 12 weeks and at the time of a suspected relapse. Brain MRIs were performed at baseline and at months 6, 12, 18, 24, 36, and then yearly until end of study.

The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 48.9 years; 61.5% were female. Median time since RRMS symptom onset was 16.2 years and the mean EDSS score was 5.5. At baseline, 12.7% of patients had one or more T1 Gd-enhancing lesions.

The primary endpoint was time to onset of 6 month confirmed disability progression (CDP). Progression of disability was defined as an increase of 1.0 point or more from the baseline EDSS score when the baseline EDSS score was 5.0 or less, or by 0.5 points or more when the baseline EDSS score was above 5.0. Disability progression was considered confirmed when the increase in the EDSS score was established at a regularly scheduled visit at least 6 months after the initial documentation of neurological worsening with both onset and confirmation EDSS assessments having no relapses in the prior 90 days. Additional outcome measures included new or enlarging T2-hyperintense lesions, delay in disability progression confirmed at 3 months, 6-month confirmed disability improvement (CDI), and 20% increase in timed 25-foot walk test (T25-FW) and in 9-hole peg test (9-HPT) confirmed for at least 3 months.

Based on a time-to-event analysis, the risk of 6-month CDP was significantly reduced by 31% in patients treated with tolebrutinib compared to placebo (see Figure 1). Tolebrutinib also significantly reduced the risk of 3-month CDP by 24%. MRI analysis demonstrated that patients treated with tolebrutinib had a significant 38% reduction in the adjusted mean number of new and/or enlarging T2-hyperintense lesions per year compared to patients treated with placebo. Overall, the results of the secondary endpoint “time to onset of sustained 20% increase in 9-HPT” did not reach statistical significance; “time to onset of sustained 20% increase in the T25-FW for at least 3 months” and “6-month CDI”, did not reach formal statistical significance based on a pre-specified hierarchical testing order.

More detailed efficacy results are presented in Table 3 and Kaplan-Meier curves for 6-month CDP are provided in Figure 1.

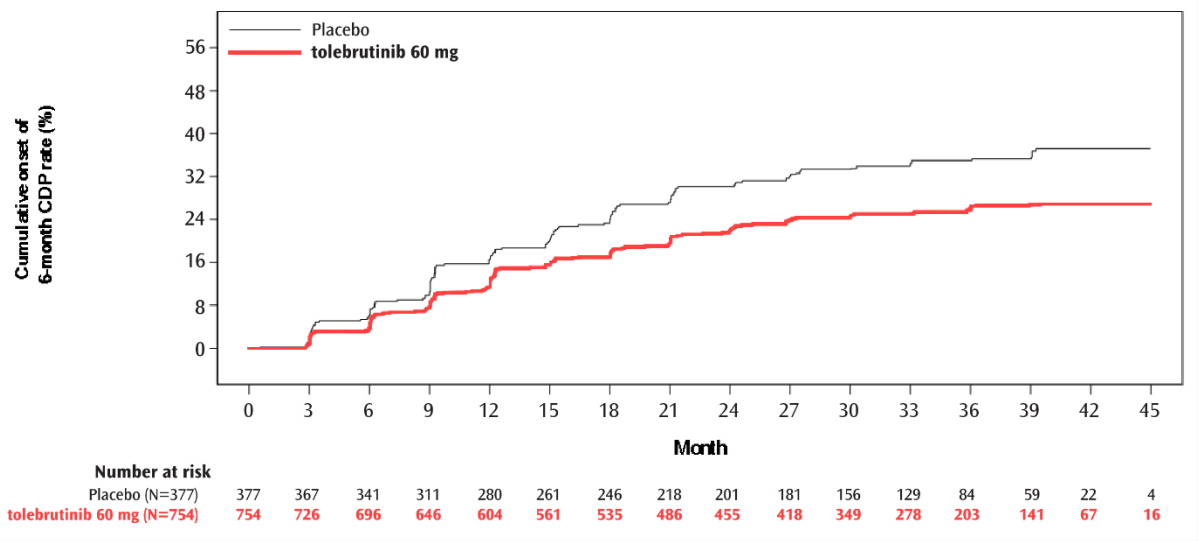
Table 3 - Clinical and MRI endpoints in adult SPMS patients for Study EFC16645 (HERCULES)

