▼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 – KESIMPTA (OFATUMUMAB) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ofatumumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ofatumumab is a recombinant fully human monoclonal immunoglobulin G1 (IgG1) antibody against human CD20 expressed on B-cells. Ofatumumab is produced in a murine cell line (NS0) by recombinant DNA technology.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Each pre-filled syringe and pre-filled pen contains 20 mg ofatumumab solution for injection (0.4 mL of 50 mg/mL solution).

20 mg/0.4 mL Solution for injection in a pre-filled syringe

20 mg/0.4 mL Solution for injection in a pre-filled pen

The single-use solution for injection is sterile, preservative-free, clear to slightly opalescent, and colourless to slightly brownish-yellow.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and reduce the frequency of relapse (refer to section 5.1).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage regimen

The recommended dose is 20 mg Kesimpta administered by subcutaneous injection with:

- initial dosing of 20 mg by subcutaneous injection at weeks 0, 1 and 2, followed by subsequent monthly dosing of 20 mg by subcutaneous injection, starting at week 4.

Missed Doses

If an injection of Kesimpta is missed, it should be administered as soon as possible without waiting until the next scheduled dose. Subsequent doses should be administered at the recommended intervals.

Method of administration

Treatment with Kesimpta should be initiated by a physician experienced in the management of neurological conditions.

Kesimpta is intended for patient self-administration by subcutaneous injection.
Administration should be performed by an individual who has been instructed to administer the product.

The usual sites for subcutaneous injections are the abdomen, the thigh and the upper outer arm.

The first injection of Kesimpta should be performed under the guidance of a healthcare professional (see section 4.4 Special warnings and precautions for use).

Comprehensive instructions for administration are provided in the instructions for use and handling.

Special populations

Renal impairment

No specific studies of ofatumumab in patients with renal impairment have been performed.

Patients with mild renal impairment were included in clinical studies. There is no experience in patients with moderate and severe renal impairment. However, as ofatumumab is not excreted via urine, it is not expected that patients with renal impairment require dose modification (see section 5 Pharmacological properties).

Hepatic impairment

No studies of ofatumumab in patients with hepatic impairment have been performed.

Since hepatic metabolism of monoclonal antibodies such as ofatumumab is negligible, hepatic impairment is not expected to impact its pharmacokinetics. Therefore, it is not expected that patients with hepatic impairment require dose modification (see section 5 Pharmacological properties).

Paediatric patients (below 18 years)

The safety and effectiveness in paediatric MS patients below the age of 18 years have not yet been studied.

Elderly patients (aged 55 years and over)

No studies have been performed in elderly MS patients. Ofatumumab was studied in patients with RMS aged 18 to 55 years.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Injection-related reactions

Injection site reaction (local) symptoms observed in clinical studies included erythema, swelling, itching and pain.

Systemic injection-related reactions (SIRRs) observed in clinical studies occurred predominantly with the first injection. Symptoms observed include fever, headache, myalgia, chills and fatigue and were predominantly (99.7%) non-serious and mild to moderate in severity. There were no life-threatening injection reactions in RMS clinical studies.

Additional SIRRs reported in the post-marketing setting include rash, urticaria, dyspnea, angioedema (e.g., tongue, pharyngeal or laryngeal swelling), and rare cases which were reported as anaphylaxis. Most of the cases were non-serious and occurred with first injection. While there were some cases which were serious and resulted in discontinuation of Kesimpta treatment, there were also serious cases where patients were able to continue Kesimpta treatment without further incidents.

Some SIRR symptoms may be clinically indistinguishable from Type 1 acute hypersensitivity reactions (IgE-mediated). Patients should be informed that SIRRs generally occur within 24 hours and predominantly following the first injection. SIRRs can be managed with symptomatic treatment, should they occur.

A hypersensitivity reaction may present with any injection, although typically would not present with the first injection. For subsequent injections, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. Patients with known IgE mediated hypersensitivity to Kesimpta must not be treated with Kesimpta (see section 4.3 Contraindications).

Only limited benefit of premedication with steroids, antihistamines, or paracetamol was seen in RMS clinical studies. Ofatumumab-treated patients who received premedication with methylprednisolone (or an equivalent steroid) experienced fewer symptoms such as fever, myalgia, chills, and nausea. However, the use of steroid premedication increased the occurrence of flushing, chest discomfort, hypertension, tachycardia, and abdominal pain even in the absence of ofatumumab treatment (i.e., in patients receiving placebo injections). Therefore, use of premedication is not required.

