CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Ocrevus™

GENERIC NAME
Ocrelizumab

MANUFACTURER
Genentech, Inc.

DATE OF APPROVAL
March 28, 2017

PRODUCT LAUNCH DATE
Mid-April 2017

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
Ocrevus is indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis (MS).

OFF-LABEL USES
None identified

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CLINICAL EFFICACY

Relapsing MS (RMS)

The safety and efficacy of ocrelizumab in patients with relapsing MS were demonstrated in OPERA I and OPERA II, two phase 3, multicenter, randomized, double-bind, double-dummy, active-controlled, parallel-group trials. Both trials used identical protocols but were conducted independently at nonoverlapping sites.

Key eligibility criteria included an age of 18 to 55 years, a diagnosis of MS according to the McDonald criteria, a score on the Expanded Disability Status Scale (EDSS) of 0 to 5.5, at least 2 documented clinical relapses within the previous 2 years or 1 clinical relapse within the year before screening, magnetic resonance imaging (MRI) consistent with MS, and no neurologic worsening for at least 30 days before screening and at baseline. Patients with primary progressive MS, previous treatment with B-cell targeted therapies, or a disease duration of more than 10 years in combination with an EDSS score of ≤ 2 years were excluded from the trial.

Patients (OPERA I N=821; OPERA II N=835) were randomized in a 1:1 ratio to receive ocrelizumab intravenous (IV) infusion every 24 weeks or interferon beta-1a 44 mcg subcutaneous injection three times weekly for 96 weeks.

The primary endpoint was the annualized relapse rate at 96 weeks. In addition, there were 10 hierarchical secondary endpoints: the proportion of patients with disability progression confirmed at 12 weeks; total mean gadolinium-enhancing lesions on T_1-weighted MRI at weeks 24, 48, and 96; total number of new or newly enlarged hyperintense lesions on T_2-weighted MRI at weeks 24, 48, and 96; proportion of patients with disability improvement confirmed at 12 weeks; rate of disability progression; total number of new hypointense lesions on T_1-weighted MRI at weeks 24, 48, and 96; change in the Multiple Sclerosis Functional Composite score at week 96; percentage change in brain volume from week 24 to 96; change in Physical Component Summary score of the Medical Outcomes study 36-Item Short-Form Health Survey (SF-36) at week 96; and proportion of patients with a baseline EDSS of ≥ 2 who had no evidence of disease activity. All endpoints were analyzed in the intention-to-treat population.

At week 96, treatment with ocrelizumab resulted in a 46-47% lower annualized relapse rate compared to interferon beta-1a in both trials (0.16 vs. 0.29; p<0.001). In addition, the following was observed for the secondary endpoints when compared to interferon beta-1a:

- Disability-related endpoints:
    - Proportion of patients with disability progression confirmed at 12 weeks: 40% lower risk with ocrelizumab (9.1% vs. 13.6%; 95% CI: 0.45-0.81; p<0.001)
    - Rate of disability progression: 40% lower risk with ocrelizumab (6.9% vs. 10.5%; 95% CI: 0.43-0.84; p=0.003)
    - Proportion of patients with disability improvement confirmed at 12 weeks: 33% higher rate of improvement with ocrelizumab (20.7% vs. 15.6%; P=0.02); note: this rate was significant in OPERA I but nonsignificant in OPERA II

- MRI-related endpoints:
  - Total mean gadolinium-enhancing lesions on T_1-weighted MRI: 94-95% lower number of lesions with ocrelizumab (OPERA I: 0.02 vs. 0.29; OPERA II: 0.02 vs. 0.42; p<0.001)
  - Total number of new or newly enlarged hyperintense lesions on T_2-weighted MRI: 77-83% lower number of lesions with ocrelizumab (OPERA I: 0.32 vs. 1.41; OPERA II: 0.33 vs. 1.9; p<0.001)
  - Total number of new hypointense lesions on T_1-weighted MRI: 57-64% lower number of lesions with ocrelizumab (OPERA I: 0.42 vs.0.98; OPERA II: 0.45 vs. 1.26; p<0.001)

Because of failure in the statistical hierarchical testing, p values for all the other secondary endpoints were considered to be nonconfirmatory or nonsignificant.

