**Ocrevus®**

Ocrelizumab

# Composition

*Active substances*: Ocrelizumab (recombinant humanized monoclonal [anti-CD20] antibody produced in Chinese hamster ovary [CHO] cells).

*Excipients*: Sodium acetate trihydrate, glacial acetic acid, trehalose dihydrate, polysorbate 20 (produced from genetically modified maize), water for injection.

# Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.

Each 10 mL vial contains 300 mg ocrelizumab.

# Indications/Uses

Ocrevus is indicated for the treatment of adult patients with active relapsing forms of multiple sclerosis (MS).

Ocrevus is indicated for the treatment of adult patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.

# Dosage/Administration

Treatment with Ocrevus must be initiated and supervised by a neurologist experienced in the treatment of MS patients.

Ocrevus infusions should be administered under the direct and close supervision of an experienced healthcare professional.

Appropriate medical care, including full resuscitation equipment and drugs such as epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of severe adverse events such as severe infusion-related reactions (IRRs) or hypersensitivity reactions.

In patients who experience severe pulmonary symptoms such as bronchospasm or asthma exacerbation, the infusion must be immediately and permanently discontinued. Once symptomatic treatment has been given, the patient must be monitored until the pulmonary symptoms have resolved completely, because deterioration can occur after initial improvement of clinical symptoms.

Hypotension may occur during Ocrevus infusions as a symptom of an IRR. Interruption of antihypertensive treatment should therefore be considered for 12 hours before and during each Ocrevus infusion. Ocrevus is administered as an intravenous (IV) infusion through a dedicated line. Ocrevus must not be injected as a rapid IV injection or bolus or infused undiluted.

Isotonic (0.9%) sodium chloride solution should be used as the infusion vehicle. If the IV infusion cannot be completed on the same day, the remaining liquid in the infusion bag must be discarded (see “Special precautions for storage” and “Instructions for handling”).

Observe all patients for at least one hour after the completion of the infusion (see “Warnings and precautions, Infusion-related reactions”).

### Premedication to reduce possible IRRs

The following two premedications must be given before each Ocrevus infusion to reduce the frequency and severity of IRRs (see “Warnings and precautions”):

* 100 mg IV methylprednisolone (or equivalent) approximately 30 minutes before each Ocrevus infusion
* an antihistamine approximately 30 to 60 minutes before each Ocrevus infusion

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

### Ocrevus administration

Initiation of treatment

The initial 600 mg dose (dose 1) is divided into two separate IV infusions, i.e. administered as two 300 mg infusions two weeks apart.

### Maintenance therapy

Subsequent Ocrevus doses are administered as a single 600 mg dose by IV infusion every 6 months (see Table 1).

A minimum interval of 5 months should be maintained between separate Ocrevus doses.

Table 1: Dose and treatment schedule for Ocrevus

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Dose of Ocrevus to be administered\*** | **Infusion instructions** |
| **Initial dose (600 mg)**divided into 2 infusions | Infusion 1 | 300 mgin 250 mL | * Start infusion at 30 mL/hour.
* This can then 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 mgin 250 mL |
| Subsequent doses\*\*(600 mg)once every 6 months | Single infusion | 600 mgin 500 mL | * Start infusion at 40 mL/hour.
* This can then 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.
 |

\* Solutions of Ocrevus for IV infusion are prepared by dilution of the drug product in an infusion bag containing 0.9% sodium chloride to a final drug concentration of approximately 1.2 mg/mL.

\*\* The first subsequent single infusion should be administered 6 months after infusion 1 of the initial dose.

To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

## Dose adjustment during treatment

Dose adjustment of Ocrevus has not been studied and is not recommended if there are no tolerability problems.

## Dose adjustment following undesirable effects/interactions

### Infusion-related reactions

Treatment with Ocrevus is associated with IRRs that may be related to the release of cytokines and/or other chemical mediators. In general, the following adjustment guidelines should be followed in the event of IRRs. Further information on IRRs can be found under “Warnings and precautions, Infusion-related reactions”.

### Life-threatening IRRs

Infusion of Ocrevus must be immediately stopped if there are signs of life-threatening or disabling IRRs, such as acute hypersensitivity or acute respiratory distress syndrome. The patient must receive appropriate supportive treatment. Ocrevus treatment must be permanently discontinued in these patients and must not be restarted.

