Public Assessment Report
OCREVUS

INFORMASI PRODUK

Nama obat	:	Ocrevus
Bentuk sediaan	:	Larutan Konsentrat Untuk Infus
Zat aktif	:	Ocrelizumab 300 mg/vial
Kemasan	:	Dus, 1 vial @ 10 mL
Pendaftar	:	PT. Menarini Indria Laboratories
Produsen	:	Diproduksi oleh Roche Diagnostics Gmbh Mannheim,Federal Republic of Germany, Dirilis Oleh F. Hoffmann-La Roche AG Kaiseraugst, Switzerland, untuk F. Hoffmann-La Roche Ltd Basel, Switzerland
Kategori Registrasi	:	Produk Biologi Baru
Indikasi yang diajukan:	:	*Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1).* *Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity (see section 5.1)*
Posologi yang diajukan	:	*Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions (IRRs).* *<u>Premedication for infusion-related reactions</u>* *The following two premedications must be administered prior to each ocrelizumab infusion to reduce the frequency and severity of IRRs (see section 4.4 for additional steps to reduce IRRs):* - *100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each infusion;* - *antihistamine approximately 30-60 minutes prior to each infusion;* *In addition, premedication with an antipyretic (e.g., paracetamol) may also be considered approximately 30-60 minutes prior to each infusion.* *<u>Posology</u>* *Initial dose* *The initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion (see Table 1).* *Subsequent doses* *Subsequent doses of ocrelizumab thereafter are administered as a single 600 mg intravenous infusion every 6 months (see Table 1). The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose.* *A minimum interval of 5 months should be maintained between each dose of ocrelizumab.* *<u>Infusion adjustments in case of IRRs</u>*

Life-threatening IRRs

If there are signs of a life threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome, the infusion must be stopped immediately and the patient should receive appropriate treatment. The infusion must be permanently discontinued in these patients (see section 4.3).

Severe IRRs

If a patient experiences a severe IRR (such as dyspnea) or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately, and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

Mild to moderate IRRs

If a patient experiences a mild to moderate IRR (e.g., headache), the infusion rate should be reduced to half the rate at the onset of the event. This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion rate. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

Dose modifications during treatment

The above examples of dose interruption and slowing (for mild/moderate and severe IRRs) will result in a change in the infusion rate and increase the total duration of the infusion, but not the total dose. No dose reductions are recommended.

Delayed or missed doses

If an infusion is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval of 6 months (with a minimum of 5 months) should be maintained between doses (see Table 1).

Special populations

Adults over 55 years old and elderly population

Based on the limited data available (see section 5.1 and section 5.2), no posology adjustment is needed in patients over 55 years of age. Patients enrolled in the ongoing clinical trials continue to be dosed with 600 mg ocrelizumab every six months after they become 55 years and older.

Renal impairment

The safety and efficacy of ocrelizumab in patients with renal impairment has not been formally studied. Patients with mild renal impairment were included in clinical trials. There is no experience in patients with moderate and severe renal impairment. Ocrelizumab is a monoclonal antibody and cleared via catabolism (i.e. breakdown into peptides and amino acids), and a dose adjustment is not expected to be required for patients with renal impairment (see section 5.2).

Hepatic impairment

The safety and efficacy of ocrelizumab in patients with hepatic impairment has not been formally studied. Patients with mild hepatic impairment were included in

clinical trials. There is no experience in patients with moderate and severe hepatic impairment. Ocrelizumab is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a dose adjustment is not expected to be required for patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of ocrelizumab in children and adolescents aged 0 to 18 years has not yet been established. No data are available.

Method of administration

After dilution, treatment is administered as an intravenous infusion through a dedicated line. Infusions should not be administered as an intravenous push or bolus.

If patients did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent doses (Table 1, Option 2).