Of the 827 ocrelizumab patients and 829 interferon beta-1a patients enrolled in both trials, 88% (n=726) and 80% (n=660), respectively, completed the 96-week treatment. 29 ocrelizumab patients and 51 interferon beta-1a patients withdrew due to an adverse event.

Primary progressive MS (PPMS)
The safety and efficacy of ocrelizumab in patients with primary progressive MS were demonstrated in ORATORIO, a phase 3, randomized, parallel-group, double-blind, placebo-controlled trial. Key eligibility criteria included an age of 18 to 55 years, a diagnosis of primary progressive MS, a score on the EDSS of 3 to 6.5, a duration of MS symptoms for < 15 years if the baseline EDSS score was > 5 (duration < 10 years if the baseline EDSS score was < 5), and elevated IgG index or at least one IgG oligoclonal band in the cerebrospinal fluid. Patients who had other forms of MS (relapsing-remitting, secondary progressive, or progressive relapsing), were contraindicated to MRI/glucocorticoids, or received previous treatment with B-cell targeted therapies were excluded from the trial.

Patients (N=732) were randomized in a 2:1 ratio to receive ocrelizumab or placebo by IV infusion every 24 weeks. Double-blind treatment was administered for a minimum of 5 doses (120 weeks) until approximately 253 events of disability progression that were confirmed for at least 12 weeks occurred in the trial cohort.

The primary endpoint was the percentage of patients with disability progression confirmed at 12 weeks. Disability progression was defined as an increase in EDSS score of ≥ 1 point from baseline that was sustained for at least 12 weeks if the baseline EDSS score was ≤ 5.5 (increase of ≥ 0.5 points if the baseline EDSS score was > 5.5). Secondary endpoints included the percentage of patients with disability progression confirmed at 24 weeks, change in performance on the timed 25-foot walk at week 120, change in total volume of brain lesions on T_2-weighted MRI at week 120, change in brain volume from week 24 to 120, and change in Physical Component Summary score of the SF-36 at week 120. All endpoints were analyzed in the intention-to-treat population.

At week 12, treatment with ocrelizumab was associated with a 24% relative risk reduction in disability progression compared to placebo; 32.9% of ocrelizumab patients vs. 39.3% of placebo patients had confirmed disease progression (95% CI: 0.59-0.98; p=0.03). There were similar results at week 24: 29.6% of ocrelizumab patients vs. 35.7% of placebo patients had confirmed disease progression (25% relative risk reduction; 95% CI: 0.58-0.98; p=0.04). In addition, the following results were observed for the other secondary endpoints:

- Change in performance on the timed 25-foot walk at week 120: 29.3% relative reduction with ocrelizumab compared to placebo (38.9% ocrelizumab vs. 55.1% placebo; 95% CI: -1.6-51.5; p=0.04)
- Change in total volume of brain lesions at week 120: decreased with ocrelizumab and increased with placebo (mean percent change -3.4 vs. 7.4; p<0.001)
- Change in brain volume from week 24 to 120: lower with ocrelizumab than placebo (-0.9 vs. -1.09; p=0.02)
- Change in Physical Component Summary score of the SF-36 at week 120: no significant difference between ocrelizumab and placebo

Of the 488 ocrelizumab patients and 244 placebo patients, 82% (n=402) and 71% (n=174), respectively, reached 120 weeks in the trial. 20 ocrelizumab patients and 8 placebo patients withdrew due to an adverse event. The median trial duration was 2.9 years in the ocrelizumab group and 2.8 years in the placebo group.

CONTRAINDICATIONS
Contraindications to Ocrevus therapy include active hepatitis B virus infection and history of life-threatening infusion reactions to Ocrevus.

BLACK BOX WARNINGS
None

DRUG INTERACTIONS
The concomitant use of Ocrevus and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression. Consider the risk of additive immune system effects when co-administering immunosuppressive therapies with Ocrevus. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating Ocrevus.

ADVERSE REACTIONS
The most common adverse reactions were upper respiratory tract infections and infusion reactions for RMS (incidence ≥ 10% and > Rebif); and upper respiratory tract infections,

infusion reactions, skin infections, and lower respiratory tract infections for PPMS (incidence ≥ 10% and > placebo).

