Ofatumumab (Kesimpta®) Abbreviated New Drug Update (ANDU)

September 2020

OVERVIEW[1]

- Indication – CD20-directed cytolytic antibody 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
- Contraindications/Warnings
  - Contraindications – Active hepatitis B infection
  - Warnings – Increased risk of infection; injection related reactions; possible risk of decreased immunoglobulin levels; possible increased risk of immunosuppressant effects with other immunosuppressants; possible reactivation of hepatitis B virus; increased risk of progressive multifocal leukoencephalopathy (PML). No cases of PML have been reported for ofatumumab in the clinical trials for MS, but PML resulting in death has occurred in patients being treated with intravenous (IV) ofatumumab for chronic lymphocytic leukemia (CLL) (at higher doses than recommended for MS). In addition, live or live-attenuated vaccines should be administered 4 weeks prior to starting therapy with ofatumumab, and inactivated vaccines should be administered 2 weeks prior to the start of therapy. There is also a risk of fetal harm due to B-cell lymphopenia and reduced antibody response.
- Drug Interactions
  - Patients who receive immunosuppressant drugs, including systemic corticosteroids, in addition to ofatumumab may be at an increased risk of infection.
- Common Adverse Effects (≥ 10%) were upper respiratory infections (39%), systemic injection-related reactions (21%), headache (13%), local injection site reactions (11%), and urinary tract infection (10%).
- Special Populations
  - Pregnancy – Based on data from animal studies and mechanism of action, ofatumumab can cause transient peripheral B-cell depletion and lymphocytopenia in infants who were exposed to ofatumumab in utero. Females of reproductive potential should use effective contraception while taking ofatumumab and for 6 months following the last dose.
  - Pediatrics – Safety and effectiveness in pediatric patients have not been established.
  - Geriatrics – Clinical studies did not include enough patients ≥ 65 years old to determine if their response differs from that of younger patients.

- Hepatic and Renal Impairment – No studies conducted in patients with hepatic or renal impairment.

- Availability
  - 20 mg/0.4 mL solution in a single-dose prefilled Sensoready® pen and a single-dose prefilled syringe for subcutaneous (SC) injection.
- Dosages
  - Starting dose is 20 mg SC at weeks 0, 1, and 2, followed by a maintenance dose of 20 mg SC every month starting at week 4. May be self- or caregiver-administered with proper training.
- Clinical Trials[2,3,4,5]
  - Two double-blind, double-dummy, active comparator-controlled clinical trials demonstrated the efficacy of SC ofatumumab compared to oral teriflunomide (Aubagio®) in 1,882 patients with relapsing forms of MS. Patients were randomized 1:1 to ofatumumab or teriflunomide and treated for a median of 85 weeks.
  - In both studies, participants were included if they had ≥ 1 relapse in the previous year, 2 relapses in the previous 2 years, or demonstrated the presence of a T1 gadolinium-enhancing (GdE) lesion in the previous year. Participants were also required to have an Expanded Disability Status Scale of (EDSS) score from 0 to 5.5.
  - Results demonstrated that ofatumumab significantly lowered the annualized relapse rate (ARR; primary endpoint) compared to teriflunomide in both studies (Study 1: 0.11 versus 0.22, respectively [51% relative reduction]; Study 2: 0.1 versus 0.25, respectively [59% relative reduction]; $p<0.001$ in both trials). In addition, ofatumumab significantly reduced the risk of 3-month confirmed disability progression compared to teriflunomide across both studies (relative reduction, 10.9% versus 15%, respectively; relative risk reduction, 34.4%; $p=0.002$). Lastly, the mean number of T1 GdE lesions and the number of new or enlarging T2 lesions were significantly reduced in both studies with ofatumumab compared with teriflunomide.

CLINICAL CONSIDERATIONS[6,7]

- Regarding treatment initiation, the 2018 American Academy of Neurology (AAN) practice guidelines state that clinicians should offer disease modifying therapy (DMT) to patients with relapsing forms of MS with recent clinical relapses or MRI activity (Level B). In addition, clinicians should prescribe DMT to patients with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS in those amenable to DMT (Level B). The guidelines also state that providers should prescribe alemtuzumab (Lemtrada®), fingolimod (Gilenya®), or natalizumab (Tysabri®; in select patients) for patients with highly active MS (Level B). Due to a high incidence of severe adverse effects, mitoxantrone should not be prescribed unless the potential therapeutic benefits greatly outweigh the risks (Level B).
- Ofatumumab (Kesimpta) was not included in the 2018 MS guidelines.