Table 1: Dose and schedule

		Amount of ocrelizumab to be administered	**Infusion instructions**
Initial dose (600 mg) divided into 2 infusions	Infusion 1	300 mg in 250 mL	• Initiate the infusion at a rate of 30 mL/hour for 30 minutes • The rate can be increased in 30 mL/hour increments every 30 minutes to a maximum of 180 mL/hour. • Each infusion should be given over approximately 2.5 hours
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent doses (600 mg) single infusion once every 6 months	Option 1 Infusion of approximately 3.5 hours duration	600 mg in 500 mL	• Initiate the infusion at a rate of 40 mL/hour for 30 minutes • The rate can be increased in 40 mL/hour increments every 30 minutes to a maximum of 200 mL/hour • Each infusion should be given over approximately 3.5 hours
	OR		
	Option 2 Infusion of approximately 2 hours duration	600 mg in 500 mL	• Initiate the infusion at a rate of 100 mL/hour for the first 15 minutes • Increase the infusion rate to 200 mL/hour for the next 15 minutes • Increase the infusion rate to 250 mL/hour for the next 30 minutes • Increase the infusion rate to 300 mL/hour for the remaining 60 minutes • Each infusion should be given over approximately 2 hours

Solutions for intravenous infusion are prepared by dilution of the concentrate into an infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, to a final ocrelizumab concentration of approximately 1.2 mg/mL.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Patients should be monitored during the infusion and for at least one hour after the completion of the infusion (see section 4.4).

PENGANTAR

Ocrelizumab (RO4964913 / PRO70769 / rhuMAb 2H7) merupakan antibodi monoclonal rekombinan humanized. Obat ini dikembangkan untuk terapi multiple sclerosis. Multiple sclerosis (MS) adalah penyakit demyelinisasi kronis, inflamatori pada susunan saraf pusat (SSP). MS ditandai dengan peningkatan permeabilitas sawar darah-otak sehingga memungkinkan sel imun untuk menginfiltrasi ke dalam SSP. CD4+ T cells bereaksi dengan komponen myelin dan memicu kaskade inflamasi destruktif di SSP mengakibatkan demielinisasi dan kehilangan aksonal. Sel B diidentifikasi terdapat dalam lesi dan cairan serebrospinal pasien dengan MS. Hal ini menguatkan teori bahwa sel B juga dapat memainkan peran kunci dalam patofisiologi MS (Disanto et al. 2012; Frischer et al. 2009; Meinl et al. 2006; Lovato dkk. 2011; von Büdingen et al. 2012)

Mekanisme kerja obat ini yaitu secara selektif mengurangi (deplesi) CD20 yang mengekspresikan sel B, sambil mempertahankan kapasitas rekonstitusi sel B dan imunitas humoral yang existing.

ASPEK MUTU

Ocrevus adalah produk biologi dengan zat aktif Ocrelizumab yang merupakan humanized monoclonal antibody, yang dibuat dengan teknologi rekombinan DNA. Ocrelizumab mengacu pada human immunoglobulin G1 (IgG1) framework yang terdiri atas heavy chain dan light chain subgroup sequences. Antibodi recombinan diproduksi di sel CHO Obat jadi diformulasi dalam bentuk sediaan Larutan konsentrat untuk infus, yang mengandung eksipien. Produk ini disimpan pada suhu 2 to 8 °C dan memenuhi persyaratan mutu pada kondisi penyimpanan tersebut sampai selama 24 bulan.

Zat Aktif
Ocrevus dengan zat aktif Ocrelizumab diproduksi dalam proses *fed-batch*. Proses produksi mencangkup upstream dan downstream. Proses upstream terdiri atas proses cell culture process yang teridiri atas 3 tahapan: seed train, inoculum train dan production culture kemudian dipurifikasi untuk mendapatkan Drug Substance.
Karakterisasi dilakukan terhadap sifat fisikokimia serta biologi dan imunokimia. Karakterisasi terhadap sifat fisikokimia mencakup primary structure, post-translation modification, dan higher - order structure. Selain itu, dilakukan detailed characterization dari structural variants, termasuk molecular size dan charge variants.
Hasil studi stabilitas mendukung stabilitas zat aktif pada penyimpanan 2-8° C selama 24 bulan.

Obat Jadi
Produk Obat Ocrelizumab disajikan dalam botol vial sebagai larutan steril, sekali pakai, bening hingga agak opalescent dan tidak berwarna hingga coklat pucat untuk infus intravena (IV) dan tidak mengandung bahan pengawet. Mengingat obat jadi tidak mengandung pengawet, pencegahan terhadap kontaminasi mikroba dilakukan selama produksi dan pelulusan produk. Data stabilitas yang diserahkan berupa studi stabilitas jangka panjang pada kondisi penyimpanan 2 – 8°C, studi stabilitas dipercepat pada kondisi penyimpanan 25°C, dan stressed conditions pada suhu 40°C. Studi stabilitas jangka panjang pada 2 – 8°C menunjukkan hasil yang memenuhi persyaratan mutu hingga bulan ke-24.