The first injection of Kesimpta should be performed under the guidance of an appropriately trained healthcare professional.

Infections

It is recommended to evaluate the patient's immune status prior to initiating therapy with Kesimpta.

Serious, including life-threatening or fatal, bacterial, fungal, and new or reactivated viral infections have been observed during and following completion of treatment with anti-CD20 B-cell depleting therapies. Based on its mode of action and available clinical experience, ofatumumab has the potential for an increased risk of infections (see section 4.8 Adverse effects (Undesirable effects)). Administration should be delayed in patients with a severe active infection until the infection is resolved.

Kesimpta should not be given to patients with severe immunosuppression (e.g. significant neutropenia or lymphopenia).

In RMS clinical studies, the proportion of patients with infections was similar in the ofatumumab and the teriflunomide treatment groups. In the Phase 3 pivotal clinical studies, 51.6% of ofatumumab-treated patients experienced at least one infection compared to 52.7% of teriflunomide-treated patients.

Progressive Multifocal Leukoencephalopathy

No cases of progressive multifocal leukoencephalopathy (PML) have been reported for ofatumumab in the RMS clinical studies. However, since John Cunningham (JC) virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies (including ofatumumab at higher doses in other indications) and other MS therapies, physicians should be vigilant for any clinical symptoms or magnetic resonance imaging (MRI) findings that may be suggestive of PML. If PML is suspected, treatment with Kesimpta should be suspended until PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, treatment with Kesimpta should be discontinued.

Hepatitis B Virus Reactivation

Patients with active hepatitis B disease should not be treated with Kesimpta. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Kesimpta. At a minimum screening should include Hepatitis B surface antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. Patients who are negative for HBsAg and positive for Hepatitis B core antibody [HBcAb+] or are carriers of HBV [HBsAg+] should consult liver disease experts before starting and during treatment with Kesimpta.

No cases of HBV reactivation were identified in Kesimpta RMS clinical studies. However, hepatitis B reactivation has occurred in patients treated with anti-CD20 antibodies, which in some cases resulted in fulminant hepatitis, hepatic failure and death.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves. It is not recommended to use other immunosuppressants concomitantly with Kesimpta except corticosteroids for symptomatic treatment of relapses.

Vaccinations

All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of Kesimpta for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of Kesimpta for inactivated vaccines.

Kesimpta may interfere with the effectiveness of inactivated vaccines.

The safety of immunisation with live or live-attenuated vaccines following Kesimpta therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion (see section 5 Pharmacological properties).

Vaccination of infants born to mothers treated with Kesimpta during pregnancy

In infants of mothers treated with Kesimpta during pregnancy, live or live-attenuated vaccines should not be administered before confirming the B-cell count is within normal range. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

Inactivated vaccines may be administered as indicated prior to confirming the B-cell count is within normal range, however assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted (see section 4.6 Fertility, Pregnancy and Lactation).

Malignancies

An increased risk of breast cancer has been observed with other anti-CD20 B cell-depleting therapies in MS. Patients with existing active malignancies (including patients actively monitored for relapse of a malignancy) must not be treated with ofatumumab. In patients with known risk factors for malignancies the benefit-risk ratio of ofatumumab should be carefully considered and relevant tumour monitoring performed before and during treatment.

Liver Injury

Clinically significant liver injury, without findings of viral hepatitis, has been reported in the post marketing setting in patients treated with anti-CD20 B-cell depleting therapies approved for the treatment of MS, including Kesimpta. Signs of liver injury, including markedly elevated serum hepatic enzymes with elevated total bilirubin, have occurred weeks to months after administration.

Patients treated with Kesimpta found to have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3x the upper limit of normal (ULN) with serum total bilirubin greater than 2x ULN, are potentially at risk for severe drug-induced liver injury.

Obtain liver function tests prior to initiating treatment with Kesimpta and monitor for signs and symptoms of any hepatic injury during treatment. Measure serum aminotransferases, alkaline phosphatase, and bilirubin levels promptly in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, nausea, vomiting, right upper abdominal discomfort, dark urine, or jaundice. If liver injury is present and an alternative etiology is not identified, discontinue Kesimpta.