- Ocrelizumab (Ocrevus®) is also a CD20-directed cytolytic antibody indicated for patients with relapsing forms of multiple sclerosis. It is administered by a healthcare professional as an IV infusion every 6 months. Premedication with methylprednisolone as well as an antipyretic is recommended.
- Ofatumumab injection for IV use was approved under the brand name Arzerra® (Novartis) in 2009 for the treatment of CLL; it is not indicated to treat MS. Furthermore, Arzerra is administered only via IV infusion at much higher doses for CLL (300 mg initial, followed by 1,000 mg monthly for 12 cycles) than are required for MS.
- Kesimpta is the first self-administered SC formulation of ofatumumab for relapsing forms of MS. It is given every 4 weeks and does not require premedication. Unlike ocrelizumab, which is provider-administered IV given every 6 months, Kesimpta is not approved for the treatment of primary progressive MS. In clinical trials, Kesimpta demonstrated improvement over teriflunomide in annualized relapse rate.
- Ofatumumab (Kesimpta) is available from Novartis.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Multiple Sclerosis Agents
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 18 years of age; **AND** ▪ Patient has been diagnosed with a relapsing form of multiple sclerosis (e.g., relapsing remitting disease [RRMS], active secondary progressive disease [SPMS], or clinically isolated syndrome [CIS] as documented be laboratory report [e.g., MRI]); **AND** ▪ Patient has been evaluated and screened for the presence of hepatitis B virus (HBV) prior to initiating treatment and does NOT have active disease (e.g., positive for HBsAg and anti-HBV tests); **AND** ▪ Patient does NOT have an active infection, including clinically important localized infections; **AND** ▪ Patient serum immunoglobulin baseline was measured prior to the start of therapy; **AND** ▪ Patient has NOT received any live or live-attenuated vaccinations in the 4-weeks prior to, or non-live vaccinations in the 2-weeks prior to, the start of therapy; **AND** ▪ Ofatumumab (Kesimpta) will NOT be administered concurrently with live vaccines**; AND** ▪ Ofatumumab (Kesimpta) will be used as single agent therapy; **AND**

Suggested Utilization Management (continued)

Clinical Edit (continued)	**Renewal Criteria** ▪ Patient continues to meet initial approval criteria; **AND** ▪ Patient is absent of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: serious or opportunistic infections, serious injection sight reactions, prolonged hypogammaglobinemia, etc.; **AND** ▪ Patient continues to show benefit from treatment as demonstrated by continuous monitoring of response to therapy by objective measurement (manifestations of MS disease activity include, but are NOT limited to, an increase in annualized relapse rate [ARR], development of new/worsening T2 hyperintensities or enhancing lesions on brain/spinal MRI, and progression of sustained impairment as evidenced by expanded disability status scale [EDSS], timed 25-foot walk [T25-FW], 9-hole peg test [9-HPT]).
Quantity Limit	20 mg/0.4 mL 3 syringes or pens per 30 days for month 1 (therapy initiation) 20 mg/0.4 mL 1 syringes or pens per 30 days, thereafter (maintenance)
Duration of Approval	Initial: 6 months Renewal: 12 months
Drug to Disease Hard Edit	Active hepatitis B infection

REFERENCES

1 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
2 Kesimpta [package insert]. East Hanover, NJ; Novartis; August 2020.
3 Efficacy and safety of ofatumumab compared to teriflunomide in patients with relapsing multiple sclerosis (ASCLEPIOS I). ClinicalTrials.gov Identifier: NCT02792218. Available at https://clinicaltrials.gov/ct2/show/NCT02792218. Accessed September 14, 2020.
4 Efficacy and safety of ofatumumab compared to teriflunomide in patients with relapsing multiple sclerosis. (ASCLEPIOS II). ClinicalTrials.gov Identifier: NCT02792231. Available at https://clinicaltrials.gov/ct2/show/NCT02792231. Accessed September 14, 2020.
5 Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. N Engl J Med. 2020;383(6):546-557. DOI:10.1056/NEJMoa1917246.
6 National Multiple Sclerosis Society. Practice guidelines recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. Available at: https://www.aan.com/policy-and-guidelines/guidelines/. Accessed September 14, 2020.
7 Ocrevus [package insert]. South San Francisco, CA; Genentech; May 2020.