Kesimpulan
Dari aspek mutu zat aktif dan obat jadi, produk yang diajukan dapat diterima

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

Studi dilakukan pada cynomolgus monkeys menunjukkan:

- Deplesi sel B perifer diamati mulai dosis 0,05 mg/kg hingga 100 mg/kg. Deplesi *incomplete* diamati pada dosis 0,05 mg/kg, sementara deplesi dengan durasi singkat terjadi pada dosis <10 mg/kg. Durasi deplesi hingga 3 bulan diamati pada dosis 50 dan 100 mg/kg (x2).
- Deplesi pada limpa dan limfonodi pada cynomolgus monkeys bergantung dosis sementara pada sumsum tulang tidak berkorelasi dengan dosis, selain itu pada sumsum tulang lebih rendah jika dibandingkan limpa dan limfonodi.
- Pada monyet cynomolgus (spesies pengikat), farmakokinetik Ocrelizumab menunjukkan disposisi yang dimediasi target, dengan c*learance* dan t1/2 tergantung dosis dan non-linear. Saat dosis bertambah, *clearance* menurun dan t1/2 meningkat.
- Ocrelizumab dapat ditoleransi dengan baik pada cynomolgus monkeys pada dosis hingga 100 mg/kg, dan ditetapkan sebagai Maximum Feasible Dose dan NOAEL, dan dosis ini setara dengan 23 dan 7 kali dosis pada manusia berdasarkan dosis dan AUC.
- *Anti-Drug Antibody (ADA)* terhadap Ocrelizumab terdeteksi dalam penelitian dengan monyet cynomolgus. Deteksi *ADA* umumnya bergantung pada dosis, dengan insiden yang lebih tinggi diamati pada tingkat dosis yang lebih rendah. Munculnya *ADA* dikaitkan dengan peningkatan pembersihan Ocrelizumab.
- Studi embryo-fetal development menunjukkan tidak ada toksisitas pada induk dan fetus setelah pemberian tiga kali dosis harian 75 mg/kg (*daily loading doses*) dan empat kali dosis mingguan 100 mg/kg.

Studi Klinik

Farmakokinetik

Data PK diambil dari studi klinik WA21092, 21093, dan 21493. *Bioavailability* ocrelizumab 100% karena pemberian secara IV. *Concentration-time course* ocrelizumab dideskripsikan dengan dua kompartemen PK model dan dengan parameter PK steady state tipikal untuk IgG 1 Mab. Untuk subjek referensi (perempuan 75 kg, sel B saat baseline 0,225 x 10^9), volume sentral ocrelizumab diperkirakan 2,78 L. volume perifer 2,68L.

Farmakodinamik

Ocrelizumab secara selektif menargetkan dan mengurangi sel-B yang mengekspresikan CD20. Ocrelizumab berikatan dengan CD20 dan keberadaannya dalam darah mengganggu jumlah sel B berdasarkan CD20 itu sendiri; oleh karena itu, penanda permukaan sel lain CD19 digunakan sebagai penanda farmakodinamik untuk mengukur kadar sel B dalam darah, yang sebagian besar mencerminkan ekspresi CD20 selama perkembangan sel B. Pengobatan dengan ocrelizumab 600 mg menyebabkan penipisan sel B CD19+ yang cepat dan berkelanjutan dalam darah, dengan penipisan sel B yang bersirkulasi hampir seluruhnya. Mayoritas pasien menunjukkan tingkat sel B di bawah LLN (batas bawah normal, 80 sel/ul) atau di bawah 10 sel/ul (batas bawah kuantifikasi uji yang digunakan). Replesi sel B (median) dicapai dalam 72 minggu, namun bervariasi antar populasi pasien.

Diserahkan 5 studi klinik untuk menunjang indikasi dan posologi yang diajukan yaitu: 1 studi fase I/II untuk *dose finding study* (studi WA21493), 3 studi klinik fase III/IIIb (studi WA21092, WA21093 dan MA30143/ENSEMBLE) untuk mendukung indikasi Relapse Multiple Sclerosis (RMS) dan 1 studi fase III (studi WA25046) untuk mendukung indikasi Primary Progressive Multiple Sclerosis (PPMS).

