PDL DRUG REVIEW

Proprietary Name: Kesimpta®
Common Name: ofatumumab
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Ocrevus	Medical Coverage

Summary

Pharmacology/Usage: Ofatumumab, the active ingredient of Kesimpta®, is a recombinant human monoclonal immunoglobulin G1 (IgG1) antibody that binds to human CD20 expressed on B-cells. The exact mechanism of action by which ofatumumab exerts its therapeutic effects for its approved indication is not known, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ofatumumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

Indication: For the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

There is no pregnancy category for this product; however, the risk summary indicates that there are no adequate data on the developmental risk associated with use in pregnant women. Ofatumumab may cross the placenta and cause fetal B-cell depletion based on findings from animal studies. Avoid administering live vaccines to neonates and infants exposed to Kesimpta® in utero until B-cell recovery occurs. Females of childbearing potential should use effective contraception while receiving Kesimpta® and for 6 months after the last treatment of Kesimpta®. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Solution for Injection, preservative-free, available as:

- 20mg/0.4ml in a single-dose prefilled Sensoready Pen (autoinjector)
- 20mg/0.4ml in a single-dose prefilled syringe (listed in the PI but not found in the drug file)

Before administration, remove from the refrigerator and allow to reach room temperature for about 15 to 30 minutes.

Recommended Dosage: Prior to the first dose of Kesimpta®:

- Perform Hepatitis B virus (HBV) screening. Kesimpta® is contraindicated in patients with active HBV confirmed by positive results for Hepatitis B surface antigen (HBsAg) and anti-HBV tests. For patients who

are negative for HBsAg and positive for Hepatitis B core antibody (HBcAb+) or are carriers of HBV (HBsAg+), consult liver disease experts before starting and during treatment with Kesimpta®.
- Perform testing for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, consult immunology experts before starting treatment.
- Administer all immunizations per immunization guidelines at least 4 weeks prior to the start of treatment for live or live-attenuated vaccines and whenever possible, at least 2 weeks prior to the start of treatment for inactivated vaccines.

The recommended initial dosage is 20mg by SC injection at weeks 0, 1, and 2, followed by subsequent dosing of 20mg by SC injection QM starting at week 4. Administer by SC injection only, in the abdomen, thigh, or outer upper arm. Kesimpta® is intended for patient self-administration but the first injection should be performed under the guidance of a healthcare professional.

The pharmacokinetics of ofatumumab in patients with renal or hepatic impairment have not been studied.

Drug Interactions: Concomitant use of Kesimpta® with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when co-administering immunosuppressive therapies with Kesimpta®. When switching from therapies with immune effects, the duration and mechanism of action of these therapies should be taken into account because of the potential additive immunosuppressive effects when starting Kesimpta®.

Kesimpta® has not been studied in combination with other MS therapies.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Kesimpta®) minus reported % incidence for teriflunomide 14mg. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included upper respiratory tract infections (1%), injection-related reactions (systemic; 6%), headache (1%), injection-site reactions (local; 5%), urinary tract infection (2%), back pain (2%), and blood immunoglobulin M decreased (4%). [Note that upper respiratory tract infections includes the terms nasopharyngitis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, rhinitis, viral upper respiratory infection, tonsillitis, acute sinusitis, pharyngotonsillitis, laryngitis, pharyngitis streptococcal, viral rhinitis, sinusitis bacterial, tonsillitis bacterial, viral pharyngitis, viral tonsillitis, chronic sinusitis, nasal herpes, and tracheitis.]

An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. Kesimpta® has the potential for an increased risk of infections, including serious bacterial, fungal, and new or reactivated viral infections; some of these infections have been fatal in patients treated with other anti-CD20 antibodies. Delay Kesimpta® administration in patients with an active infection until the infection is resolved.

Although no cases of progressive multifocal leukoencephalopathy (PML), a viral infection of the brain caused by the JC virus that typically occurs in patients who are immunocompromised, have been reported for Kesimpta® in clinical trials, PML resulting in death has occurred in patients being treated with ofatumumab for CLL (at substantially higher IV doses than the recommended dose in MS but for a shorter duration of treatment). In addition, PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies. At the first sign or symptom of PML, withhold Kesimpta® and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. If PML is confirmed, discontinue Kesimpta® treatment.

Injection-related reactions with systemic symptoms observed in clinical studies occurred most commonly within 24 hours of the first injection but were also observed with later injections. Local injection-site reaction symptoms observed in clinical studies included erythema, swelling, itching, and pain. Only limited benefit of premedication with corticosteroids, antihistamines, or acetaminophen was observed in clinical studies. If injection-related reactions occur, symptomatic treatment is recommended.