	Tolebrutinib 60 mg daily N = 754	**Placebo N = 377**
Clinical Outcomes		
6-month CDP, Proportion of patients	22.6%	30.7%
Hazard Ratio (95% CI)	0.69 (0.55, 0.88)*	

3-month CDP, Proportion of patients	27.6%	34.2%
Hazard Ratio (95% CI)	0.76 (0.61, 0.94)*	
Sustained 20% increase in 9-HPT for at least 3 months, Proportion of patients	19.0%	19.6%
Hazard Ratio (95% CI)	0.97 (0.74, 1.29)	
Sustained 20% increase in T25-FW for at least 3 months, Proportion of patients	41.1%	49.6%
Hazard Ratio (95% CI)	0.77 (0.64, 0.92)	
6-month CDI, Proportion of patients	8.6%	4.5%
Hazard Ratio (95% CI)	1.88 (1.10, 3.21)	
MRI endpoint		
New and/or enlarging T2-hyperintense lesions per year	1.8	2.9
Relative risk (95% CI)	0.62 (0.43, 0.90)*	

* Multiplicity-controlled, statistically significant

Figure 1: Study EFC16645 (HERCULES) - Kaplan-Meier plot of cumulative incidence rate of onset of 6-month CDP - ITT population



Tolebrutinib demonstrated overall benefit on time to onset of 6-month-CDP in patients with or without baseline T1 Gd-enhancing lesions, despite numerical differences in magnitude of the treatment effects obtained. The treatment effect of tolebrutinib on time to onset of 6-month CDP in the subgroup of patients with baseline T1 Gd-enhancing lesions (i.e. active SPMS) (N = 142) (risk reduction 65%, HR 0.35 [95% CI 0.18, 0.66]) was numerically greater compared to that in the subgroup of patients without baseline T1 Gd-enhancing lesions (i.e. non-active SPMS) (N = 989) (risk reduction 22%, HR 0.78 [95% CI 0.60, 1.01]).

Studies EFC16033 (GEMINI I) and EFC16034 (GEMINI II) were randomised, double-blind, double-dummy, active-controlled studies with teriflunomide in patients with relapsing multiple sclerosis (RMS). Around 99% of the included patients were diagnosed with RRMS and around 1% with SPMS. Both studies did not achieve their primary goal of showing a significant improvement in annualised relapse rates (ARR) compared to teriflunomide. A pre-specified analysis of data pooled from both studies demonstrated a 29% relative risk reduction in 6-month Confirmed Disability Worsening (CDW) for tolebrutinib compared to teriflunomide (HR 0.71 [95% CI 0.53, 0.95]), with 77.9% of the 6-month CDW events representing progression independent of relapse activity (PIRA) defined by the absence of adjudicated relapses within 90 days before or after the onset of disability worsening.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with tolebrutinib in all subsets of the paediatric population for the treatment multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of tolebrutinib was studied in healthy subjects and patients with MS. Tolebrutinib mean maximum plasma concentration (C_{max}) and AUC values increased higher than dose proportional with doses between 5 and 60 mg, but close to dose proportional for doses between 60 and 300 mg. At the recommended dose of 60 mg daily with a meal, the mean steady state (% coefficient of variation [CV]) and maximum plasma concentration (C_{max}) for tolebrutinib were 29.6 (60%) ng•h/mL and 9.94 (62%) ng/mL, respectively, and for M2 metabolite were 84.6 (62%) ng•h/mL and 27.5 (59%) ng/mL, respectively. M2 metabolite circulates with an exposure ranging from 2.4 to 6.5-fold higher than the parent compound and exhibits similar covalent binding potency at nanomolar level on BTK to tolebrutinib.

