▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – CENRIFKI® (TOLEBRUTINIB)

Warning: Liver injury

Cenrifki can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported.

Liver function tests (ALT, AST, alkaline phosphatase and total bilirubin) must be performed prior to initiation of treatment, and after treatment initiation, weekly during the first 12 weeks, monthly during months 4 to 12, and every 6 months thereafter. Weekly monitoring should be restarted following treatment interruption due to abnormal liver function tests, or due to a gap in treatment of 1 year or longer.

Cenrifki is contraindicated in patients with severe hepatic impairment (see Section 4.3 Contraindications).

Concomitant use of Cenrifki with other hepatotoxic medicinal products, herbal or dietary supplements may increase the risk of severe liver injury.

If drug-induced liver injury (DILI) is suspected to be induced by Cenrifki, treatment must be discontinued (see Sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

1 NAME OF THE MEDICINE

Tolebrutinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 60 mg of tolebrutinib.

Contains sugars as lactose. For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Film-coated tablet.

CENRIFKI is formulated as a drop shape, orange film-coated tablet debossed with ‘60’ on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CENRIFKI is indicated in adults:

- for the treatment of non-relapsing Secondary Progressive Multiple Sclerosis (nrSPMS)
- to slow disability accumulation in the absence of relapse activity with Secondary Progressive Multiple Sclerosis (SPMS)

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dose

The recommended dose of CENRIFKI in adults is 60 mg orally once daily (see Section 4.4 Special Warnings and Precautions for use).

Method of administration

CENRIFKI must be taken with a meal preferably at the same time each day. Swallow tablets whole with water. Do not cut, crush, or chew the tablets (see Section 5.2 Pharmacokinetic properties).

Dose modifications for aminotransferase elevations

Table 1 summarises recommendations for dose adjustment and monitoring for patients who develop elevated transaminases during therapy with CENRIFKI (see Section 4.4 Special Warnings and Precautions for use).

Table 1 - Therapy modifications and monitoring for elevated transaminases

Laboratory abnormalities	CENRIFKI Therapy Modifications
ALT† or AST† > 3x and ≤ 5x ULN† with clinical symptoms‡ OR with concurrent total bilirubin > 2x ULN	Withhold CENRIFKI 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.
ALT or AST > 5x ULN	If an alternative cause other than drug-induced liver injury (DILI) is identified, reinitiation of CENRIFKI can be considered when ALT or AST decreases to less than 1.5 x ULN. Upon reinitiation of CENRIFKI, if ALT or AST greater than 3x ULN, permanently discontinue CENRIFKI treatment.

Laboratory abnormalities	CENRIFKI Therapy Modifications
	If no alternative cause to DILI is identified, permanently discontinue CENRIFKI treatment if any of the following occurred as the initial event: • ALT or AST greater than 8 x ULN • ALT or AST greater than 5 x ULN for greater than 2 weeks • 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, right upper quadrant pain or tenderness, fever, rash, anorexia, jaundice, and/or eosinophilia

Missed dose

If a dose of CENRIFKI 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.

Dosage modifications for concomitant therapy

Avoid concomitant use of CENRIFKI with moderate or strong CYP2C8 inhibitors or CYP3A inducers. If moderate or strong CYP2C8 inhibitors will be used short-term, treatment with CENRIFKI must be interrupted (see Section 4.5 Interactions with other medicines and other forms of interactions).

Hepatic impairment

No dosage adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A), although caution must be exercised when initiating treatment in these patients. CENRIFKI is contraindicated in patients with moderate (Child-Pugh Class B) to severe (Child-Pugh Class C) hepatic impairment and in patients with pre-existing acute or chronic liver disease or 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 Section 4.3 Contraindications, Section 4.4 Special Warnings and Precautions for Use, and Section 5.2 Pharmacokinetic properties).

Renal impairment

No dose adjustment is necessary for patients with renal impairment. CENRIFKI has not been studied in patients requiring dialysis (see Section 5.2 Pharmacokinetic properties).

4.3 CONTRAINDICATIONS

Patients with moderate to severe liver hepatic impairment. Patients with pre-existing acute or chronic liver disease or 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 Section 4.2 Dose and Method of Administration, Section 4.4 Special Warnings and Precautions for use and Section 5.2 Pharmacokinetic properties).