In addition, an increased risk of malignancy with Ocrevus may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in Ocrevus-treated patients. Breast cancer occurred in 6 of 781 females treated with Ocrevus and none of 668 females treated with Rebif or placebo. Patients should follow standard breast cancer screening guidelines.

DOSAGE AND ADMINISTRATION
The initial dose of Ocrevus is given as a 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion. Subsequent doses are given as single 600 mg intravenous infusions every 6 months.

Ocrevus should be administered under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion reactions. Patients should be observed for at least one hour after the completion of each infusion.

PRODUCT AVAILABILITY
Single-dose vial: 300 mg/10 mL

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Interferon beta-1a (Avonex, Rebif)	• *Avonex*: 30 mcg IM Q week • *Rebif*: 22 mcg or 44 mcg SC TIW	• 1st line • Development of neutralizing antibodies may limit long-term use
Peginterferon beta-1a (Plegridy)	125 mcg SC Q2 weeks	
Interferon beta-1b (Betaseron, Extavia)	250 mcg SC QOD	
Glatiramer acetate (Copaxone, Glatopa)	• *Copaxone*: 20 mg SC QD or 40 mg SC TIW • *Glatopa*: 20 mg SC QD	• 1st line • Copaxone and Glatopa (branded generic) are not interchangeable
Daclizumab (Zinbryta)	150 mg SC Q4 weeks	• 2nd line after failure of 2+ drugs due to safety profile
Teriflunomide (Aubagio)	7 mg or 14 mg PO QD	• 1st line • Teratogen (limits use since many MS patients are of child-bearing age)
Fingolimod (Gilenya)	0.5 mg PO QD	• 1st line

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		• Cardiovascular concerns
Dimethyl fumarate (Tecfidera)	120 mg PO BID for 7 days, followed by 240 mg PO BID	• 1st line • Only oral agent that requires titration
Alemtuzumab (Lemtrada)	IV infusion for 2 treatment courses: • First course: 12 mg/day on 5 consecutive days • Second course: 12 mg/day on 3 consecutive days 12 months after first course	• 2nd line after failure of 2+ drugs due to safety profile (Lemtrada REMS Program for risk of autoimmunity, infusion reactions, and malignancies)
Mitoxantrone	12 mg/m^2 IV infusion Q3 months	• 2nd line due to safety profile (max cumulative lifetime dose of 140 mg/m^2 due to cardiotoxicity)
Natalizumab (Tysabri)	300 mg IV infusion Q4 weeks	• 1st line per FDA labeling but more likely to be used as 2nd line in practice due to need for infusion and safety concerns (TOUCH Prescribing Program for risk of PML)

Boldface indicates generic availability

Utilization Management Recommendation
There is not significant potential for inappropriate use.
Product Comparison
For relapsing-remitting MS (RRMS): • CPAC score: 69 vs. Rebif – Modest benefits over current therapies • CPAC score: 47 vs. Tecfidera – Equal therapeutic outcomes anticipated • Modest benefits are anticipated for Ocrevus over Rebif. Equal therapeutic outcomes are anticipated for the interferon products: Avonex, Betaseron, Extavia, Plegridy, and Rebif. It is therefore clinically appropriate to provide equal access to Ocrevus or any of the interferon products, or require a trial of one before the other. • Equal therapeutic outcomes are anticipated for Ocrevus and Tecfidera. Equal therapeutic outcomes are also anticipated for Tecfidera, Aubagio, Copaxone, Gilenya, and Glatopa. It is therefore clinically appropriate to provide equal access to all of the aforementioned agents, or require a trial of one before the other. • It is not clinically appropriate to require a trial of any of the following 2nd line therapies:

mitoxantrone, Lemtrada, Tysabri, or Zinbryta before Ocrevus.

For primary-progressive MS (PPMS):

- Ocrevus was not scored for PPMS because it is the only FDA-approved therapeutic option.
- It is not clinically appropriate to require a trial of any MS agent before Ocrevus.
- It is not clinically appropriate to require screening for IgG (IgG index or at least one IgG oligoclonal band in the cerebrospinal fluid) prior to Ocrevus because oligoclonal bands are neither sensitive nor specific for PPMS.
- It is clinically appropriate to restrict treatment to patients with baseline EDSS scores between 3 and 6.5 because the currently available data only includes these patients. There is insufficient evidence to support efficacy in less sick or sicker patients.

REFERENCES

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