Absorption

Absolute oral bioavailability of tolebrutinib after a single oral 60 mg dose with a meal was 10.3%, increased by 2-fold compared to fasted state. Administration of a single oral 60 mg dose under a fed state led to an increase of tolebrutinib exposure by 1.77-fold with no increase in M2 metabolite exposure. The median time to reach C_{max} of tolebrutinib and M2 were around 1.3 hours in all studied populations).

Distribution

The steady state volume of distribution of tolebrutinib was approximately 255 L. The tolebrutinib and M2 *in vitro* unbound fraction ranged from 11.1 to 12.5% and from 8.65 to 38%, respectively. In healthy subjects, tolebrutinib and the M2 metabolite appear in the cerebrospinal fluid (CSF), with a mean CSF to plasma ratio up to 1.16 and 0.45, respectively.

Metabolism

Tolebrutinib is metabolised mainly by CYP2C8 and to a lesser extent by CYP3A4. The M2 metabolite is formed from tolebrutinib exclusively via CYP2C8 and is metabolised mainly by CYP3A4/5 and to a lesser extent by CYP2D6. M2 circulates with an exposure 2.4 to 6.5-fold higher than the parent compound and exhibits similar covalent binding potency at nanomolar level on BTK to tolebrutinib.

Elimination

After single doses up to 300 mg and repeated doses up to 240 mg, the terminal half-lives for tolebrutinib and M2 were similar (4.4 to 7.8 hours) and did not vary according to dose after single and repeated once daily administration, with no measurable accumulation after repeated administration.

Excretion

Following a single 60 mg radiolabelled tolebrutinib dose in healthy subjects, over 90% of the dose was recovered within 216 hours, with majority (85%) of radioactivity within 72 hours. 78% of the dose was recovered in the faeces and 14% of the dose was recovered in the urine. Unchanged tolebrutinib accounted for 3.8% of the radiolabelled excreted dose in faeces and none in urine.

Characteristics in specific groups of patients

Gender, body weight, race and elderly
Based on descriptive statistics on observed pharmacokinetic concentrations in patients, gender,

age (over the range 18 to 76 years), body weight (over the range 37 to 143 kg), and race had no meaningful effect on tolebrutinib pharmacokinetics.

Renal impairment
Following a single oral dose of 60 mg tolebrutinib under fed conditions in subjects with severe renal impairment (GFR less than 30 mL/min) not requiring dialysis, the total and unbound tolebrutinib C_{max} and AUC in participants were slightly higher (≤ 1.6-fold) compared to subjects with normal renal function. The total and unbound M2 C_{max} were similar, and the AUC were slightly higher (≤ 1.2-fold). There is very limited data in patients with severe renal impairment. Tolebrutinib has not been studied in patients requiring dialysis (see section 4.2).

Hepatic impairment
Following a single oral dose of 60 mg tolebrutinib under fed conditions in subjects with mild hepatic impairment, total and unbound tolebrutinib AUC and M2 AUC were similar (between 0.87-fold and 1.26-fold). No formal studies were conducted to examine the effects of moderate or severe hepatic impairment on the pharmacokinetics of tolebrutinib. Tolebrutinib is contraindicated in patients with moderate or severe hepatic impairment and in patients with baseline serum ALT or AST greater than 1.5 x ULN, alkaline phosphatase greater than 2 x ULN (unless explained by a stable chronic liver disorder) or total bilirubin greater than 1.5 x ULN (unless due to Gilbert syndrome or non-liver-related disorder) (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Repeated-dose toxicity

In rats, dose-limiting toxicity was observed in the 6-month oral tolebrutinib toxicity study, consisting of immune system effects (decreased antigen response and increased susceptibility to rectal parasites), haemorrhage in various tissues and organs (including intraocular bleeding), and skin lesions. Microscopic findings in the pancreas (fibrosis, chronic inflammation and haemorrhages) correlated with species-specific pancreatic toxicity of BTK inhibitors in rats. In general, toxicities were observed at the lowest dose administered corresponding to 23- and 29-times the steady-state AUC at the maximum recommended human dose (MRHD), in male and female rats.