1. **Studi fase I/II WA21493 (*dose finding study*)**. Tujuan primer yaitu menilai efek ocrelizumab (OCR) 600 mg dan 1000 mg IV pada *total number of gadolinium-enhancing T1 lesions* (MRI) pada minggu 12, 16, 20 dan 24 jika dibandingkan plasebo. Disain studi yaitu *multicenter, randomized, parallel group, partially blinded, placebo and Avonex (interferon beta 1a) controlled dose finding study*. Dua dosis OCR dan placebo (kelompok A, B dan C) dilakukan secara *double blind* sampai dosis pilihan diberikan. Sementara pemberian Avonex (kelompok D) dilakukan secara *open label*. Subjek akan menjalani 96 minggu studi klinik, yang terbagi dalam 4 siklus (masing-masing 24 minggu).
   Kriteria inklusi adalah laki laki dan perempuan usia 18-55 tahun, inklusif, dengan diagnosa relapsing remitting MS sesuai kriteria McDonald 2005. Pasien mengalami setidaknya 2 kali *relapse* dalam 3 tahun sebelum skrining dan satu diantaranya terjadi dalam tahun terakhir skrining.

Parameter efikasi primer yaitu jumlah total kesi T1 gadolinium enhancing yang ditangkap oleh MRI pada minggu ke 12, 16, 20 dan 24.
Parameter efikasi sekunder yaitu:

- ARR minggu ke 24
- Proporsi subjek yang tetap bebas relapse sampai minggu ke 24 (protocol-defined relapses)
- Jumlah total lesi T1 gadolinium enhancing minggu ke 4,8
- Jumlah lesi T1 gadolinium enhancing baru pada minggu ke 4,8,12,16,20 dan 24.
- Perubahan total volume lesi T2 dari baseline hingga minggu ke 24

Parameter keamanan yaitu AE, pemeriksaan fisik dan neurologis regular, vital sign, EKG, hematologi rutin, kimia rutin, urin rutin, tes fungsi tiroid, pemeriksaan HAHA (*human anti-humanized antibodies*), titer antibody mumps, rubella, S. pneumoniae, Epstein Barr virus, tes kehamilan.
Jumlah subjek dirandom sebanyak 220, 218 menerima terapi dan 205 mengikuti sampai 24 minggu.

2. Studi fase III WA21092 (indikasi *relapsing forms of multiple sclerosis - RMS*)
Tujuan primer adalah menilai efikasi Ocrelizumab 600 mg yang diberikan 300 mg hari ke-1 dan 300 mg hari ke-15 pada 24 minggu pertama, dan infus tunggal 600 mg subsequent, superior dibanding interferon beta-1a (44 mcg SC) dalam hal menurunkan ARR selama 2 tahun. Disain studi yaitu *Randomized, 96-week, double-blind, double-dummy, parallel-group, active-controlled phase III study*. Pembanding yang digunakan yaitu interferon beta 1a. Kriteria inklusi adalah subjek 18-55 tahun dengan RMS (berdasarkan kriteria McDonald 2010) yang mengalami setidaknya 2 serangan klinis terdokumentasi dalam 2 tahun atau 1 serangan klinik dalam 1 tahun terakhir (tapi tidak dalam 30 hari sebelum skrining), EDSS (*Expanded Dissability Status Scale*) 0 sampai 5,5, MRI menunjukkan abnormalitas di otak yang konsisten dengan MS. Untuk subjek *reproductive potential* menggunakan dua metode kontrasepsi sampai 48 minggu setelah dosis terakhir OCR atau sampai sel B kembali normal (perempuan) atau sampai 24 minggu setelah dosis terakhir OCR (laki-laki). Parameter evaluasi
   - Parameter primer: Annualized relapse (protocol defined) rate
   - Parameter sekunder:
     - *Confirmed disability progression (CDP) for at least 12 weeks (pooled Studies WA21092 and WA21093).*
     - *Total number of T1 gadolinium (Gd) - enhancing lesions*
     - *Total number of new, and/or enlarging T2 hyperintense lesions*
     - *Confirmed disability improvement (CDI) for at least 12 weeks (pooled Studies WA21092 and WA21093)*
     - *CDP for at least 24 weeks (pooled Studies WA21092 and WA21093) The total number of new T1 hypointense lesions*
     - *Multiple Sclerosis Functional Composite Scale (MSFCS) score*
     - *Brain volume*
     - *Short Form 36 (SF-36) Physical Component Summary (PCS) Score*
     - *No evidence of disease activity (NEDA)*
   - Parameter farmakodinamik: CD19+ B cells
   - Parameter farmakokinetik: *clearance*, volume
   - Keamanan: Adverse events (AEs), standard laboratory assessments, vital signs, anti-drug antibodies (ADAs), antibody titers, serum immunoglobulins

