Formulary Drug Review: Ocrelizumab

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Generic Name: Ocrelizumab

Proprietary Name: *Ocrevus* (Roche)

Approval Rating: BLA

Therapeutic Class: Humanized Anti-CD20 Monoclonal Antibodies

Similar Drugs: Ofatumumab, Rituximab

Sound-/Look-Alike Names: Octazamide, Octreotide, Omalizumab

Indications

Ocrelizumab is approved for the treatment of adults with relapsing or primary progressive forms of multiple sclerosis (MS).^{1,2} In phase 3 clinical trials, ocrelizumab reduced relapses in both relapsing MS (OPERA I and II trials) and primary progressive MS (PPMS) (ORATORIO trial).³⁻⁵

MS is a chronic immune-mediated inflammatory disorder. Patients typically develop symptoms, which vary depending on the location of plaques within the central nervous system, in their late 20s. MS has an unpredictable course, but the most common pattern of progression is relapsing-remitting MS (RRMS), followed by secondary progressive MS (SPMS), then PPMS, and finally progressive-relapsing MS (PRMS). Disease-modifying therapies include interferon beta-1a, glatiramer acetate, and mitoxantrone, which are mostly used for relapsing forms of MS. Other drugs used for the treatment of MS include corticosteroids, cyclophosphamide, methotrexate, azathioprine, cladribine, and cyclosporine.^{6,7} Newer agents (ie, natalizumab, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab) have demonstrated short-term efficacy, but data regarding effects on disease progression or long-term efficacy are limited.⁸ There are no recommendations for the management of MS in terms of a particular order or preference for any of the individual medications (or therapeutic classes). Treatment should be individualized and focused on

suppressing the immune system, preventing progression, reducing relapses, and treating symptoms.^{6,7,9}

Rituximab and ofatumumab have mechanisms of action similar to ocrelizumab, and all 3 agents are being studied for use as disease-modifying therapy for MS.^{8,10} In a phase 2 trial, rituximab reduced relapses and gadolinium-enhancing lesions in patients with RRMS; however, disease-modifying benefits were not observed in a trial of patients with PPMS, and study of rituximab for MS was not advanced to phase 3 trials.^{8,10} Phase 3 trials of ofatumumab for relapsing forms of MS have been completed or are ongoing.^{8,10,11}

Clinical Pharmacology

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-positive B cells; ocrelizumab is associated with increased antibody-dependent cell-mediated cytotoxic effects and reduced complement-dependent cytotoxic effects.^{1,12}

Rituximab and ofatumumab are also humanized monoclonal antibodies that target CD20-positive B cells.^{8,10,12} Ocrelizumab might be less immunogenic than rituximab.¹²

Pharmacokinetics

Ocrelizumab exhibits linear pharmacokinetics, with dose-proportional plasma concentrations for doses between 400 mg and 2000 mg. The mean maximum plasma concentration was 212 µg/mL for a 600 mg infusion dosed every 6 months,

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and 141 µg/mL for two 300 mg infusions given 14 days apart every 6 months.¹

The central volume of distribution for ocrelizumab is 2.78 L; peripheral volume clearance is 2.68 L, and intercompartment clearance is 0.29 L/d. Initial, time-dependent clearance is 0.05 L/d, and constant clearance is 0.17 L/d. The terminal half-life of the maintenance dose (600 mg infusion every 6 months) was 26 days.¹

Comparative Efficacy

Indication: Multiple Sclerosis

Guidelines

Guideline: Multiple sclerosis in adults: management

Reference: National Institute for Health and Care Excellence, 2014⁷

Comments: NICE 2014 guidelines on the management of MS in adults recommend short-term methylprednisolone for treatment of an acute relapse of MS. The guidelines provide direction to NICE guidance documents as well as to the NICE website for information regarding the use of other agents, including beta-interferon, glatiramer acetate, and natalizumab. Newer agents, such as ocrelizumab, are not discussed in these guidelines.