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Liver Injury

Clinically significant liver injury, including acute liver failure resulting in/leading to transplant and/or death, has been reported in patients treated with Bruton tyrosine kinase inhibitors, including CENRIFKI in clinical trials. Patients with pre-existing liver disease and patients taking other hepatotoxic drugs, herbal or dietary supplements may be at increased risk for developing liver injury when taking CENRIFKI. Prior to initiating CENRIFKI, evaluate patients for concomitant use of hepatotoxic drugs, herbal products, and dietary supplements. Concomitant use of CENRIFKI with other hepatotoxic drugs 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 CENRIFKI treatment. CENRIFKI is contraindicated in patients with moderate to severe hepatic impairment (see Section 4.3 Contraindications).

In Phase 3 clinical trials for Relapsing Multiple Sclerosis (RMS) and non-relapsing Secondary Progressive Multiple Sclerosis (nrSPMS), ALT elevations greater than three times the upper limit of normal (ULN) were observed in 4.9% of patients treated with CENRIFKI, 6.3% of RMS patients treated with teriflunomide, and 1.6% of nrSPMS patients receiving placebo. Among the 1685 CENRIFKI-treated patients, 0.42% experienced ALT elevations greater than twenty times ULN, and 0.2% had ALT elevations greater than three times ULN with concurrent bilirubin increases greater than two times ULN, all without alternative causes of liver injury and all occurred within three months of initiating CENRIFKI treatment. All but one patient's liver enzymes resolved spontaneously without sequelae following permanent discontinuation of CENRIFKI. One patient developed liver failure requiring a liver transplant and subsequently died due to a post-transplant complication.

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

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

To mitigate the risk of significant or irreversible liver injury, 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. From month 12 onwards, perform monitoring every 6 months. 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 transaminases and bilirubin on CENRIFKI therapy, 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 drugs. At each scheduled visit, prescribers should reassess the benefit-risk balance of continuing CENRIFKI treatment, considering hepatic function, disease status, and

concomitant medications. If liver injury is suspected to be CENRIFKI-induced, discontinue CENRIFKI. If CENRIFKI-induced liver injury is unlikely because another probable cause has been found, resumption of CENRIFKI therapy may be considered when ALT or AST decreases to less than 1.5 x ULN. Withhold or permanently discontinue CENRIFKI if no alternative causes of liver injury are identified (see Section 4.2 Dose and Method of Administration).

All healthcare professionals must be familiar with the CENRIFKI educational materials prepared for the management of the liver injury risk, including the monitoring of the liver function. Prescribers must ensure the patient / caregiver is aware of or have been provided with the patient guide and patient card and have educated them on the importance of adherence with scheduled laboratory monitoring, early signs and symptoms of liver injury, and what to do should they experience signs of liver injury. Prior to initiating treatment with CENRIFKI, prescribers must complete the Risk Awareness Dialogue Form with the patient/caregiver to confirm that the key safety information regarding liver injury risk has been discussed and understood.

Infections

Serious, including fatal, infections have been reported in patients receiving CENRIFKI in phase 3 clinical trials. The most common infection adverse reactions were COVID-19 (24.7%) and nasopharyngitis (11.2%) in the CENRIFKI 60 mg group. The majority of infections were Grade 1 or 2. A higher proportion of CENRIFKI-treated patients experienced severe (Grade 3 or higher) infections (3.6%) compared to those on teriflunomide (1.9%) or placebo (2.9%) [see section 4.8]. The majority of these patients had symptom resolution without permanent discontinuation of CENRIFKI. However, one fatal case of pneumonia (bacterial) occurred in a patient with Expanded Disability Status Scale (EDSS) score of 6.5 who had a significant delay in seeking and receiving treatment. The patient was taking CENRIFKI 60 mg for 1.8 years.

CENRIFKI is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections. Immunomodulators like CENRIFKI may cause patients to be more susceptible to infections. The use of live attenuated or live vaccines may carry a risk of infections and must therefore be avoided. Patients with active acute or chronic infections must not start treatment until the infection(s) is resolved. Monitor patients for signs and symptoms of infection, evaluate promptly, and treat appropriately.

Use in hepatic impairment

No dosage adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A), although caution must be exercised when initiating treatment in these patients. CENRIFKI is contraindicated in patients with moderate (Child-Pugh Class B) to severe (Child-Pugh Class C) hepatic impairment and in patients with pre-existing acute or chronic liver disease or 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 Section 4.3 Contraindications, Section 4.4 Special Warnings and Precautions for Use, and Section 5.2 Pharmacokinetic properties).

Use in renal impairment

No dose adjustment is necessary for patients with renal impairment. CENRIFKI has not been studied in patients requiring dialysis (see Section 5.2 Pharmacokinetic properties).

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 Interactions with other medicines and other forms of interactions).

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 Interactions with other medicines and other forms of interactions).