   Jumlah subjek 821 subjek direkrut, 411 di kelompok IFN (Interferon beta 1a), 410 di kelompok OCR.

3. Studi fase III WA21093 (indikasi *relapsing forms of multiple sclerosis - RMS*).
Tujuan studi, disain, kriteria inklusi dan eksklusi dan parameter evaluasi sama dengan studi 21092. Jumlah subjek yang direkrut 835 (417 di kelompok OCR dan 418 di kelompok IFN).

4. Studi fase IIIb MA30143/ENSEMBLE PLUS / Substudi ENSEMBLE (posologi *shortening infusion duration* – RMS)
Studi ini sebagai data dukung untuk pencantuman klim posologi yaitu infus dengan durasi yang lebih singkat.Tujuan studi yaitu membandingkan proporsi subjek yang mengalami infusion-related reactions

(IRRs) setelah mendapat infus OCR dengan durasi yang lebih singkat (2 jam) vs durasi konvensional (3,5 jam). Disain studi Prospective, multicenter, randomized, double-blind, controlled, parallel arm. Studi melibatkan 580 subjek.

5. Studi fase III WA25046 (indikasi *primary progressive multiple sclerosis* - PPMS).

   Tujuan primer yaitu menilai efikasi ocrelizumab vs plasebo pada subjek dengan PPMS dalam hal *time to onset of clinical disability progression* (CDP) yang didefinisikan sebagai peningkatan *Expanded Dissability Status Scale* (EDSS) score yang terjaga setidaknya selama 12 minggu. Disain studi *Multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase III study*. Subjek dibagi dalam dua kelompok untuk menerima Ocrelizumab 600 mg setiap 24 minggu (300 mg IV interval 14 hari) atau plasebo._Kriteria inklusi yaitu subjek 18-55 tahun dengan PPMS (berdasarkan kriteria McDonald revisi tahun 2005), EDSS saat skrining 3-6,5, Fungsional System (FS) scale >=2,0, telah menderita MS selama <15 tahun untuk subjek dengan EDSS > 5 atau <10 tahun untuk subjek dengan skor EDSS <=5, bersedia menggunakan kontrasepsi (2 metode). Parameter evaluasi primer: *Time to onset of CDP for at least 12 weeks (12-week CDP) during the double-blind treatment period.*
   Parameter sekunder:
   - *Time to onset of CDP for at least 24 weeks (≥ 161 days, 24-week CDP)*
   - *Change in T25-FW from baseline to Week 120*
   - *Change in total volume of T2 lesions from baseline to Week 120*
   - *Percent change in total brain volume from Week 24 to Week 120*
   - *Change in PCS (SF-36) from baseline to Week 120.*

   Sebanyak 732 subjek direkrut (488 di kelompok Ocrelizumab dan 244 di kelompok plasebo).

Hasil evaluasi terhadap studi di atas:

1. Studi fase I/II WA21493 (dose finding study) menunjukkan bahwa Ocrevus (OCR) 600 mg dipilih sebagai dosis optimum berdasarkan hasil studi:
   a. OCR dosis 600 dan 1000 mg superior dibanding plasebo dan Avonex (interferon beta 1a) dalam menurunkan lesi MRI yaitu total number of gadolinium-enhancing T1 lesions (p<0,001), dan penurunan pembentukan new gadolinium-enhancing lesions (p<0,001), dan juga Anualized Relapse Rate/ARR (OCR 600 mg p=0,0019; OCR 1000 mg p=0,0136).
   b. Kedua dosis OCR dapat ditoleransi (AE 600 mg vs 1000 mg yaitu 63,6% vs 65,5%, AE yang paling sering terjadi adalah Infusion Related Reactions (IRR) 38,2% OCR 600 mg vs 49,1% (OCR 1000 mg). Tidak ada perbedaan kejadian infeksi antara Ocrelizumab dan plasebo, tidak ada infeksi fatal atau oportunistik.
2. Berdasarkan 3 studi klinik fase III/IIIb yang diserahkan untuk mendukung indikasi Relapse Multiple Sclerosis (RMS) , disimpulkan hal-hal sebagai berikut:
   a. Studi WA21092 dan WA21093:
      i. Pemberian OCR 600 mg pada subjek RMS menunjukkan efikasi yang lebih baik dibandingkan interferon beta-1a 44 mcg, berdasarkan parameter utama ARR yang diukur pada pengamatan 96 minggu, yaitu 0,156 vs 0,292 (p<0,0001; studi 21092) dan 0,155 vs 0,290 (p<0,0001; studi 21093)
      ii. OCR juga menunjukkan penurunan progresi disabilitas (CDP sustained for at least 12 weeks and CDP sustained for at least 24 weeks) dan menurunkan lesi MRI (T1 Gdenhancing lesions, new and/or enlarging T2 hyperintense lesions, and new T1 hypointense lesions) jika dibandingkan interferon beta-1a.
      iii. Profil keamanan sebanding dengan interferon beta-1a, kecuali untuk kejadian IRR yang lebih banyak pada Ocrelizumab yaitu 30,9% vs 7,3% (studi WA21092) dan 37,6% vs 12,0% (studi WA21093) serta injection site reactions yang lebih banyak pada interferon beta-1a yaitu 18,1% vs 0% (studi WA21092) dan 6,7% vs 0,5% (studi WA21093).
      iv. Proporsi subjek yang melaporkan adanya infeksi adalah Ocrelizumab: 56.9% vs IFN: 54.3% (studi WA21092) dan Ocrelizumab: 60.2% vs IFN: 52.5% (studi WA21093).
   b. Studi MA30143/ENSEMBLE PLUS / Substudi ENSEMBLE membandingkan posologi durasi

singkat (subjek menerima 600 mg OCR selama 2 jam, diikuti 100 mL NaCl selama 1,5 jam) vs durasi konvensional (subjek menerima 600 mg OCR selama 3,5 jam) menunjukkan:

i. Kejadian IRR antara kelompok durasi singkat dan konvensional sebanding, baik pada dosis pertama (24,6% vs 23,1%) maupun keseluruhan (27,3% vs 24,8%). Tidak ada IRR serius yang terjadi.
ii. AE secara keseluruhan sebanding (AE: 41.2% vs 43.4% dan SAE: 1.0% vs 1.0%).

3. Berdasarkan studi klinik fase III untuk indikasi Primary Progressive Multiple Sclerosis/PPMS (studi WA25046), disimpulkan hal-hal sebagai berikut:
    a. Aspek Efikasi
        i. Pemberian OCR 600 mg setiap 24 minggu pada subjek PPMS menurunkan 12- week Confirmed Dissability Progression sebesar 24% dibandingkan dengan plasebo (HR 0,76 (95% CI 0,59 – 0,98) p<=0,0321.
        ii. Endpoint sekunder seperti T25 foot walk, volume lesi T2 dan total brain volume juga superior dibanding plasebo, namun Quality of Life sebanding dengan plasebo.
    b. Aspek Keamanan
        i. Kejadian IRR lebih banyak pada kelompok OCR namun sebagian besar grade 1 dan 2.
        ii. Infeksi (Ocrelizumab: 71.4% vs Placebo: 69.9%) dan infeksi serius (Ocrelizumab: 7.6% vs Placebo: 8.8%).
        iii. Dilaporkan 2 kematian terkait OCR (serious desquamative pneumonia with associated bacterial component complicated by cardiopulmonary failure dan pneumonia aspirasi)
        iv. Keganasan lebih banyak terjadi pada kelompok OCR, namun tetap berada dalam jangkauan data epidemiologi dari populasi MS:
            - Ocrelizumab: 0.425 (0.256-0.664) vs Epidemiologi populasi MS: 0.67 (0.63-0.71) *Incidence Rates per 100PY*.

KEPUTUSAN
Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi Ocrevus diterima dengan **indikasi dan posologi** sebagai berikut:

Indication
Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section 5.1).
Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity (see section 5.1).

Posologi

Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions (IRRs).