As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed (decrease in IgM was reported in 7.7% treated with Kesimpta® vs 3.1% with teriflunomide in clinical trials). No decline in IgG was observed at the end of the study. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, and after discontinuation of therapy until B-cell repletion. Consider discontinuing Kesimpta® therapy if a patient with low immunoglobulins develop a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with IV immunoglobulins.

Contraindications: In patients with active hepatitis B virus infection

Manufacturer: Novartis Pharmaceuticals Corp

Analysis: The safety and efficacy of Kesimpta® were assessed in 2 randomized, double-blind, double-dummy, active comparator-controlled trials of identical design that included patients with relapsing forms of MS. Both studies enrolled patients with at least one relapse in the previous year, 2 relapses in the previous 2 years, or the presence of a T1 gadolinium-enhancing (GdE) lesion in the previous year, in addition to an Expanded Disability Status Scale (EDSS) score from 0 to 5.5.

The mean age of included patients in Study 1 (N=927) was 38 years, while 89% were white and 69% were female. The mean time since MS diagnosis was 5.7 years and the median EDSS score at baseline was 3. At baseline, the mean number of relapses in the previous year was 1 and the mean number of T1 GdE lesions on MRI scan was 1.5.

The mean age of included patients in Study 2 (N=955) was 38 years, while 87% were white and 67% were female. The mean time since MS diagnosis was 5.5 years, and the median EDSS score at baseline was 2.5. At baseline, the mean number of relapses in the previous year was 1.3 and the mean number of T1 GdE lesions on MRI scan was 1.6.

Patients were randomized to receive either Kesimpta® 20mg SC on days 1, 7, and 14, followed by 20mg Q4W thereafter starting at week 4 with a daily oral placebo or the active comparator teriflunomide 14mg PO QD with a placebo administered subcutaneously on days 1, 7, 14, and every 4 weeks thereafter. Treatment duration was variable based on when the end of the study criteria were met, with the maximal duration of treatment for an individual patient being 120 weeks.

The primary endpoint of both trials was the annualized relapse rate (ARR) over the treatment period. Other outcomes assessed included the time to 3-month confirmed disability progression for the pooled populations; the number of T1 GdE lesions per scan at weeks 24, 48, and 96; and the annualized rate of new or enlarging T2 MRI lesions. Disability progression was defined as an increase in EDSS of at least 1.5, 1, or 0.5 points in patients with a baseline EDSS of 0, 1 to 5, or 5.5 or greater, respectively.

Results suggested that in both studies, Kesimpta® significantly lowered the ARR compared to teriflunomide. Kesimpta® significantly reduced the risk of 3-month confirmed disability progression compared to teriflunomide. Kesimpta® significantly reduced the number of T1 GdE lesions and the rate of new or enlarging T2 lesions in both studies. Results can be seen in the table below, which was adapted from the prescribing information.

	Study 1		Study 2	
Endpoints	Kesimpta® 20mg (N=465)	Teriflunomide 14mg (N=462)	Kesimpta® 20mg (N=481)	Teriflunomide 14mg (N=474)
Clinical Endpoints				
Annualized relapse rate	0.11	0.22	0.10	0.25
Relative reduction	51% (p<0.001)		59% (p<0.001)	
Proportion with confirmed disability progression, 3-month	10.9% Kesimpta® Vs 15% teriflunomide (pooled analysis of study 1 and 2)			

	Study 1		Study 2	
Endpoints	Kesimpta® 20mg (N=465)	Teriflunomide 14mg (N=462)	Kesimpta® 20mg (N=481)	Teriflunomide 14mg (N=474)
Relative risk reduction	34.4% (p=0.002)			
MRI Endpoints				
Mean # of T1 Gd-enhancing lesions per MRI scan	0.01	0.45	0.03	0.51
Relative reduction	98% (p<0.001)		94% (p<0.001)	
# of new or enlarging T2 lesions per year	0.72	4.00	0.64	4.15
Relative reduction	82% (p<0.001)		85% (p<0.001)	

Place in Therapy: Kesimpta® is a patient self-administered subcutaneous injection indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Use of Kesimpta® is contraindicated in patients with active hepatitis B virus infection. In two phase 3 clinical trials, Kesimpta® was found to be significantly more effective than teriflunomide for the primary endpoint of ARR, with Kesimpta® being associated with lower annualized relapse rates than teriflunomide. Kesimpta® was significantly more effective than teriflunomide for other secondary endpoints assessed.

It is recommended that Kesimpta® should be non-preferred with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:

☐ **Preferred**

☒ **Non-Preferred with Conditions**

References

[1] Kesimpta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020.