Haemorrhages

Haemorrhagic events were reported in patients treated with tolebrutinib (see Section 4.8 Adverse effects). 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 Interactions with other medicines and other forms of interactions). 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.

Use in the elderly

The safety and efficacy of CENRIFKI in patients greater than 65 years of age have not been established.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of enzymes and transporters on tolebrutinib

Enzymes

In vitro tolebrutinib is metabolised mainly by CYP2C8 and CYP3A4 and to a lesser extent by CYP2J2 and CYP2D6. *In vivo*, tolebrutinib is mainly metabolised 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.

Transporters

Tolebrutinib is not a substrate of P-glycoprotein, BCRP, BSEP, MRP2, OATP, OCT1, NTCP, OCT2, OAT1, OAT3, MATE1 and MATE2-K. M2 is a substrate of P-glycoprotein, BCRP and MATE1, but not of BSEP, MRP2, OCT2, OAT1, OAT3, MATE2-K, OATP, OCT1 and NTCP.

Effect of other medicinal products on tolebrutinib

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 Special Warnings and Precautions for use).

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 Special Warnings and Precautions for use).

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 Special Warnings and Precautions for use).

Agents that may increase tolebrutinib plasma concentrations

Strong 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 96% and 98%, compared to single administration of tolebrutinib under fed conditions. Avoid co-administration of tolebrutinib with strong CYP2C8 inhibitors (e.g., gemfibrozil). If a strong CYP2C8 inhibitor must be used short-term, treatment with tolebrutinib must be interrupted (see Section 4.2 Dose and Method of Administration).

Moderate CYP2C8 inhibitors

Simulations using fed conditions suggested that moderate CYP2C8 inhibitor letermovir may increase tolebrutinib AUC and C_{max} by 5.9-fold and 5-fold, while M2 AUC and C_{max} may decrease by 9 to 12%. Avoid co-administration of tolebrutinib with moderate CYP2C8 inhibitors (e.g., deferasirox, letermovir, selpercatinib). If a moderate CYP2C8 inhibitor must be used short-term, treatment with tolebrutinib should be interrupted (see Section 4.2 Dose and Method of Administration).

Agents that may decrease tolebrutinib plasma concentrations

Strong CYP3A inducers

Co-administration of a strong CYP3A inducer (rifampicin 600 mg once daily) decreased both tolebrutinib AUC and C_{max} by 84%, while M2 AUC and C_{max} decreased by 58% and 42% in healthy subjects. Avoid co-administration of tolebrutinib with strong CYP3A inducers (e.g., carbamazepine, phenytoin, St. John's wort). If a strong CYP3A inducer must be used short-term, treatment with tolebrutinib can be continued (see Section 4.2 Dose and Method of Administration).

Moderate CYP3A inducers

Simulations using fed conditions suggested that moderate CYP3A inducer efavirenz may decrease tolebrutinib AUC_{0-24} and C_{max} by 62% and 60%, while M2 AUC_{0-24} and C_{max} may decrease by 41% and 34%. Avoid co-administration of tolebrutinib with moderate CYP3CA inducers (e.g., bosentan, efavirenz, etravirine). If a moderate CYP3A inducer must be used short-term, treatment with tolebrutinib can be continued (see Section 4.2 Dose and Method of Administration).

No significant interaction

Strong CYP3A inhibitors

Some differences were observed (combined tolebrutinib and M2 effective AUC increased 1.68 fold and C_{max} increased 1.56 fold) when tolebrutinib was co-administered with a strong CYP3A inhibitor (itraconazole 200 mg daily).

Gastric Acid Reducing Agents

Coadministration of tolebrutinib with medication that increase gastric pH (pantoprazole 40 mg twice daily) reduced combined tolebrutinib and M2 effective AUC by 9% and C_{max} by 37%.

Effect of tolebrutinib on other medicinal products

Enzymes

Tolebrutinib, M2 and the major human metabolite M8 are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2J2, CYP3A4/5 or xanthine oxidase enzyme nor inducers of CYP1A2, CYP2B6 or CYP3A4 at clinically-relevant concentrations *in vitro*.

Transporters

Tolebrutinib, M2 and M8 were not inhibitors of P-glycoprotein, BCRP, BSEP, MRP2, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2-K at clinically-relevant concentrations *in vitro*.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of tolebrutinib on fertility in humans are unknown.

Male and female fertility was unaffected in rats following oral administration of tolebrutinib at doses up to 25 mg/kg/day (86 and 265 times the exposures of the unbound AUC at the clinical dose in male and female rats, respectively).