In a dedicated 6-month toxicity study with oral administration of the M2 metabolite to rats, similar toxicities to that of tolebrutinib were observed at the lowest dose administered, corresponding to 6- and 12-times the steady-state AUC of M2 at the MRHD of tolebrutinib in male and female rats.

In the 2-year tolebrutinib carcinogenicity study in rats, haemorrhages, skin lesions, immune system effects, and pancreatic findings occurred at the lowest dose administered corresponding to 1.2- and 4.4-times the steady-state AUC at the MRHD, in male and female rats. Increased mortality occurred in male rats at exposures 10-times steady-state AUC at the MRHD, notably as a result of premature euthanasia due to severe intraocular haemorrhages. Taken together, these findings indicate that prolonged tolebrutinib treatment appear to lower the exposure margin for toxicities to the clinically relevant area of concern.

In the 9-month tolebrutinib toxicity study in dogs, a non-adverse increased haemorrhagic tendency was seen in multiple organs from 15-times the steady-state AUC at the MRHD.

Genotoxic and carcinogenic potential

No genotoxic or carcinogenic potential was seen for tolebrutinib or the M2 metabolite based on conventional *in vitro* and *in vivo* studies.

Reproductive toxicity

No effects of tolebrutinib on reproductive, embryo-foetal and pre-/postnatal development were observed in rats and rabbits at exposures sufficiently in excess to human exposure (> 100-times the steady-state AUC at the MRHD).

However, dose-dependent incomplete hyoid ossification was noted at clinically relevant exposure of the M2 metabolite in the embryo-foetal development study of tolebrutinib in rabbits (< 1.3-times the steady-state AUC of M2 at the MRHD of tolebrutinib). The human relevance is unknown.

No biologically meaningful effects of the M2 metabolite were seen following direct oral administration in fertility or pre- and post-natal development studies in rats at clinically relevant exposures.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Crospovidone Type A
Magnesium stearate

Tablet coating

Hypromellose
Titanium dioxide
Yellow iron oxide (E172)
Red iron oxide (E172)
Macrogol - polyethylene glycol (400)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30˚C.

6.5 Nature and contents of container

Polyamide/aluminium/poly(vinyl chloride) - aluminium blisters inserted in wallets (7 or 28 film-coated tablets) and packed in cartons containing 7, 28, and 98 film-coated tablets.

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.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 Avenue Raspail
94250, Gentilly
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2011/001
EU/1/25/2011/002
EU/1/25/2011/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

Sanofi S.r.l.
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**

Prior to the launch of Cenrifki in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at minimising the risk of drug-induced liver injury (DILI).

The MAH shall ensure that in each Member State where Cenrifki is marketed, all healthcare professionals and patients who are expected to prescribe, dispense, or use Cenrifki have access to/are provided with the following educational package:

- Healthcare professionals (HCPs) educational materials

- Patients' educational materials

1. <u>HCP educational materials:</u>

- Summary of Product Characteristics (SmPC).
- Prescriber Guide.

1.1. Prescriber Guide:

The **Prescriber Guide** includes the following key elements:

- List of contraindications.
- Relevant information about the risk of DILI, its monitoring and management:
  - Background:
    - Clinically significant DILI has been reported in tolebrutinib Phase 3 clinical trials, including one patient who developed liver failure resulting in transplant and subsequently died due to a post-transplant complication.
    - Incidence of increased serum alanine transaminase (ALT) cases in clinical trials, consistently with SmPC information.
    - All cases of ALT elevations > 20 x the upper limit of normal (ULN) or ALT elevations > 3 x ULN with concurrent bilirubin increases > 2 x ULN occurred within 12 weeks of initiating tolebrutinib treatment.
    - Justification for the weekly monitoring during the first 12 weeks.
  - Treatment initiation:
    - Obtain serum transaminase and total bilirubin levels before initiation then weekly in the first 12 weeks, monthly in months 4 to 12, then every 6 months between months 12 and 24, of tolebrutinib therapy:
      - Consider additional monitoring when tolebrutinib is given with other potentially hepatotoxic medicinal products.
  - During treatment:
    - Follow recommended actions (including therapy modifications) for the management of elevated transaminases and symptoms suggestive of hepatic dysfunction.
    - Avoid the use of herbal or dietary supplements with potential hepatotoxicity.
- Important information to communicate to patient:
  - Provide the Patient Guide to the patient and inform the patient that a Patient Card is included in the pack and that the patient should carry this card with them at all times during treatment.
  - Educate patient on the importance on doing the serum transaminase and total bilirubin tests before initiation then weekly in the first 12 weeks, monthly in months 4 to 12, then every 6 months between months 12 and 24, of tolebrutinib therapy.
  - Educate patient on signs and symptoms of DILI.
  - Educate patient on the importance to alert the prescriber in case of elevated liver enzymes.
  - Educate patient on the importance to alert the prescriber in case of signs of DILI.
  - Educate patient to immediately inform the prescriber in case of missed liver function test.
  - Educate patient to avoid the use of herbal or dietary supplements with potential hepatotoxicity during treatment