Use in hepatic impairment

Since hepatic metabolism of monoclonal antibodies such as ofatumumab is negligible, hepatic impairment is not expected to impact its pharmacokinetics. Therefore, it is not expected that patients with hepatic impairment require dose modification.

Use in renal impairment

Ofatumumab is not excreted via urine; therefore, it is not expected that patients with renal impairment require dose modification.

Use in the elderly

No studies have been performed in elderly MS patients.

Paediatric use

The safety and effectiveness in paediatric patients below the age of 18 years have not yet been established.

Effects on laboratory tests

Immunoglobulins

During the course of the RMS Phase 3 clinical studies, decrease in mean value of immunoglobulin M (IgM) was observed and was not associated with a risk of infections including serious infections. A decrease in mean IgM value of 30.9% after 48 weeks and 38.8% after 96 weeks was noted, while mean serum IgM levels remained well within reference ranges overall. In 14.3% of patients, treatment with ofatumumab resulted in a decrease in IgM that reached a value below 0.34 g/L. Ofatumumab was associated with a transient decrease of 4.3% in mean IgG levels after 48 weeks of treatment but an increase of 2.2% after 96 weeks.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ofatumumab does not share a common clearance pathway with chemical drugs that are metabolized by the cytochrome P450 system or other drug metabolizing enzymes. Additionally, there is no evidence that CD20 monoclonal antibodies (mAbs) are involved in the regulation of the expression of drug metabolizing enzymes. Interactions between Kesimpta and other medicinal products have not been investigated in formal studies.

Vaccinations

The safety of and the ability to generate a primary or anamnestic (recall) response to immunization with live, live-attenuated or inactivated vaccines during ofatumumab treatment has not been investigated. The response to vaccination could be impaired when B-cells are depleted. It is recommended that patients complete immunizations prior to the start of Kesimpta therapy (see section 4.4 Special warnings and precautions for use).

Other Immunosuppressive or Immune-Modulating Therapies

The risk of additive immune system effects should be considered when co-administering immunosuppressive therapies with Kesimpta.

When initiating Kesimpta after other immunosuppressive therapies with prolonged immune effects or initiating other immunosuppressive therapies with prolonged immune effects after Kesimpta, the duration and mode of action of these medicinal products should be taken into account because of potential additive immunosuppressive effects.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of Kesimpta on human fertility. No effects on fertility parameters such as reproductive organs, menstrual cycle and semen analysis were observed in male and female cynomolgus monkeys that were administered ofatumumab at intravenous doses up to 100 mg/kg weekly followed by 20 mg/kg bi-weekly for 13 weeks (>260 times the systemic exposure [based on AUC]).

Women of childbearing potential

Females of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Kesimpta and for 2 months after the last treatment of Kesimpta.

Use in pregnancy – Pregnancy Category C

Clinical data from the Kesimpta Pregnancy Registry and the Kesimpta PRegnancy outcomes Intensive Monitoring (PRIM) study have not identified any specific safety concerns for pregnancy or infant outcomes after in utero exposure to Kesimpta. The majority of patients were treated with Kesimpta pre-conception and/or during the first trimester of pregnancy. Experience with administration during the second and third trimesters is limited (see Human Data).

In the embryofetal development study in pregnant cynomolgus monkeys, ofatumumab was administered intravenously at doses up to 100 mg/kg/week (1280 times the systemic exposure [AUC] in patients). Ofatumumab did not cause maternal toxicity or embryofetal harm. In a separate pre-and postnatal development study, ofatumumab given intravenously at doses up to 100 mg/kg weekly followed by 20 mg/kg bi-weekly did not cause any adverse developmental effects on neonates (160 times the exposure in patients, based on AUC).

Ofatumumab, like other IgG antibodies, was shown to cross the placental barrier in cynomolgus monkeys. In humans, IgG transport across the placenta is an active process mediated by the neonatal Fc receptor (FcRn), which is low in the first trimester and increases progressively from the early second trimester.

Transient peripheral B-cell depletion and lymphocytopenia have been observed in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. The potential duration of B-cell depletion in infants exposed to ofatumumab in utero, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are unknown (see sections 4.4 Special warnings and precautions for use and see section 5 Pharmacological properties).

Treatment with Kesimpta is not recommended during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.

To help determine the effects of ofatumumab in pregnant women, healthcare professionals are encouraged to report all pregnancy cases and complications that happen during treatment or within 2 months after the last dose of Kesimpta to Novartis, in order to allow monitoring of these patients through the PRIM study.