Use in pregnancy (Category B3)

There are no available data on tolebrutinib use 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-fetal development regarding the active metabolite M2, therefore, a risk to the unborn child cannot be excluded (see Section 5.3 Preclinical Safety Data). Tolebrutinib should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the fetus.

Use in lactation

There is insufficient information on the excretion of tolebrutinib or its metabolites in human milk. A risk to breast-fed children 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

CENRIFKI is not expected to influence the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of CENRIFKI has been evaluated in 1685 patients across 3 phase 3 clinical studies, which included 752 patients in a placebo-controlled study (HERCULES) in patients with nrSPMS and 933 patients in active-controlled clinical trials (GEMINI 1 and 2) in patients with RMS.

Adverse events led to discontinuation of treatment in 3.9% of CENRIFKI group vs 2.9% in placebo group (HERCULES) and 4.5% of CENRIFKI group vs 4.4% in teriflunomide group (GEMINI 1 and 2). The most commonly reported adverse reactions were COVID-19 (27%, 26% in nrSPMS and RMS, respectively) and upper respiratory infections (17%, 28% in nrSPMS and RMS, respectively).

Tabulated List of Adverse Reactions

Adverse reactions reported in phase 3 clinical trials with CENRIFKI are listed below in Table 2. The adverse reactions are presented by frequency categories: very common ≥ 10%,

common ≥1 and < 10%, uncommon ≥ 0.1 and < 1%, rare ≥ 0.01 and < 0.01%, very rare <0.01%, Not known: (cannot be estimated from the available data).

Table 2 - Adverse reactions reported in 2% or more of subjects treated with CENRIFKI in Study 1 (HERCULES) or pooled Studies 2 and 3 (GEMINI I and II)

	Study 1		Pooled Studies 2 and 3	
Adverse Reactions	CENRIFKI 60 mg daily N = 752	Placebo N = 375	CENRIFKI 60 mg daily N = 933	Teriflunomide 14 mg daily N = 939
COVID-19*	27%	23%	26%	28%
Upper respiratory tract infections[δ]	17%	14%	28%	23%
Viral upper respiratory tract infections	4%	3%	5%	6%
Influenza	6%	3%	5%	6%
Lower respiratory tract infections[τ]	4%	2%	3%	3%
Petechiae	3%	0.3%	5%	0.3%
Abdominal pain[§]	4%	1%	4%	6%
ALT elevation[φ]	4%	2%	6%	6%
Increased tendency to bruise	1%	0	2%	0.3%
Heavy menstrual bleeding	1%	0.3%	3%	1%

* COVID-19 includes preferred terms COVID-19, COVID-19 pneumonia, suspected COVID-19, coronavirus infection, and post-acute COVID-19 syndrome. The studies were conducted during the COVID-19 pandemic.

[δ] Upper respiratory tract infections include preferred terms acute sinusitis, sinusitis, tonsillitis, chronic tonsillitis, nasopharyngitis, pharyngitis, laryngitis, laryngopharyngitis, pharyngotonsillitis, rhinitis, tracheitis, chronic sinusitis, croup infections

[τ] Lower respiratory tract and lung infections include preferred terms bronchitis, pneumonia, pleural infection, pneumonia aspiration, and lower respiratory tract infection.

[§] Abdominal pain includes preferred terms abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

[φ] ALT greater than 3-fold ULN.

Clinical Trial experience

A total of 752 patients on CENRIFKI 60 mg daily and 375 patients on placebo constituted the safety population in the placebo-controlled Study 1 (HERCULES). Table 2 presents adverse drug reactions observed during the study, which are considered to have a possible causal relationship with CENRIFKI treatment. In contrast, Table 3 presents treatment-emergent adverse events observed during the study, which do not necessarily have a causal relationship to CENRIFKI.

Table 3 - Treatment-emergent adverse events reported in 2% or more of subjects treated with CENRIFKI in placebo-controlled Study 1 (HERCULES)