Indication: Primary Progressive Multiple Sclerosis

Studies

Drug: Ocrelizumab vs Placebo

Reference: Montalban X, et al, 2017 (ORATORIO trial)^{4,13}

Study Design: Randomized, double-blind, placebo-controlled, international, multicenter phase 3 study

Study Funding: F. Hoffmann-La Roche Ltd.

Patients: 732 patients (18 to 55 years of age) with PPMS. Patients were eligible if they had an Expanded Disability Status Scale (EDSS) score of 3 to 6.5 and disease duration (from onset of MS symptoms) less than 10 or 15 years (depending on EDSS score). Patients of reproductive potential were required to use 2 methods of contraception throughout the treatment phase and for 48 weeks after the last dose of study medication. Patients were excluded if they had forms of MS other than primary progressive; other neurologic disorders; active infection or history of recurrent or chronic infection; history of cancer (solid tumors and hematological malignancies except for basal cell, in situ squamous cell carcinomas of the skin, or in situ carcinoma of the cervix that had been excised or resolved); any concomitant disease requiring treatment with systemic glucocorticoids or immunosuppressants during the study; history of treatment with B-cell-targeted therapy (eg, rituximab, atacept, belimumab, ofatumumab, ocrelizumab), lymphocyte trafficking blockers, anti-CD4 agents,

alemtuzumab, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplant; or contraindication to magnetic resonance imaging (MRI). In the ocrelizumab and placebo groups, respectively, mean age was 44.7 and 44.4 years, 48.6% and 50.8% were women, mean time since MS symptom onset was 6.7 and 6.1 years, mean time since MS diagnosis was 2.9 and 2.8 years, and 88.7% and 87.7% were naive to MS disease-modifying therapy; mean EDSS score was 4.7 for both groups. Approximately 28% and 25% of patients, respectively, had T1 Gd⁺ lesions; brain T2 hyperintense lesion volume was 12.7 cm³ and 10.9 cm³, and normalized brain volume was 1462.9 cm³ and 1469.9 cm³.

Intervention: Patients were randomized 2:1 (stratified by age [45 years and younger or older than 45 years] and region [the United States or other]) to receive intravenous (IV) ocrelizumab 600 mg or placebo. Ocrelizumab was administered as two 300 mg IV infusions 14 days apart every 24 weeks for at least 120 weeks, until the prespecified number of 12-week confirmed disability progression events occurred. Prophylactic IV methylprednisolone 100 mg was administered prior to each infusion; prophylaxis with an analgesic or antipyretic and antihistamine was also recommended.

Results

Primary End Point(s)

- Percentage of patients with 12-week confirmed disability progression (defined as an increase in EDSS score lasting at least 12 weeks): 32.9% receiving ocrelizumab and 39.3% receiving placebo; risk of 12-week confirmed disability progression was reduced 24% with ocrelizumab compared with placebo (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.59 to 0.98; *P* = .03). The number needed to treat for ocrelizumab to prevent 12-week confirmed disability progression was 16.

Secondary End Point(s)

- Percentage of patients with 24-week confirmed disability progression: 29.6% receiving ocrelizumab and 35.7% receiving placebo; risk of 24-week confirmed disability progression was reduced 25% with ocrelizumab compared with placebo (HR, 0.75; 95% CI, 0.58 to 0.98; *P* = .04).
- Mean percent change in performance on timed 25-foot walk from baseline to week 120: Performance worsened by 38.9% with ocrelizumab and 55.1% with placebo. There was a 29.3% relative reduction in change in the timed 25-foot walk from baseline to week 120 in the ocrelizumab group (*P* = .04).

- Change from baseline in T2 lesion volume was -3.4% with ocrelizumab compared with $+7.4\%$ with placebo ($P < .001$). In addition, there was a 17.5% relative reduction in rate of whole brain volume loss from week 24 to week 120 in the ocrelizumab group ($P = .02$).
- Patient-reported outcomes were evaluated via Short Form-36 (SF-36), which assessed patient perception of functional health and was used to provide a Physical Component Summary (PCS) and Mental Component Summary (MCS). There was no significant difference between ocrelizumab and placebo for the change in SF-36 PCS scores (adjusted mean, -0.7 vs -1.1 ; $P = .6$).