2. <u>Patient educational materials</u>

- Package leaflet
- Patient Guide
- Patient Card

2.1. Patient Guide:

The Patient Guide includes the following key elements:

- A recommendation to read the package leaflet and Patient Guide prior to initiating treatment.
- A description of the risk of DILI.
- A description of the signs and symptoms of DILI.
- A description of the best course of action if signs and symptoms of DILI present themselves.

- Importance and need to do serum transaminase and total bilirubin tests before initiation then weekly in the first 12 weeks, monthly in months 4 to 12, then every 6 months between months 12 and 24, of tolebrutinib therapy.
- Immediately inform the prescriber in case of missed liver function test.

2.2. Patient Card:

The Patient Card (included in each pack, together with the package leaflet) is aligned with the product labelling and includes the following key elements:

- Remind the patient that tolebrutinib can cause serious liver problems and requires strict adherence to regular liver-function monitoring.
- Symptoms can include tiredness, nausea, vomiting, pain in the abdomen, fever, rash or itching of your skin, loss of appetite or interest in food, dark urine, or yellowing of skin or eyes.
- Seek medical attention or advice immediately if symptoms of liver problems occur.
- Include contact details of the prescribing physician.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Cenrifki 60 mg film-coated tablets
tolebrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 60 mg of tolebrutinib.

3. LIST OF EXCIPIENTS

Also contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

7 film-coated tablets
28 film-coated tablets
98 film coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30˚C.

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 Winthrop Industrie
82 Avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2011/001 (7 film-coated tablets)
EU/1/25/2011/002 (28 film-coated tablets)
EU/1/25/2011/003 (98 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cenrifki 60 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

WALLET

1. NAME OF THE MEDICINAL PRODUCT

Cenrifki 60 mg film-coated tablets
tolebrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 60 mg of tolebrutinib.

3. LIST OF EXCIPIENTS

Also contains: lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

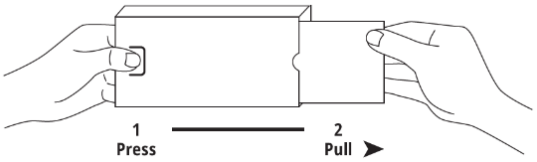
7 film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

Opening instructions:
Press down at 1 and at the same time pull at 2.



Press and hold here
Pull out blister card

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

Do not store above 30˚C.

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 Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2011/001 (7 film-coated tablets)
EU/1/25/2011/002 (28 film-coated tablets)
EU/1/25/2011/003 (98 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cenrifki 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTER

BLISTER CARD

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cenrifki 60 mg film-coated tablets
tolebrutinib

Oral use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Calendar days
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER ALUMINUM FOIL

1. NAME OF THE MEDICINAL PRODUCT

Cenrifki 60 mg film-coated tablets
tolebrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Patient Card

Front of the card

Patient Card - Cenrifki (tolebrutinib)

This card contains important information about tolebrutinib. **Carry with you at all times**.
Read the package leaflet and patient guide carefully before use.