Primary system organ class Preferred Term N (%)	Placebo N = 375	CENRIFKI 60 mg daily N = 752
Any event	293 (78.1)	613 (81.5)
Infections and infestations	185 (49.3)	409 (54.4)
COVID-19	85 (22.7)	192 (25.5)
Urinary tract infection	49 (13.1)	85 (11.3)
Nasopharyngitis	26 (6.9)	70 (9.3)
Influenza	13 (3.5)	42 (5.6)
Cystitis bacterial	15 (4.0)	31 (4.1)
Upper respiratory tract infection	18 (4.8)	31 (4.1)
Cystitis	14 (3.7)	29 (3.9)
Viral upper respiratory tract infection	12 (3.2)	28 (3.7)
Bronchitis	5 (1.3)	19 (2.5)
Pharyngitis	4 (1.1)	17 (2.3)
Blood and lymphatic system disorders	19 (5.1)	64 (8.5)
Anaemia	2 (0.5)	16 (2.1)
Neutropenia	8 (2.1)	12 (1.6)
Psychiatric disorders	30 (8.0)	65 (8.6)
Depression	2 (0.5)	17 (2.3)
Insomnia	11 (2.9)	16 (2.1)
Nervous system disorders	77 (20.5)	176 (23.4)
Headache	27 (7.2)	54 (7.2)
Dizziness	7 (1.9)	17 (2.3)
Muscle spasticity	6 (1.6)	17 (2.3)
Vascular disorders	16 (4.3)	57 (7.6)
Hypertension	11 (2.9)	38 (5.1)
Respiratory, thoracic and mediastinal disorders	22 (5.9)	55 (7.3)
Cough	9 (2.4)	16 (2.1)
Oropharyngeal pain	5 (1.3)	15 (2.0)
Gastrointestinal disorders	59 (15.7)	150 (19.9)
Diarrhoea	14 (3.7)	33 (4.4)
Constipation	12 (3.2)	22 (2.9)
Abdominal pain upper	2 (0.5)	19 (2.5)
Nausea	8 (2.1)	17 (2.3)
Dyspepsia	7 (1.9)	15 (2.0)
Skin and subcutaneous tissue disorders	36 (9.6)	125 (16.6)
Petechiae	1 (0.3)	20 (2.7)

Primary system organ class Preferred Term N (%)	Placebo N = 375	CENRIFKI 60 mg daily N = 752
Alopecia	6 (1.6)	18 (2.4)
Musculoskeletal and connective tissue disorders	94 (25.1)	186 (24.7)
Arthralgia	19 (5.1)	49 (6.5)
Back pain	24 (6.4)	47 (6.3)
Muscular weakness	10 (2.7)	18 (2.4)
Pain in extremity	9 (2.4)	18 (2.4)
Neck pain	9 (2.4)	9 (1.2)
General disorders and administration site conditions	54 (14.4)	128 (17.0)
Fatigue	11 (2.9)	35 (4.7)
Oedema peripheral	12 (3.2)	27 (3.6)
Pyrexia	17 (4.5)	25 (3.3)
Investigations	36 (9.6)	108 (14.4)
Alanine aminotransferase increased	6 (1.6)	33 (4.4)
Injury, poisoning and procedural complications	88 (23.5)	179 (23.8)
Fall	41 (10.9)	72 (9.6)
Contusion	4 (1.1)	29 (3.9)
Accidental overdose	19 (5.1)	25 (3.3)
Ligament sprain	7 (1.9)	15 (2.0)
Rib fracture	9 (2.4)	7 (0.9)

Description of Selected Adverse Reactions

Petechiae, Increased Tendency to Bruise, Heavy Menstrual Bleeding

In clinical trials, 3.7% of CENRIFKI-treated patients experienced petechiae, compared to 0.3% of those on placebo and teriflunomide. Most cases were mild. Additionally, in pooled active-controlled studies, 2% of CENRIFKI-treated patients showed an increased tendency to bruise, versus 0.3% of those on teriflunomide and heavy menstrual bleeding occurred in 3% of CENRIFKI-treated patients, compared to 1% of those on teriflunomide. Some patients with heavy menstrual bleeding also developed mild to moderate anaemia. None of the petechiae, bruising, or heavy menstrual bleeding were associated with thrombocytopenia in clinical trials. Patients on anticoagulants or anti-platelet medications, those with significant bleeding history within 6 months prior to screening, bleeding disorders, known platelet dysfunction, platelet counts below 150 000/µL, or major surgery within 4 weeks prior to screening were excluded from the trials.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems (Australia).

4.9 OVERDOSE

There is no experience regarding CENRIFKI overdose or intoxication in humans. CENRIFKI 240 mg daily up to 14 days was well tolerated by healthy adult subjects.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: L04AA62

Mechanism of action

Tolebrutinib is a brain-penetrant and bioactive inhibitor of Bruton's tyrosine kinase (BTK). The BTK pathway is critical to signalling in B cells and myeloid cells including CNS-resident macrophages and microglia. Each of these cell types are implicated in the pathophysiology of MS. 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. Tolebrutinib forms a covalent bond with cysteine 481 near the ATP-binding site leading to inhibition of BTK enzymatic activity in B cells and microglia.