Comments: This multicenter study enrolled patients from Europe, the United Kingdom, Australia, New Zealand, and North and South America. Patients were randomized using an interactive web-response system, and concealed allocation and blinding were maintained for the 120-week study duration. Patients who completed the blinded treatment were eligible to enter the open-label extension phase. The estimated sample size was 630 patients, randomized 2:1 to receive ocrelizumab or placebo, to achieve 80% power for 253 expected disease progression events, with a type I error rate of 0.01. Efficacy end points were analyzed in the intention-to-treat population; patients with missing EDSS score data at baseline were excluded from the analysis, and patients with an initial disability progression during the blinded trial period who discontinued ocrelizumab or placebo early and did not have a subsequent visit with confirmatory measurement of the EDSS score were considered to have confirmed disease progression (ie, worst case scenario). Missing data for the 25-foot walk and the volume of lesions on T2-weighted images were imputed using the last-observation-carried-forward method. Ocrelizumab reduced clinical and MRI disease activity compared with placebo. The most common adverse events included infusion-related reactions and infections. Infusion-related reactions were more common in patients receiving ocrelizumab but were mostly mild to moderate in severity and were managed with premedication (ie, methylprednisolone) or symptomatic treatment (ie, analgesics or antipyretics).^{4,14} Neoplasms, including breast cancer, basal cell carcinoma, endometrial adenocarcinoma, anaplastic large-cell lymphoma, malignant fibrous histiocytoma, and pancreatic carcinoma, were reported in 2.3% of patients receiving ocrelizumab compared with 0.8% in the placebo group. No progressive multifocal leukoencephalopathy (PML), a treatment-limiting factor in MS, was reported.

Limitations: The study included patients in the earlier stages of PPMS, with fewer disabilities (per EDSS scores) than in later stages. A hierarchical analysis of end points was used, and the authors did not report data for any of the exploratory end points.

Indication: Relapsing Multiple Sclerosis

Studies

Drug: Ocrelizumab vs Interferon Beta-1a

Reference: Hauser SL, et al, 2017 (OPERA I and OPERA II trials)³

Study Design: Two identical randomized, double-blind, double-dummy, active-controlled, international, multicenter phase 3 studies

Study Funding: F. Hoffmann-La Roche Ltd.

Patients: 1656 patients (821 in OPERA I and 835 in OPERA II) 18 to 55 years of age with relapsing MS diagnosed via 2010 McDonald criteria. Patients were required to have at least 2 documented clinical attacks/relapses within the last 2 years or at least 1 clinical attack/relapse within 1 year prior to screening, neurologic stability for at least 30 days prior to both screening and baseline, and EDSS score of 0 to 5.5. Patients were excluded if they had PPMS; disease duration of more than 10 years if EDSS score was 2 or less at screening; other neurological disorder; immunodeficiency or infection; severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies; contraindication to study drugs; or a history of PML. Other exclusion criteria included previous treatment with B-cell-targeted therapies (ie, rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab), alemtuzumab, anti-CD4 agents, cladribine, mitoxantrone, daclizumab, teriflunomide, total body irradiation, or bone marrow transplantation; cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate (within 24 months of screening); natalizumab (duration of treatment was required to be less than 1 year); any investigational agent, fingolimod, or dimethyl fumarate (within 6 months prior to screening); and IV immune globulin (within 12 weeks prior to baseline). Patient demographic and disease characteristics at baseline (eg, age, gender, time since MS onset, time since MS diagnosis, EDSS score) were well balanced between studies and treatment groups.