### Severe IRRs

The infusion must be immediately stopped and symptomatic treatment given if a patient experiences a severe IRR or a symptom complex of flushing, fever and throat pain. The infusion may be resumed only after all symptoms have resolved. The infusion should be restarted at half the infusion rate at the time of onset of the 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 IRR. This reduced rate should be maintained for at least 30 minutes. If tolerated, it may then be increased to the patient’s initially scheduled infusion rate.

### Patients with hepatic impairment

The safety and efficacy of Ocrevus in patients with hepatic impairment have not been formally studied. Patients with mild hepatic impairment were included in the clinical trials. There is no experience in patients with moderate and severe hepatic impairment. Ocrevus is a monoclonal antibody and is cleared by catabolism (rather than hepatic metabolism). Dose adjustment is therefore not expected to be required in patients with hepatic impairment (see “Pharmacokinetics, Kinetics in specific patient groups, Hepatic impairment”).

### Patients with renal impairment

The safety and efficacy of Ocrevus in patients with renal impairment have not been formally studied. Patients with mild renal impairment were included in the clinical trials. There is no experience in patients with moderate and severe renal impairment. Ocrevus is a monoclonal antibody and is cleared by catabolism (rather than renal excretion). Dose adjustment is therefore not expected to be required in patients with renal impairment (see “Pharmacokinetics, Kinetics in specific patient groups, Renal impairment”).

### Elderly patients

The safety and efficacy of Ocrevus in patients >55 years have not been established.

### Children and adolescents

The safety and efficacy of Ocrevus in children and adolescents (<18 years) have not been studied.

### Delayed administration

If a planned infusion of Ocrevus is missed, it should be administered as soon as possible; do not wait until the next scheduled dose. The treatment interval for Ocrevus should be maintained between individual doses.

### Mode of administration

Intravenous infusion.

# Contraindications

Hypersensitivity to ocrelizumab or any of the excipients

Patients with severe heart failure (NYHA class IV)

Patients with severe immunosuppression, including patients who are currently receiving immunosuppressive therapy (other than symptomatic treatments with corticosteroids for relapses) or whose immune system is compromised by prior therapies (see “Warnings and precautions, Treatment with immunosuppressants before, during or after Ocrevus”)

Presence of active infection (see “Warnings and precautions”)

Existing active malignancies, except for patients with cutaneous basal cell carcinoma

Initiation of treatment during pregnancy

# Warnings and precautions

Before each infusion, the healthcare professional must make sure that the patient has read and understood the safety information.

## Infusion-related reactions

Ocrevus can cause infusion-related reactions (IRRs) that may be related to the release of cytokines and/or other chemical mediators.

Symptoms of IRRs may occur during any infusion, but have been most frequently reported during the first infusion. IRRs can occur within 24 hours of the infusion. These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea and tachycardia (see “Undesirable effects”). Patients treated with Ocrevus should be observed for at least one hour after the completion of the infusion for any symptom of an IRR. Physicians should fully inform patients about the possible occurrence of an IRR within 24 hours of infusion.

A hypersensitivity reaction (an acute allergic reaction to the medicinal product) may also occur. IRRs are clinically indistinguishable from type 1 (IgE-mediated) acute hypersensitivity reactions (see “Warnings and precautions, Hypersensitivity reactions”).

For premedication to reduce the frequency and severity of IRRs, see “Dosage/Administration”.

### Managing IRRs

For measures to be taken in patients with life-threatening severe, or mild to moderate IRR symptoms, see “Dosage/Administration, Dose adjustments following undesirable effects/interactions”.

In patients with severe pulmonary symptoms such as bronchospasm or asthma exacerbation, the infusion must be immediately and permanently discontinued. Once symptomatic treatment has been given, the patient must be monitored until the pulmonary symptoms have resolved completely, because deterioration could occur after initial improvement.

Hypotension may occur as a symptom of an IRR during any Ocrevus infusion. Interruption of antihypertensive treatment should therefore be considered for 12 hours before and during each Ocrevus infusion. Patients with a history of congestive heart failure (New York Heart Association III & IV) have not been studied (see “Contraindications”).