This medicine may cause serious liver problems. Your doctor needs to check that your liver is working well. You must complete the following blood tests:

- **Prior to initiation of treatment**
- **Once every 7 days** for the first 12 weeks,
- **Monthly** in months 4 to 12,
- **Every 6 months** between months 12 and 24.

Refer to the package leaflet for additional safety information.

Back of the card

Signs and symptoms of liver problems:
Tell your doctor immediately if you have symptoms such as tiredness, nausea, vomiting, pain in the abdomen, fever, rash or itching of your skin, loss of appetite or interest in food, dark urine, or yellowing of skin or eyes.

Other medicines including supplements:
Tell your doctor, pharmacist, or nurse if you are taking, have recently taken or might take any other medicines, especially those that may affect your liver, including herbal and dietary supplements. If you are unsure, talk to your doctor.

Prescribing physician name: ……..
Prescribing physician phone number: ...…….

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Cenrifki 60 mg film-coated tablets
tolebrutinib

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

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

What is in this leaflet

1. What Cenrifki is and what it is used for

Cenrifki contains the active substance tolebrutinib. It is a protein kinase inhibitor, which is a type of substance that adjusts the immune system.

Cenrifki is used in adults to treat secondary progressive multiple sclerosis (SPMS) who have not experienced any relapses in the last 2 years.

Multiple sclerosis (MS) affects the central nervous system, especially the nerves in the brain and spinal cord. In MS, the immune system (the body's defence system) works incorrectly and attacks a protective layer (called the myelin sheath) around nerve cells and causes inflammation which stops the nerves from working properly. Secondary progressive multiple sclerosis (SPMS) is described as a stage of the disease that follows an initial period of relapsing MS (RMS) and is marked by a gradual, steady worsening of neurological function and increasing disability.

Although the way the active substance in Cenrifki, tolebrutinib, works is not clearly understood it is thought to target specific immune cells in the central nervous system, known as B cells and microglia. This is expected to reduce activation of the immune system and prevents inflammation caused by MS, which slows the progression of the disease.

2. What you need to know before you take Cenrifki

Do not take Cenrifki:
- if you are allergic to tolebrutinib or any of the other ingredients of this medicine (listed in section 6).
- if you have moderate to severe liver problems.
- if you have a severely weakened immune system (e.g., if you have acquired immunodeficiency syndrome (AIDS), bone marrow disease, or severe infections that are not under control).

If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor or pharmacist before taking Cenrifki:
- if you suffer from liver disease
- if you are taking or plan to take other medicines that may affect your liver, especially during the first 12 weeks of Cenrifki treatment. Your doctor may need to consider alternative options for those medicines.
- if you are using or plan to use herbal or dietary supplements. Some of these may potentially affect your liver, and you should avoid using them while taking Cenrifki.
- if you have an infection, or you are unable to fight infections (see section 2 'Infections').
- if you are going to have a vaccination (see section 2 'Vaccinations').
- if you have a bleeding disorder, have recently undergone surgery or have one scheduled, or are taking medicines that may increase your risk of bleeding (see section 2 'Other medicines and Cenrifki').
- if you have a history of irregular heartbeat particularly atrial fibrillation.
- if you have or have had thoughts of harming or killing yourself. You (or your caregiver) should contact your doctor immediately if any such thoughts occur.
- if you are taking medicines that can affect the levels of Cenrifki in your blood (see section 2 'Other medicines and Cenrifki')

This medicine may cause your liver to not work properly, particularly in the first 12 weeks. Inform your doctor immediately if you have signs that could indicate potential liver problems such as:
- tiredness
- nausea
- vomiting
- pain in the abdomen (belly)
- fever
- rash or itching of your skin
- loss of appetite or loss of interest in food
- dark urine
- yellowing of skin or eyes (jaundice)

To help reduce your risk of liver problems, your healthcare provider will do a blood test to check your liver:
- before you start taking this medicine,
- after you start taking this medicine,
    - once every 7 days for the first 12 weeks,
    - then once a month from months 4 to 12,
    - then once every 6 months from months 12 till 24,
    - thereafter, your healthcare provider will advise you on when to schedule future blood tests and how often they should be carried out.