Intervention: Patients were randomized 1:1 (stratified by baseline EDSS score [less than 4 or greater than or equal to 4] and region [United States or other]) to receive ocrelizumab 600 mg via IV infusion every 24 weeks or interferon beta-1a 44 μ g via subcutaneous injection 3 times a week for 96 weeks. Patients received 4 cycles of ocrelizumab, which was given as two 300 mg infusions on days 1 and 15 of the first 24-week treatment cycle, and then as a single 600 mg infusion for the remaining 24-week cycles. Interferon beta-1a was initiated at 8.8 μ g for weeks 1 and 2, then 22 μ g for weeks 3 and 4, and then 44 μ g for the remainder of the 96-week treatment period. All patients received IV methylprednisolone 100 mg prior to each infusion; prophylaxis with an analgesic or antipyretic and an antihistamine was also recommended. To ensure blinding, patients in the ocrelizumab group

received interferon beta-1a placebo injections 3 times a week, and patients in the interferon beta-1a group received ocrelizumab placebo infusions every 24 weeks.

Results

Primary End Point(s)

- Protocol-defined annualized relapse rate (ARR) at 96 weeks: Protocol-defined ARR and ARR for all clinical relapses were reduced with ocrelizumab. In OPERA I, there was a 46% reduction in protocol-defined ARR ($P < .001$) and a 42% reduction in ARR for all clinical relapses ($P < .001$). In OPERA II, protocol-defined ARR was reduced by 47% ($P < .001$), and ARR for all clinical relapses was reduced by 43% ($P < .001$).

Secondary End Point(s)

- Confirmed disability progression: Pooled analysis of OPERA I and OPERA II showed that ocrelizumab reduced the risk of 12-week confirmed disability progression by 40% ($P < .001$) and the risk of 24-week confirmed disability progression by 40% ($P = .003$).
- Confirmed disability improvement: Pooled analysis of OPERA I and OPERA II showed that a greater proportion of patients treated with ocrelizumab achieved confirmed disability improvement at week 12, with a 33% higher rate of improvement with ocrelizumab than interferon beta-1a ($P = .02$).
- The difference in the adjusted mean change in the Multiple Sclerosis Functional Composite (MSFC) score from baseline to week 96 between ocrelizumab and interferon beta-1a was 0.04 (95% CI, -0.04 to 0.12) for OPERA I ($P = .33$) and 0.11 (95% CI, 0.03 to 0.18) for OPERA II ($P = .004$).
- Total number of T1 Gd⁺-enhancing lesions by week 96 was reduced with ocrelizumab (OPERA I: 94% [$P < .001$]; OPERA II: 95% [$P < .001$]). The number of new or enlarging T2 lesions by week 96 was also reduced with ocrelizumab (OPERA I: 77% [$P < .001$]; OPERA II: 83% [$P < .001$]). The mean number of new T1 hypointense lesions by week 96 was reduced with ocrelizumab (OPERA I: 57% [$P < .001$]; OPERA II: 64% [$P < .001$]). The rate of brain volume change from week 24 to 96 was lower for patients on ocrelizumab. The difference in brain volume loss was 22.8% for OPERA I ($P = .004$) and 14.9% for OPERA II ($P = .09$).
- Proportion of patients with no evidence of disease activity from baseline to week 96 was higher for patients treated with ocrelizumab (OPERA I: 47.9% vs 29.2% with interferon beta-1a [$P < .001$]; OPERA II: 47.5% of patients receiving ocrelizumab vs 25.1% with interferon beta-1a [$P < .001$]).

- Difference in mean change in SF-36 PCS score from baseline to week 96 between ocrelizumab and interferon beta-1a was 0.69 (95% CI, -0.41 to 1.8) for OPERA I and 1.16 (95% CI, 0.05 to 2.27) for OPERA II.

Comments: The OPERA I and OPERA II trials used the same study design, with 89 trial sites across more than 30 countries; the majority of study sites were in the United States. The estimated sample size for each trial was 400 patients per treatment arm, to achieve 84% power to detect a 50% lower ARR with ocrelizumab compared with interferon beta-1a. An additional assumption for the sample size was an estimated ARR of 0.165 in the ocrelizumab group and of 0.33 in the interferon beta-1a group. There were 10 hierarchically ordered secondary end points, with subsequent end points evaluated only if the primary end point, and each preceding end point in the ordered hierarchy, achieved statistical significance. After the first P value greater than .05, all subsequent P values were deemed nonconfirmatory and only nominally significant. Over the 96-week treatment period, ocrelizumab reduced incidence of clinical relapses and disease progression.