Epidemiologic studies from USA, Canada, major EU countries and South American countries have shown that the risk of birth defects in MS population is similar to that in the general population. For spontaneous abortions and still births, the background risk in the MS population in the US appears to be similar to that in the general US population.

Human Data

In the Kesimpta Pregnancy Registry and the Kesimpta PRIM study, over 1000 prospective pregnancy cases with maternal exposure during pregnancy were retrieved including approximately 500 cases with known pregnancy outcomes.

No specific safety concerns for pregnancy or infant outcomes were identified based on the available data; however, limitations in the evidence mean that potential risks cannot be excluded. No increased risk of major congenital anomalies was observed in the available data. The majority of patients were treated with Kesimpta pre-conception and/or during the first trimester of pregnancy. Experience with administration during the second and third trimesters is limited.

The prevalence of spontaneous abortions was similar to that in the general population. Based on published literature with other anti-CD20 antibodies in women with MS, in utero exposure was not associated with an increased risk of adverse pregnancy or infant outcomes.

Use in lactation

There are limited data on the use of ofatumumab in women during lactation. There are no data on the effects of Kesimpta on milk production (see Human Data). Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Kesimpta and any potential adverse effects on the breastfed infant from Kesimpta or from the underlying maternal condition.

Human Data

In an observational study of lactating women receiving ofatumumab treatment, twelve women started breastfeeding while receiving ofatumumab between 0.6 and 19.6 months postpartum. The concentration of Kesimpta in breast milk was generally low. In the milk samples from exclusively breastfeeding women where ofatumumab was detected (quantification limit of 0.0015 μg/mL), the Cavg ranged from 0.002 to 0.012 μg/mL and the Cmax ranged from 0.003 to 0.017 μg/mL.

In the same observational study, five infants with available B-cells had normal levels. Eight infants received live vaccines during/after exposure during breastfeeding with no complications. Infants (up to 24 months postpartum) did not show abnormalities in infections, antibiotic use, hospitalisations or developmental delays.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of this registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Approximately 1500 patients with RMS received ofatumumab in clinical studies. In the two Phase 3 pivotal studies comparing ofatumumab and teriflunomide, 1882 patients with RMS were randomized, 946 of whom were treated with ofatumumab for a median duration of 85 weeks; 33% of patients receiving ofatumumab were treated for more than 96 weeks (see section 5.1 Pharmacodynamic properties, Clinical Studies).

The proportion of patients with adverse events (AEs) (83.6% versus 84.2%) and the AEs leading to drug discontinuation (5.7% versus 5.2%) were similar in the ofatumumab and teriflunomide groups.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions that have been reported in pivotal clinical studies are listed by MedDRA system organ class (Table 1). Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 1 Summary of Adverse Events by PTs and frequency categorization based on >1% in OMB and >1% higher rate than TER – Safety Set

Preferred term	OMB 20mg N=946 n (%)	TER 14mg N=936 n (%)	Frequency Category for OMB
Injection related reaction	195 (20.6)	143 (15.3)	very common
Nasopharyngitis	170 (18.0)	156 (16.7)	very common
Injection site reaction	103 (10.9)	52 (5.6)	very common
Urinary tract infection	97 (10.3)	78 (8.3)	very common
Back pain	72 (7.6)	58 (6.2)	common
Blood immunoglobulin M decreased	56 (5.9)	21 (2.2)	common
Anxiety	43 (4.5)	33 (3.5)	common
Pyrexia	37 (3.9)	26 (2.8)	common
Constipation	24 (2.5)	14 (1.5)	common
Muscular weakness	23 (2.4)	13 (1.4)	common
Influenza like illness	21 (2.2)	10 (1.1)	common
Immunoglobulins decreased	15 (1.6)	2 (0.2)	common

Source: T032a Table 1.6
- A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
- Preferred terms are sorted in descending frequency of AEs in the OMB frequency column.
- N is the number of patients in the treatment group, n is the number of patients with at least one event in the treatment group.
- % is calculated by n/N*100.
- MedDRA Version 22.0
- Frequency category is based on the clinical trial database (N) according to the CIOMS III convention: very common (>=1/10); common (>=1/100 to <1/10)

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from postmarketing experience with Kesimpta via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders	Neutropenia
Immune system disorders	Hypersensitivity reaction
Hepatobiliary Disorders	Liver injury

Description of selected adverse drug reactions

Upper Respiratory Tract Infections

A higher proportion of ofatumumab-treated patients experienced upper respiratory tract infections compared to teriflunomide-treated patients. In the RMS clinical studies, 39.4% of ofatumumab-treated patients experienced upper respiratory tract infections compared to 37.8% of teriflunomide-treated patients. The infections were predominantly mild to moderate and mostly consisted of nasopharyngitis, upper respiratory tract infection and influenza.