If you had to stop taking Cenrifki because of abnormal liver test results, or if there has been a break in your treatment of one year or more, you should begin the blood test schedule outlined above from the start when you restart Cenrifki treatment.

If you miss a scheduled blood test, immediately inform your doctor and reschedule the blood test to be completed as soon as possible.

Infections
- Talk to your doctor before taking Cenrifki if you have an infection or are unable to fight infections. Cenrifki may make you more likely to get infections. If you have an active infection, you must not start taking Cenrifki until the infection has cleared up.
- Tell your doctor straight away if you develop any signs or symptoms of infection such as cough, fever, blocked or runny nose, sore throat, or headache, during treatment with Cenrifki. Your doctor will evaluate you and may need to stop your treatment temporarily if you develop a serious infection.

- Medicines that can weaken your immune system (such as immunosuppressants), may increase your risk of getting infections when used together with Cenrifki (see section 2 'Other medicines and Cenrifki'). Your doctor will advise you on the most appropriate course of action should you need to take such medicines while on Cenrifki treatment.

Vaccinations
- Tell your doctor if you have recently been given any vaccine or are going to get one in the near future.
- You must avoid vaccinations with live or live attenuated vaccines during treatment with Cenrifki, as it may make you more likely to get infections (see section 2 'Other medicines and Cenrifki').
- If you need a live or live attenuated vaccine, it should be given at least 2 months before you start treatment with Cenrifki.
- Cenrifki may affect how well non-live vaccines work. Your doctor may advise you to complete all recommended non-live vaccinations before you start treatment with Cenrifki.

Patient guide
Your doctor will give you a patient guide which contains important safety information you need to be aware of when receiving treatment with Cenrifki. It is important that you read this guide.

Patient card
A patient card is included in this pack. Read the card carefully, keep it with you at all times during treatment, and show it to any healthcare professional involved in your care.

Children and adolescents
Do not give this medicinal product to children and adolescents less than 18 years of age. The safety and efficacy of Cenrifki have not been established.

Other medicines and Cenrifki
Tell your doctor, pharmacist, or nurse if you are taking, have recently taken or might take any other medicines. This includes prescription medicines, medicines obtained without a prescription, herbal medicines, and supplements. Cenrifki may affect the way some other medicines work and because some other medicines can affect the way this medicine works. Medicines, herbal or dietary supplements that could be harmful to the liver, may increase the chance of liver damage when taken with Cenrifki (see section 2 ‘Warnings and precautions’).

In particular, before taking this medicine, tell your doctor if you are taking or have recently taken any of the following medicines.

Medicines that can increase the levels of Cenrifki in your blood, which may increase your risk of side effects. Examples include:
- Gemfibrozil – a medicine used to lower cholesterol
- Deferasirox – a medicine used to treat iron overload
- Letermovir – a medicine used to prevent viral infections after bone marrow transplant
- Selpercatinib – a medicine used to treat certain types of cancer

Medicines that can decrease the levels of Cenrifki in your blood, which may make Cenrifki less effective. Examples include:
- St John’s wort – a herbal product used to treat depression
- Rifampicin, Nafcillin – antibiotics used to treat bacterial infections
- Carbamazepine, Phenytoin – medicines used to treat epilepsy and nerve pain
- Efavirenz, Etravirine – medicines used to treat HIV infection
- Bosentan – a medicine used to treat high blood pressure in the lungs

Medicines that can thin your blood, which may increase your risk of bleeding. Examples include:
- Warfarin, Heparin, Apixaban, Rivaroxaban, Edoxaban – medicines that prevent blood clots (anticoagulants)

- Clopidogrel, Ticagrelor, Prasugrel – medicines that prevent blood platelets from clumping together (antiplatelet agents)

Medicines that may increase your risk of infections. Examples include:
- Medicines that can weaken your immune system – immunosuppressants like mycophenolate mofetil, cyclophosphamide, or azathioprine, as well as medicines used to treat inflammation such as Disease-Modifying Antirheumatic Drugs (DMARDs) or long-term corticosteroids (see section 2 'Infections').
- Live or live attenuated vaccines – such as chickenpox, oral polio, or nasal flu vaccines (see section 2 'Vaccinations').