Adverse effects of the study medication included infusion-related reactions, infections, and herpes-associated infections. The incidence of adverse events was similar for ocrelizumab and interferon beta-1a. Infusion-related reactions that occurred with ocrelizumab were generally mild to moderate in severity and were manageable with premedication (IV methylprednisolone), infusion adjustments, or symptomatic treatment (analgesics, antipyretics).^{3,15} The incidence of adverse events leading to treatment discontinuation was generally lower for patients receiving ocrelizumab, for both OPERA I and II. Ocrelizumab had no effect on preexisting humoral immunity to common viral and bacterial antigens.¹⁶ Estimated primary completion dates are November 2019 for OPERA I and January 2020 for OPERA II. Patients who complete the 96-week trial have the option to continue treatment in an open-label trial extension phase if they (continue to) meet eligibility criteria. The findings reported thus far align with results of a phase 2 study in which ocrelizumab showed reduced disease progression as well as lower ARRs in patients with RRMS after 24 weeks of therapy.¹²

Limitations: Some secondary efficacy end points were reported only as pooled analysis; however, given the identical trial designs, pooled analysis was considered valid if between-group treatment differences for ARR through week 96 and 12-week confirmed disability progression were consistent between trials.³ The difference in the adjusted mean change in the MSFC score between the ocrelizumab group and the interferon beta-1a group was

not statistically significant, and subsequent end points, including change in SF-36 quality-of-life PCS score and measure of no evidence of disease activity, were considered nominally different, but nonconfirmatory.

Contraindications, Warnings, and Precautions

Contraindications

Ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection, as well as in patients with a history of a life-threatening infusion reaction to ocrelizumab. Another potential contraindication is hypersensitivity to ocrelizumab or to any of its inactive ingredients.¹

Warnings and Precautions

Infusion reactions were reported in patients treated with ocrelizumab, despite pretreatment with methylprednisolone (or an equivalent steroid) and other premedications. Infusion reactions included pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia, and were reported in 34% to 40% of patients in clinical trials, with the highest incidence occurring with the first infusion. Infusion reactions can also occur up to 24 hours after completion of the infusion. None of the reported infusion reactions were fatal, but hospitalization was required by 0.3% of patients who had an infusion reaction. Premedication with methylprednisolone (or an equivalent steroid) and an antihistamine (eg, diphenhydramine) 30 minutes prior to each infusion may be administered to reduce the frequency and severity of infusion reactions; addition of an antipyretic (eg, acetaminophen) may also be considered. For mild to moderate reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment. Ocrelizumab must be discontinued permanently in patients who experience a life-threatening infusion reaction.¹

Ocrelizumab may increase the risk of infections, including upper and lower respiratory tract infections, skin infections, and herpes-related infections. The infection rate was 70% with ocrelizumab compared with 68% with placebo in a PPMS trial, and was 58% with ocrelizumab versus 52% with interferon beta-1a in relapsing MS trials. Respiratory tract infections were mostly mild to moderate, consisting mainly of upper respiratory tract infections and bronchitis. Herpes infections included herpes zoster, herpes simplex, oral herpes, genital herpes, and herpes virus infection, but were mostly mild to moderate in severity; there were no reports of disseminated herpes.¹

There were no reports of PML in clinical trials. Patients treated with anti-CD20 antibodies may be at risk for this

viral infection, and ocrelizumab therapy should be withheld at the first sign or symptom of PML (eg, progressive unilateral weakness; clumsiness of limbs; vision abnormalities; changes in thinking, memory, and orientation leading to confusion; personality changes).¹

There were no reports of HBV reactivation in patients treated with ocrelizumab. Patients treated with anti-CD20 antibodies may be at increased risk for fulminant hepatitis, hepatic failure, and death caused by HBV reactivation. HBV screening is required for all patients prior to starting ocrelizumab. Active HBV must be confirmed with positive results for hepatitis B serum antigen (HBsAg) and anti-hepatitis B tests; liver disease experts may be consulted before starting ocrelizumab if patients test negative for HBsAg but are positive for hepatitis B core antibody (HBcAb+) or are carriers of HBV (HBsAg+).¹