Injection related reactions and injection site reactions

In patients treated with ofatumumab in the RMS Phase 3 clinical studies, injection related reactions (systemic) and injection-site reactions (local) were reported in 20.6% and 10.9% of patients treated with ofatumumab, respectively.

The incidence of injection-related reactions was highest with the first injection (14.4%), decreasing significantly with subsequent injections (4.4% with second, <3% from third injection). Injection-related reactions were mostly (99.8%) mild to moderate in severity. Only two (0.2%) ofatumumab-treated MS patients reported serious injection-related reactions. There were no life-threatening injection-related reactions. The most frequently reported symptoms (≥2%) included fever, headache, myalgia, chills, and fatigue.

Local reactions at the administration site were very common. Injection-site reactions were all mild to moderate in severity and non-serious in nature. The most frequently reported symptoms (≥2%) included erythema, pain, itching, and swelling (see section 4.4 Special warnings and precautions for use).

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.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

No cases of overdose have been reported in RMS clinical studies.

Doses up to 700 mg have been administered intravenously in clinical studies with MS patients without dose-limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies ATC code: L04AG12

B-cell depletion

In the RMS Phase 3 studies, ofatumumab 20 mg every 4 weeks, after an initial dose regimen of 20 mg on days 1, 7 and 14, resulted in a rapid and sustained reduction of B-cells to below the lower limit of normal as early as two weeks after treatment initiation, and sustained for as long as 120 weeks while on treatment.

Similar results were observed in a study of bioequivalence using the same dosing regimen as in the Phase 3 studies. Before initiation of the maintenance phase starting at week 4, total B-cell levels <10 cells/μL were reached in 94% of patients increasing to 98% of patients at week 12.

B-cell repletion

Data from RMS Phase 3 studies indicate a median time to B-cell recovery to LLN or baseline value of 24.6 weeks post treatment discontinuation. PK-B-cell modelling and simulation for B-cell repletion corroborate this data, predicting median time to B-cell recovery to LLN of 23 weeks post treatment discontinuation.

Mechanism of action

B-cells play an important role in MS pathogenesis due to production of pro-inflammatory cytokines, release of auto-reactive antibodies and activation of pathogenic T cells. Ofatumumab is a fully human anti-CD20 monoclonal antibody (IgG1). It binds to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule giving rise to a slow off-rate and high binding affinity. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage. The CD20 molecule is also expressed on a small fraction of activated T cells.

The binding of ofatumumab to CD20 induces lysis of CD20+ B-cells primarily through complement-dependent cytotoxicity (CDC) and to a lesser extent, through antibody-dependent cell-mediated cytotoxicity (ADCC). Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells. CD20-expressing T cells are also depleted by ofatumumab.

Clinical trials

The efficacy and safety of Kesimpta were evaluated in two randomized, double-blind, active-controlled Phase 3 pivotal studies of identical design (G2301 (ASCLEPIOS I) and G2302 (ASCLEPIOS II)) in patients with relapsing forms of MS (RMS), aged 18 to 55 years, a disability status at screening with an Expanded Disability Status Scale (EDSS) score from 0 to 5.5, and who had experienced at least one documented relapse during the previous year or two relapses during the previous two years or a positive gadolinium (Gd)-enhancing MRI scan during the previous year. Both newly diagnosed patients and patients switching from their current treatment were enrolled.

In the two studies, 927 and 955 patients with RMS, respectively, were randomized 1:1 to receive either Kesimpta 20 mg subcutaneous injections every 4 weeks starting at Week 4 after an initial dosing regimen of three weekly 20 mg doses in the first 14 days (on Days 1, 7 and 14) or teriflunomide 14 mg capsules orally once daily. Patients also received matching placebo corresponding to the other treatment arm to ensure blinding (double-dummy design).

The treatment duration for individual patients was variable based on when the end of study criteria were met. Across both studies, the median treatment duration was 85 weeks, 33.0% of

patients in the Kesimpta group vs 23.2% of patients in the teriflunomide group were treated more than 96 weeks.