Premedication for infusion-related reactions

The following two premedications must be administered prior to each ocrelizumab infusion to reduce the frequency and severity of IRRs (see section 4.4 for additional steps to reduce IRRs):

- *100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each infusion;*
- *antihistamine approximately 30-60 minutes prior to each infusion;*

In addition, premedication with an antipyretic (e.g., paracetamol) may also be considered approximately 30-60 minutes prior to each infusion.

Posology

Initial dose

The initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion (see Table 1).

Subsequent doses

Subsequent doses of ocrelizumab thereafter are administered as a single 600 mg intravenous infusion every 6 months (see Table 1). The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose.

A minimum interval of 5 months should be maintained between each dose of ocrelizumab.

Infusion adjustments in case of IRRs

Life-threatening IRRs

If there are signs of a life threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome, the infusion must be stopped immediately and the patient should receive appropriate treatment. The infusion must be permanently discontinued in these patients (see section 4.3).

Severe IRRs

If a patient experiences a severe IRR (such as dyspnea) or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately, and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

Mild to moderate IRRs

If a patient experiences a mild to moderate IRR (e.g., headache), the infusion rate should be reduced to half the rate at the onset of the event. This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion rate. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

Dose modifications during treatment

The above examples of dose interruption and slowing (for mild/moderate and severe IRRs) will result in a change in the infusion rate and increase the total duration of the infusion, but not the total dose. No dose reductions are recommended.

Delayed or missed doses

If an infusion is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval of 6 months (with a minimum of 5 months) should be maintained between doses (see Table 1).

Special populations

Adults over 55 years old and elderly population

Based on the limited data available (see section 5.1 and section 5.2), no posology adjustment is needed in patients over 55 years of age. Patients enrolled in the ongoing clinical trials continue to be dosed with 600 mg ocrelizumab every six months after they become 55 years and older.

Renal impairment

The safety and efficacy of ocrelizumab in patients with renal impairment has not been formally studied. Patients with mild renal impairment were included in clinical trials. There is no experience in patients with moderate and severe renal impairment. Ocrelizumab is a monoclonal antibody and cleared via catabolism (i.e. breakdown into peptides and amino acids), and a dose adjustment is not expected to be required for patients with renal impairment (see section 5.2).

Hepatic impairment

The safety and efficacy of ocrelizumab in patients with hepatic impairment has not been formally studied. Patients with mild hepatic impairment were included in clinical trials. There is no experience in patients with moderate and severe hepatic impairment. Ocrelizumab is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a dose adjustment is not expected to be required for patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of ocrelizumab in children and adolescents aged 0 to 18 years has not yet been established. No data are available.

Method of administration

After dilution, treatment is administered as an intravenous infusion through a dedicated line. Infusions should not be administered as an intravenous push or bolus.

If patients did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent doses (Table 1, Option 2).

Table 1: Dose and schedule

		Amount of ocrelizumab to be administered	Infusion instructions
Initial dose (600 mg) divided into 2 infusions	Infusion 1	300 mg in 250 mL	• Initiate the infusion at a rate of 30 mL/hour for 30 minutes • The rate can be increased in 30 mL/hour increments every 30 minutes to a maximum of 180 mL/hour. • Each infusion should be given over approximately 2.5 hours
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent doses (600 mg) single infusion once every 6 months	Option 1 Infusion of approximately 3.5 hours duration	600 mg in 500 mL	• Initiate the infusion at a rate of 40 mL/hour for 30 minutes • The rate can be increased in 40 mL/hour increments every 30 minutes to a maximum of 200 mL/hour • Each infusion should be given over approximately 3.5 hours
	OR		
	Option 2 Infusion of approximately 2 hours duration	600 mg in 500 mL	• Initiate the infusion at a rate of 100 mL/hour for the first 15 minutes • Increase the infusion rate to 200 mL/hour for the next 15 minutes • Increase the infusion rate to 250 mL/hour for the next 30 minutes • Increase the infusion rate to 300 mL/hour for the remaining 60 minutes • Each infusion should be given over approximately 2 hours

Solutions for intravenous infusion are prepared by dilution of the concentrate into an infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, to a final ocrelizumab concentration of approximately 1.2 mg/mL.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Patients should be monitored during the infusion and for at least one hour after the completion of the infusion (see section 4.4).