Clinical Trials

The efficacy of CENRIFKI was studied in three clinical trials. Study 1 (EFC16645/HERCULES) was a randomised, double-blind, 2-arm, placebo-controlled, parallel group, multicentre, event-driven trial with a variable treatment duration ranging from approximately 24 to 48 months in patients with nrSPMS. Studies 2 (EFC16033/GEMINI I) and 3 (EFC16034/GEMINI II) were randomised, double-blind, double-dummy, 2 arm, active-controlled with teriflunomide, parallel group, multicentre, event driven trials with a variable treatment duration ranging from approximately 24 to 48 months in patients with RMS. Common end of study was determined by accumulation of a prespecified number of events of 6-month confirmed disability worsening.

In Study 1, patients were randomised 2:1 to receive either CENRIFKI 60 mg daily or a matching placebo daily. All patients 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. 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 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. Secondary outcomes analysed were Time to onset of 3-month CDP as assessed by the EDSS score, Number of new and/or enlarging T2 hyperintense lesions per year, Time to onset of sustained 20% increase in the 9-hole Peg Test (9-HPT) for at least 3 months, Time to onset of sustained 20% increase in the timed 25-foot walk test (T25-FW) for at least 3 months, Time to onset of CDI confirmed over at least 6 months, Percent change in brain volume as detected by MRI scans at the end of study (EOS) compared to Month 6.

In Study 1, 1131 patients with nrSPMS were randomised to receive CENRIFKI 60 mg (n = 754) or placebo (n = 377). 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, 12.6% of patients had one or more T1 Gd-enhancing lesions.

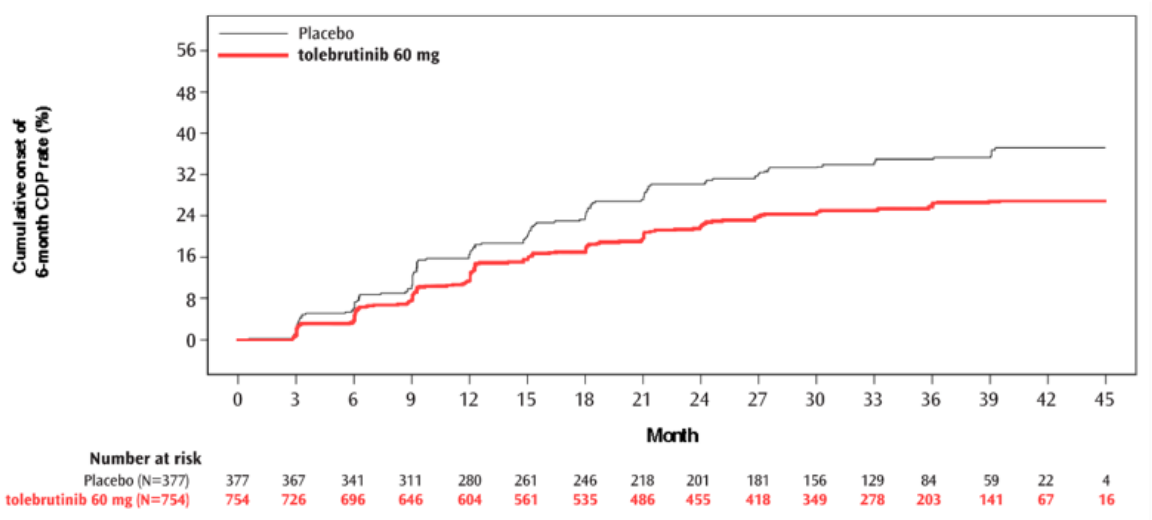
CENRIFKI was superior to placebo in reducing the risk of confirmed disability progression, based on a time-to-event analysis (hazard ratio 0.69; p=0.0026; see Figure 1). The number of participants who experienced confirmed disability improvement increased by nearly two-fold, 8.6% with CENRIFKI compared to 4.5% with placebo (HR 1.88). The results for the primary endpoint are detailed in Table 4 and Figure 1.

Table 4 - Clinical and MRI endpoints in adult nrSPMS patients for Study 1

	CENRIFKI 60 mg daily N = 754	**Placebo N = 377**
Clinical Outcomes		
6-month CDP	22.6%	30.7%
Relative reduction	31%; p= 0.003	
3-month CDP	27.6%	34.2%
Relative reduction	24%; p= 0.013	
Sustained 20% increase in 9-HPT for at least 3 months	19.0%	19.6%
Relative reduction	3% NS	
Sustained 20% increase in T25-FW for at least 3 months	41.1%	49.6%
Relative reduction	23% *	
6-month CDI	8.6%	4.5%
Hazard Ratio	1.88 *	
MRI endpoint		
New and/or enlarging T2-hyperintense lesions per year	1.8	2.9
Rate reduction	38%; p = 0.011	

*As per the pre-specified hierarchical testing procedure, statistical testing was stopped after the previous endpoint failed to reach statistical significance. Therefore, no formal statistical testing was conducted for this endpoint.