Demographics and baseline characteristics were well-balanced across treatment arms and both studies (see Table 3). Mean age was 38 years, mean disease duration was 8.2 years since onset of first symptom, and mean EDSS score was 2.9; 40% of patients had not been previously treated with a disease modifying therapy (DMT) and 40% had gadolinium (Gd)-enhancing T1 lesions on their baseline MRI scan.

The primary efficacy endpoint of both studies was the annualized rate of confirmed relapses (ARR) based on EDSS. Key secondary efficacy endpoints included the time to disability worsening on EDSS (confirmed at 3 months and 6 months), defined as an increase in EDSS of ≥1.5, ≥1, or ≥0.5 in patients with a baseline EDSS of 0, 1 to 5, or ≥5.5, respectively. Further key secondary endpoints were the number of Gd-enhancing T1 lesions per MRI scan and the annualized rate of new or enlarging T2 lesions. Disability-related key secondary endpoints were evaluated in a meta-analysis of combined data from studies G3201 and G2302, as defined in the study protocols.

Table 3 Demographics and baseline characteristics

Characteristics	**Study G2301 (ASCLEPIOS I)**		**Study G2302 (ASCLEPIOS II)**	
	Kesimpta (N=465)	Teriflunomide (N=462)	Kesimpta (N=481)	Teriflunomide (N=474)
Mean age (years)	38.9	37.8	38.0	38.2
Age range (years)	19 - 55	18 - 55	18 - 55	18 - 55
Female (%)	68.4	68.6	66.3	67.3
Mean/Median duration of MS since first symptoms (years)	8.36 / 6.41	8.18 / 6.69	8.20 / 5.70	8.19 / 6.30
Mean/Median duration of MS since diagnosis (years)	5.77 / 3.94	5.64 / 3.49	5.59 / 3.15	5.48 / 3.10
Previously treated with DMTs (%)	58.9	60.6	59.5	61.8
Number of relapses in last 12 months	1.2	1.3	1.3	1.3
Mean/Median EDSS score	2.97 / 3.00	2.94 / 3.00	2.90 / 3.00	2.86 / 2.50
Mean total T2 lesion volume (cm^3)	13.2	13.1	14.3	12.0
Patients free of Gd+ T1 lesions (%)	62.6	63.4	56.1	61.4
Number of Gd+ T1 lesions (mean)	1.7	1.2	1.6	1.5

The efficacy results for both studies are summarized in Table 4, and Figure 1.

In both Phase 3 studies (G2301 and G2302), Kesimpta demonstrated a significant reduction in the annualized relapse rate of 50.5% and 58.4%, respectively (both $p<0.001$) compared to teriflunomide.

The pre-specified meta-analysis of combined data showed that Kesimpta significantly reduced the risk of 3-month confirmed disability worsening (CDW) (risk reduction = 34.3%, p=0.003) and 6-month CDW (risk reduction = 32.4%, p=0.012) compared to teriflunomide (see Figure 1).

Kesimpta significantly reduced the number of Gd-enhancing T1 lesions and the rate of new or enlarging T2 lesions by 95.9% and 83.5%, respectively (both studies combined).

Efficacy results were consistent across the two Phase 3 studies (G2301 and G2302) and across subgroups defined based on gender, age, prior MS therapy and baseline disability and disease activity.