There is an increased risk of additive immunosuppression if ocrelizumab is used concurrently with other immunosuppressive therapies, or if it is started after immunosuppressive therapy.¹

Concurrent use of live vaccines is not recommended with ocrelizumab. Administer all vaccines, live or live-attenuated, at least 6 weeks prior to initiating therapy. There are no data on the effects of nonlive vaccines in patients receiving ocrelizumab.¹

Malignancies, including breast cancer, were reported with higher frequency in patients treated with ocrelizumab. Breast cancer occurred in 0.77% of patients treated with ocrelizumab and in 0% of patients treated with interferon beta-1a or placebo. Patients should be monitored for breast cancer using standard breast cancer screening guidelines.¹

Ocrelizumab is a humanized monoclonal antibody with the potential to cross the placental barrier. Although there are no human data on the effects of ocrelizumab in human neonates following maternal exposure, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. In addition, perinatal deaths (some associated with bacterial infections), renal toxicity (glomerulopathy and inflammation), lymphoid follicle formation in the bone marrow, and severe reductions in circulating B-lymphocytes in neonates were seen in embryofetal and pre- and postnatal development studies in monkeys. Women of childbearing potential should use contraception during treatment and for 6 months after the last infusion of ocrelizumab.¹

There are no data on the presence of ocrelizumab in human breast milk, or its effects on breastfeeding infants or milk production. Ocrelizumab was detected in the milk of treated monkeys. Potential adverse effects on infant development should be weighed against the clinical benefits of ocrelizumab use for the mother.¹

In clinical trials, the small subset of patients 65 years of age and older was not sufficient to determine age-related differences in the safety and efficacy of ocrelizumab.¹

The safety and efficacy of ocrelizumab in pediatric patients have not been established.¹

Adverse Reactions

In an active-controlled trial for relapsing MS, the most commonly reported adverse effects among patients treated with ocrelizumab were upper respiratory tract infections (40%), infusion reactions (34%), depression (8%), lower respiratory tract infections (8%), back pain (6%), herpes virus–associated infections (6%), and pain in extremities (5%).¹

Commonly reported adverse effects in patients with PPMS treated with ocrelizumab were upper respiratory tract infections (49%), infusion reactions (40%), skin infections (14%), lower respiratory tract infections (10%), cough (7%), diarrhea (6%), peripheral edema (6%), and herpes virus–associated infections (5%).¹

Laboratory abnormalities, including decreased immunoglobulin (Ig) and neutrophil levels, were reported in patients treated with ocrelizumab. The proportion of relapsing MS patients with baseline levels of IgG, IgA, and IgM below the lower limit of normal was 0.5%, 1.5%, and 0.1%, respectively; at the end of 96 weeks, levels had increased to 1.5%, 2.4%, and 16.5%, respectively, for patients treated with ocrelizumab. The proportion of PPMS patients with baseline levels of IgG, IgA, and IgM below the lower limit of normal was 0%, 0.2%, and 0.2%, respectively; at the end of 120 weeks, levels had increased to 1.1%, 0.5%, and 15.5%, respectively, for patients treated with ocrelizumab. In the PPMS trial, decreased neutrophil counts occurred in 13% of patients treated with ocrelizumab compared with 10% of patients receiving placebo. The neutrophil changes were not persistent and were not associated with an infection.¹

Of 1311 patients treated with ocrelizumab in MS trials, approximately 1% (12 patients) developed antibodies to the medication. Of the patients who developed antidrug antibodies, 16.7% (2 patients) had antibodies that were classified as neutralizing.¹

Drug Interactions

When used concomitantly with other immune-modulating or immunosuppressive therapies, including immunosuppressive doses of corticosteroids, ocrelizumab may increase the risk of immunosuppression. When switching from medications with prolonged immune-modulating effects (daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone), additive immunosuppressive effects should be considered prior to initiating ocrelizumab.¹