Figure 1 - Study 1 – Kaplan-Meier plot of cumulative incidence rate of onset of 6-month CDP – ITT population



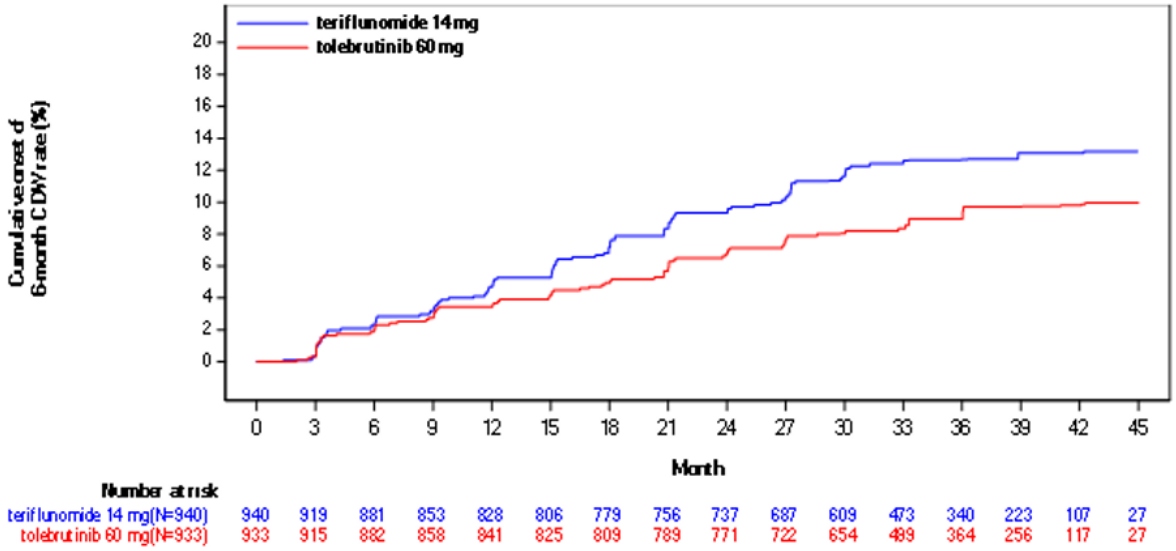
Results from Study 2 and Study 3 are presented in Table 5 and Figure 2. Both studies did not achieve their primary goal of showing a statistically significant improvement in annualised relapse rates (ARR) compared to teriflunomide. The key secondary endpoint for both studies combined showed a 29% relative risk reduction for CENRIFKI compared to teriflunomide in delaying the time to onset of 6-month Confirmed Disability Worsening (CDW) (hazard ratio 0.71).

Table 5 - Clinical and MRI endpoints in adult RMS patients for Studies 2 and 3

	Study 2		Study 3	
	CENRIFKI 60 mg daily N = 486	Teriflunomide 14 mg daily N = 488	CENRIFKI 60 mg daily N = 447	Teriflunomide 14 mg daily N = 452
Clinical Endpoints				
Annualised Relapse Rate (Primary Endpoint)	0.13	0.12	0.11	0.11
Rate Ratio	1.1 (p = 0.669)		1.0 (p = 0.976)	
6-month CDW (pooled analysis)	8.3% CENRIFKI vs 11.3% teriflunomide			
Relative Reduction*	29%			
3-month CDW (pooled analysis)	11.7% CENRIFKI vs 15.3% teriflunomide			
Relative Reduction*	27%			
MRI Endpoints				
New and/or enlarging T2-hyperintense lesions per year*	5.6	5.2	5.1	4.4
New Gd-enhancing T1 lesions per scan*	0.53	0.29	0.46	0.22

*As per the pre-specified hierarchical testing procedure, statistical testing was stopped after the primary endpoint failed to reach statistical significance.

Figure 2 - Kaplan-Meier plot of cumulative incidence rate of onset of 6-month CDW – ITT population (Study 2 & Study 3)



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 proportionally with doses between 5 and 60 mg. In patients with nrSPMS at the recommended dose of 60 mg daily with a meal, the mean steady state (% coefficient of variation [CV]) for AUC_{0-24} 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.

Absorption

Absolute oral bioavailability of tolebrutinib after a single oral 60 mg dose with a meal was 10.3%. The median time to reach C_{max} of tolebrutinib and M2 were around 1.3 hours in all studied patient populations.