Table 4 Overview of results from Phase 3 studies in RMS

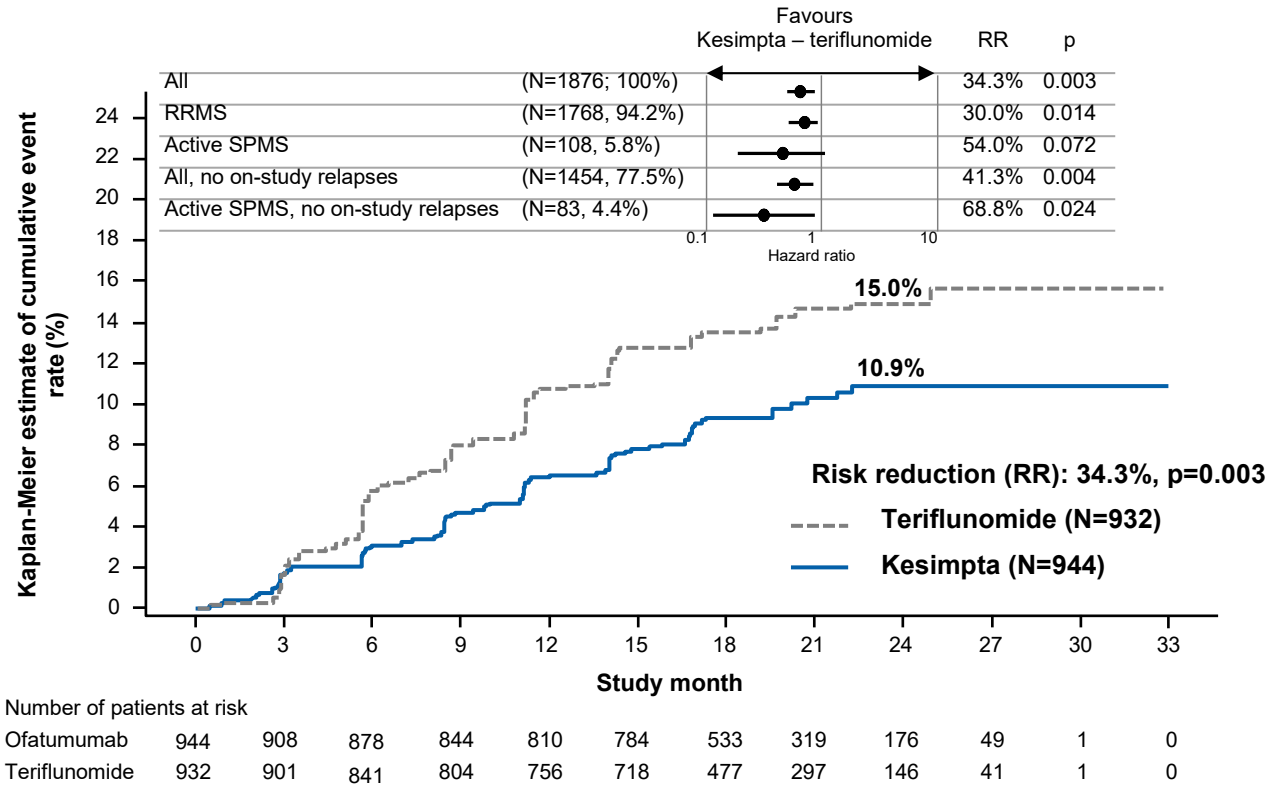
Endpoints	**Study G2301 (ASCLEPIOS I)**		**Study G2302 (ASCLEPIOS II)**	
	Kesimpta 20 mg (n=465)	**Teriflunomide 14 mg (n=462)**	**Kesimpta 20 mg (n=481)**	**Teriflunomide 14 mg (n=474)**
Endpoints based on separate studies				
Annualized relapse rate (ARR) (Primary Endpoint)[1]	0.11	0.22	0.10	0.25
Rate reduction	50.5% (p<0.001)		58.4% (p<0.001)	
Mean number of T1 Gd-enhancing lesions per MRI scan	0.0115	0.4555	0.0317	0.5172
Relative reduction	97.5% (p<0.001)		93.9% (p<0.001)	
Number of new or enlarging T2 lesions per year	0.72	4.00	0.64	4.16
Relative reduction	81.9% (p<0.001)		84.6% (p<0.001)	
Endpoints based on pre-specified meta-analyses				
Proportion of patients with 3-month confirmed disability worsening[3] Risk reduction	10.9% Kesimpta vs. 15.0% teriflunomide 34.3% (p=0.003)			
Proportion of patients with 6-month confirmed disability worsening[3] Risk reduction	8.1% Kesimpta vs. 12.0% teriflunomide 32.4% (p=0.012)			

[1] confirmed relapses (accompanied by a clinically relevant change in the EDSS)

[2] in serum

[3] Disability worsening was defined as an increase in EDSS of at least 1.5, 1 or 0.5 points in patients with baseline EDSS of 0, 1 to 5, or 5.5 or greater, respectively.

Figure 1 Time to first 3-month CDW by treatment (G2301 and G2302 combined, full analysis set) and subgroups



Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and the underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ofatumumab products may be misleading.