Ocrelizumab has not been studied in combination with other MS therapies.¹

Recommended Monitoring

Patients should be monitored for signs and symptoms of infusion reaction during an ocrelizumab infusion and for at

least 1 hour afterward. Patients should also be monitored for infections, including upper and lower respiratory tract infection, herpes-associated infections, and PML. There is a potential increased risk of malignancy, including breast cancer, in patients treated with ocrelizumab. Patients should follow standard cancer screening guidelines.¹

Dosing

The recommended initial dose of ocrelizumab in adults is 300 mg as an IV infusion, followed 2 weeks later by another 300 mg IV infusion. Subsequently, a single 600 mg IV infusion is given every 6 months. Ocrelizumab should be administered under the close supervision of a trained health care professional, and the patient should be observed for at least 1 hour after completion of the infusion.¹

Ocrelizumab should be prepared by a health care professional using aseptic technique. The solution should be prepared by diluting the drug product into an infusion bag containing sodium chloride 0.9% injection, to a final concentration of 1.2 mg/mL. Other diluents should not be used to dilute ocrelizumab. The prepared infusion solution should be used immediately.¹

The infusion rate should be started at 30 mL/h for the initial dose (2 infusions of 300 mg, separated by 2 weeks). It can be increased by 30 mL/h every 30 minutes, up to a maximum of 180 mL/h. The total duration of the infusion should be 2.5 hours or longer. Subsequent doses (one infusion of 600 mg every 6 months) can be started at 40 mL/h and can be increased by 30 mL/h every 30 minutes, up to a maximum of 200 mL/h. The total duration of the infusion should be 3.5 hours or longer. All infusions should be given by a dedicated line using an infusion set with a 0.2- or 0.22- μ m in-line filter.¹

Dose modification may be required to manage infusion-related reactions, depending on the severity of the reaction (see Table 1).¹

A missed dose should be administered as soon as possible, and the dose schedule should be reset to administer the next dose 6 months after the missed dose is administered; each dose needs to be separated by at least 5 months.¹

Product Availability

Ocrelizumab was approved by the US Food and Drug Administration on March 28, 2017.² It is available as a 300 mg per 10 mL single-dose vial for injection.¹

The vials should be stored at 2°C to 8°C (36°F to 46°F) in the original packaging and protected from light, direct heat, or direct sunlight. The syringe should not be frozen, exposed to heat, or shaken.¹ Ocrelizumab may be stable for 15 months from the date of manufacture.²

The diluted drug solution should be used immediately because it contains no preservative, but can be stored for up to 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F) and for 8 hours at room temperature (25°C [77°F]), including infusion time.¹

Table 1. Ocrelizumab Dose Modifications to Manage Infusion-Related Reactions.¹

Severity of infusion reaction	Recommendation
Mild to moderate infusion reactions	The infusion rate may be reduced to half the rate and maintained at the reduced rate for at least 30 minutes; the rate may then be increased by 30 mL/h every 30 minutes for the initial dose, or by 40 mL/h every 30 minutes for the subsequent doses.
Severe infusion reactions	Interrupt the infusion and administer supportive treatment; restart the infusion only upon symptom resolution. When restarting the infusion, begin at half the infusion rate at the time of onset of infusion reaction. The infusion rate may then be increased as described for mild to moderate infusion reactions.
Life-threatening infusion reactions	Immediately stop the infusion and provide appropriate supportive care. Ocrelizumab must be discontinued permanently in patients who experience life-threatening infusion reactions.

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for ocrelizumab.^{1,2}

Conclusion

Ocrelizumab is a humanized anti-CD20 monoclonal antibody approved for the treatment of relapsing and progressive forms of MS. It can reduce time to disease progression and was more effective than interferon beta-1a in clinical trials. No other anti-CD20 agent is currently approved for the treatment of MS. Preliminary results of studies in which ocrelizumab was administered IV every 24 weeks indicate beneficial clinical effects that are sustained over 96 weeks of treatment.

Declaration of Conflicting Interests

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