Distribution

The steady state volume of distribution of tolebrutinib was approximately 255L. The tolebrutinib and M2 *in vitro* unbound fraction ranged from 11.1 to 12.5 % and from 8.6 to 38%, respectively. In n=2 healthy subjects receiving 60mg, tolebrutinib and the M2 metabolite appear in the cerebrospinal fluid (CSF), with a mean maximal CSF to unbound plasma ratio of 0.90 and 0.38, respectively.

Metabolism

In vitro, tolebrutinib is metabolised mainly by CYP2C8 and CYP3A4 and to a lesser extent by CYP2J2 and CYP2D6. *In vivo*, tolebrutinib is mainly metabolised 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 5.7- fold higher than the parent compound and exhibits similar covalent binding potency on BTK to tolebrutinib.

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. Seventy-eight percent 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.

Special Populations

Age

Based on the population pharmacokinetic analysis age over 40 years had no meaningful effect on tolebrutinib pharmacokinetics. There is no data on patients aged greater than 60 years.

Gender

Based on the population pharmacokinetic analysis gender had no meaningful effect on tolebrutinib pharmacokinetics

Race

Based on the population pharmacokinetic analysis race had no relevant difference between Chinese vs. non-Chinese patients tolebrutinib pharmacokinetics but exposure was increased ~70-80% in Japanese vs. non-Japanese patients.

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 between 87% and 126% of those with normal hepatic function. No formal studies were conducted to examine the effects of moderate or severe hepatic impairment on the pharmacokinetics of tolebrutinib. A physiologically based pharmacokinetics model was used to predict that the exposure in this population after a single 60 mg dose in fed conditions would be above the exposure achieved in healthy trial participants at the maximum 240 mg dose under fed conditions. Tolebrutinib is contraindicated in patients with moderate or severe hepatic impairment and in patients with pre-existing acute or chronic liver disease or 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 Section 4.2 Dose and Method of Administration, Section 4.3 Contraindications, and Section 4.4 Special Warnings and Precautions for use).

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 higher (20-64%) compared to subjects with normal renal function. The total and unbound M2 C_{max} were similar, and the AUC were higher (36%).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tolebrutinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay or clastogenic in an *in vivo* micronucleus test in rats. Elevated numbers of structural chromosome aberrations were observed in the *in vitro* chromosome aberration test in human lymphocytes in the presence of substantial cytotoxicity only at concentrations ≥ 1000 times higher than the plasma levels in patients exposed to 60 mg tolebrutinib with meals. Negative results from *in vivo* chromosomal damage studies with similar structures support the conclusion that the *in vitro* effect observed with tolebrutinib is not biologically relevant.

Carcinogenicity

No evidence of carcinogenicity was observed in a 2-year rat carcinogenicity study at oral doses of tolebrutinib up to the maximally tolerated doses of 2 and 6 mg/kg/day in males and females, respectively (4 and 28 times the exposures of the unbound AUC at the clinical dose in male and female rats, respectively). No evidence of carcinogenicity was observed in a 26-week carcinogenicity study in male and female RasH2-Tg mice up to the maximally tolerated dose of 330 mg/kg/day (estimated 1625 times the clinical AUC at the MRHD).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone, magnesium stearate.

The film coating is made up of hypromellose, titanium dioxide, iron oxide yellow, iron oxide red, macrogol 400.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30˚C.

6.5 NATURE AND CONTENTS OF CONTAINER

7 film-coated tablets in a carton containing 1 wallet composed of 1 polyamide/aluminium/polyvinylchloride-aluminium blister of 7 tablets per blister.

28 film-coated tablets in a carton containing 1 wallet composed of 2 folded polyamide/aluminium/polyvinylchloride-aluminium blisters of 14 tablets per blister.

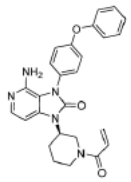
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CENRIFKI (tolebrutinib) is a kinase inhibitor. The empirical formula of tolebrutinib is $C_{26}H_{25}N_5O_3$ and the molecular weight is 455.52. The chemical name is (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-phenoxyphenyl)-1H-imidazo[4,5-c]pyridin-2(3H)-one.

Tolebrutinib is a white to beige powder that is freely or very soluble in dichloromethane, tetrahydrofuran, soluble in acetonitrile and methanol, sparingly soluble in ethanol, acetone, and ethyl acetate, slightly soluble in isopropanol and isopropyl acetate, practically insoluble in water and methyl tert-butyl ether.

CAS number

1971920-73-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Toll Free Number (medical information): 1800 818 806
E-mail: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

18 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New document