Treatment-induced anti-drug antibodies (ADA) in the Phase 3 studies were detected in 2 of 946 (0.2%) KESIMPTA treated patients; no patients with treatment enhancing or neutralizing ADAs were identified. There was no impact of positive ADA titers on PK, safety profile or B-cell kinetics in any patient, however, these data are not adequate to assess the impact of ADAs on the safety and efficacy of KESIMPTA.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Based on the 12 week bioequivalence study in RMS patients (COMB157G2102) a monthly subcutaneous dose of 20 mg leads to a mean AUCtau of 483 µg·h/mL and a mean Cmax of 1.43 µg/mL at steady state. The Tmax was generally achieved within the first week of treatment.

After subcutaneous administration, ofatumumab is believed to be predominantly absorbed via the lymphatic system similarly to other therapeutic monoclonal antibodies.

Distribution

The volume of distribution at steady state was estimated to be 5.42 litres following repeated subcutaneous administration of Kesimpta at a dose of 20 mg.

Metabolism

Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes.

Excretion

Ofatumumab exhibits a long half-life and low volume of distribution similar to that of other monoclonal antibodies. Ofatumumab is eliminated through a non-linear target-mediated route as well as a target-independent route mediated by non-specific endocytosis followed by intracellular catabolism. Higher baseline B-cell count results in greater component of target-mediated elimination clearance and shorter ofatumumab half-life at the start of therapy. Subsequent ofatumumab dosing leads to potent depletion of B-cells resulting in reduced overall clearance.

Ofatumumab is eliminated in two ways: a target-independent route mediated by non-specific endocytosis followed by intracellular catabolism, as with other IgG molecules and a target-mediated route that is related to binding to B-cells. B-cells present at baseline result in a greater component of target-mediated clearance of ofatumumab at the start of therapy. Ofatumumab dosing leads to potent depletion of B-cells resulting in reduced overall clearance. The half-life at steady state was estimated to be approximately 11 days following repeated subcutaneous administration of ofatumumab at a dose of 20 mg.

Ofatumumab had non-linear pharmacokinetics related to its decreasing clearance over time.

Special populations

Paediatric patients (below 18 years)

The safety and effectiveness in pediatric patients below the age of 18 years have not yet been established.

Elderly patients (65 years or above)

No studies have been performed in elderly MS patients. Ofatumumab was studied in patients with RMS aged 18 to 55 years. Results from population pharmacokinetics suggest that dose adjustment is not required in elderly patients.

Gender

Gender had a modest (12%) effect on ofatumumab central volume of distribution in a cross-study population analysis, with higher Cmax and AUC values observed in female patients (48% of the patients in this analysis were male and 52% were female); these effects are not considered clinically relevant, and no dose adjustment is recommended.

Renal impairment

Ofatumumab is not excreted via urine; therefore, it is not expected that patients with renal impairment require dose modification.

Hepatic impairment

Since hepatic metabolism of monoclonal antibodies such as ofatumumab is negligible, hepatic impairment is not expected to impact its pharmacokinetics. Therefore, it is not expected that patients with hepatic impairment require dose modification.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No dedicated genotoxicity studies have been conducted with ofatumumab. As an antibody, ofatumumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

No dedicated carcinogenicity studies have been conducted with ofatumumab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Arginine; sodium acetate trihydrate; sodium chloride; polysorbate 80; disodium edetate; hydrochloric acid and water for injection.

6.2 INCOMPATIBILITIES

This product must not be mixed with other medicinal products.

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 between 2°C to 8°C.

Do not freeze.

Store in the original carton to protect from light.

If necessary, Kesimpta may be stored unrefrigerated for a single period of up to 7 days at room temperature (not above 30°C). If not used during this period, Kesimpta can then be returned to the refrigerator for a maximum of 7 days.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pre-filled syringe and pre-filled pen contains 20 mg ofatumumab solution for injection (0.4 mL of 50 mg/mL solution).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Ofatumumab is a recombinant fully human monoclonal immunoglobulin G1 (IgG1) antibody against human CD20 expressed on B-cells. Ofatumumab is produced in a murine cell line (NS0) by recombinant DNA technology.

CAS number

679818-59-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
Level 25, Victoria Cross Tower
155 Miller Street
North Sydney NSW 2060
Telephone 1 800 671 203
Web site: www.novartis.com.au
® = Registered trademark

9 DATE OF FIRST APPROVAL

4 March 2021

10 DATE OF REVISION

1 October 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6	Change in timeframe for use of effective contraception
5.2	Updated elimination half-life

Internal document code: kes011026i based on CDS dated 15 June 2026