Medicines whose levels in your blood may be increased when taken with Cenrifki, which may increase their risk of side effects. Caution should be taken when such medicines are taken with Cenrifki. Examples include:
- Cyclosporin and tacrolimus – medicines used to reduce immune reactions and prevent organ rejection
- Digoxin – a medicine used to treat abnormal heart rhythm or disorders

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is limited information about using Cenrifki during pregnancy in humans. A risk to your unborn child cannot be completely ruled out. Therefore, Cenrifki is not recommended during pregnancy and in women who could become pregnant and are not using contraception.

It is not known whether Cenrifki passes into breast milk. A risk to breast-fed babies cannot be ruled out. If you are breast-feeding or planning to breast-feed, talk to your doctor before using this medicine. You and your doctor must decide if you should breast-feed while on this medicine, considering the benefits of breast-feeding for your baby and the benefits of this treatment for you.

Driving and using machines
Cenrifki is not expected to affect your ability to drive or to use machines.

Cenrifki contains lactose
Cenrifki contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Cenrifki

Treatment with Cenrifki should be started and supervised by a doctor who is experienced in the treatment of multiple sclerosis.

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

Cenrifki is available as a tablet which is taken by mouth. The recommended dose is 60 mg taken once daily with a meal preferably at the same time each day. Your doctor will monitor your liver function before and during treatment with Cenrifki. Depending on the results of these liver function tests, your treatment may be temporarily stopped or permanently discontinued.

If you take more Cenrifki than you should
If you have taken too much Cenrifki, talk to a doctor or pharmacist.

If you forget to take Cenrifki
Take the dose as soon as possible on the same day. Do not take a double dose to make up for a missed dose.

If you stop taking Cenrifki
Do not stop taking Cenrifki or change your dose without talking to your doctor first. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Serious side effects:

Cenrifki may cause your liver not to work properly (may affect up to 1 in 10 people)**.**
Tell your doctor if you have symptoms such as tiredness, nausea, vomiting, pain in the abdomen, fever, rash or itching of your skin, loss of appetite or interest in food, dark urine, or yellowing of skin or eyes.

Cenrifki may increase your likelihood of developing infections (may affect more than 1 in 10 people)**.**
This medicine may cause infection of the chest (bronchitis) or lungs (pneumonia). Tell your doctor if you have or develop symptoms of infection such as cough, fever, blocked or runny nose, sore throat, and headache.

Other side effects:

Very Common (may affect more than 1 in 10 people)
- COVID-19

Common (may affect up to 1 in 10 people)
- Influenza
- Small red or purple spots caused by bleeding into the skin (petechiae).
- Increased chance of bruising
- Belly (abdominal) pain
- Heavy menstrual bleeding
- Bruising (contusion)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 Cenrifki

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, wallet card and the blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30˚C.

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 Cenrifki contains
The active substance is tolebrutinib. Each film-coated tablet contains 60 mg of tolebrutinib.

The other ingredients are lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone (Type A), magnesium stearate, titanium dioxide, yellow iron oxide (E172), red iron oxide (E172), macrogol - polyethylene glycol (400) (see section 2 “Cenrifki contains lactose”).

What Cenrifki looks like and contents of the pack
60 mg film-tablet: orange, drop shape, film-coated tablet of 12.7 mm in length, debossed with “60” on one side.

Your medicine is supplied in the following pack sizes:

Packs of 7 film-coated tablets in 1 aluminium-aluminium blister sealed inside a cardboard wallet.
Packs of 28 film-coated tablets in 2 aluminium-aluminium blisters (each with 14 tablets) sealed inside a cardboard wallet.
Packs of 98 film-coated tablets in 7 aluminium-aluminium blisters (each with 14 tablets) sealed inside a cardboard wallet.

Not all pack sizes may be marketed.

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Other sources of information

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