## Hypersensitivity reactions

Hypersensitivity reactions may occur (acute IgE-mediated allergic reaction to the medicinal product). Symptoms of a hypersensitivity reaction may be difficult to distinguish from IRRs. A hypersensitivity reaction may occur during any infusion, but generally not during the first infusion. Subsequent infusions that cause more severe symptoms than before, or cause new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. The infusion must be stopped immediately and permanently if a hypersensitivity reaction is suspected during the infusion. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated (see “Contraindications”).

## Infections

Ocrevus must not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections) or severely immunocompromised patients (e.g. with greatly reduced CD4 or CD8 cell counts). In patients with an active infection, Ocrevus administration must be delayed until the infection has resolved (see “Contraindications”).

Further information on the risk factors for serious infections associated with conditions other than MS can be found in the “Undesirable effects” section (“Severe infections from clinical studies of autoimmune conditions other than MS”).

Serious infections, including deaths (principally in the context of pneumonia), can occur during treatment with Ocrevus (see “Undesirable effects”). The incidence of fatal infections reported during treatment with Ocrevus is within the incidence of fatal infections reported for placebo-treated patients in other MS studies.

Patients reporting signs or symptoms of infection after treatment with Ocrevus should be rapidly investigated and treated accordingly. The patients should be reassessed for potential risk of infection before further treatment.

### Progressive multifocal leukoencephalopathy (PML)

The risk of PML with Ocrevus cannot be ruled out. Since John Cunningham (JC) virus infections resulting in PML have been observed in patients treated with anti-CD20 antibodies and other MS therapies and exposed to risk factors (e.g. patient population, polytherapy with immuno­suppressants), the risk of PML with Ocrevus cannot be ruled out.

PML is an opportunistic infection caused by the John Cunningham virus (JCV) that may be fatal or lead to severe disability. PML can only occur in the presence of a JCV infection. It should be noted that a negative anti-JCV antibody test does not preclude the possibility of subsequent JCV infection. Physicians should be alert to early signs and symptoms of PML, which may include any kind of emergent or worsening neurological signs or symptoms, as these may resemble the symptoms of an MS relapse. PML is frequently fatal and resistant to all therapy. PML signs and symptoms are varied, progress over days to weeks and may comprise increasing weakness in one side of the body or clumsiness in the limbs, loss of balance, visual disturbances and impairment of cognition, memory and orientation, leading to confusion and personality changes.

Ocrevus must be withheld if PML is suspected. Suspected PML should be evaluated by MRI (preferably with contrast) in comparison with a pretreatment MRI (preferably no older than 3 months), confirmatory CSF testing for JC viral DNA and repeat neurological assessments.

If PML is confirmed, treatment must be permanently discontinued.

### Hepatitis B reactivation

There have been no reports of hepatitis B reactivation in MS patients treated with Ocrevus. Hepatitis B virus (HBV) reactivation, in some cases with fulminant hepatitis, hepatic failure and death, has been reported in patients treated with other anti-CD20 antibodies.

HBV screening should be performed in all patients before initiation of treatment with Ocrevus as per local guidelines. Patients with active hepatitis B virus (HBV) infection (i.e. an active infection confirmed by positive results for HBsAg and anti-HB testing) must not be treated with Ocrevus (see “Contraindications”). Patients with positive serology (i.e. negative for HBsAg and positive for HB core antibody [HBcAb+] and HBV carriers [positive for surface antigen, HBsAg+]) should consult a liver disease specialist before starting treatment and should be monitored and managed according to local medical standards to prevent hepatitis B reactivation.

## Treatment with immunosuppressants before, during or after Ocrevus

In other autoimmune conditions, coadministration of Ocrevus and immunosuppressive medications (e.g. chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) resulted in an increase of serious infections, including opportunistic infections. Infections included, but were not limited to, atypical pneumonia and *Pneumocystis jirovecii* pneumonia, varicella pneumonia, tuberculosis and histoplasmosis. In rare cases, some of these infections were fatal. An exploratory analysis has identified the following factors associated with a risk of serious infections: Ocrevus doses higher than those recommended in MS, other comorbidities, chronic use of immunosuppressants/
corticosteroids and Asian patients. Coadministration of other immuno­suppressants and Ocrevus except for corticosteroids for symptomatic treatment of relapses is not recommended.

When initiating Ocrevus after an immunosuppressive therapy or initiating an immunosuppressive therapy after Ocrevus, the potential for overlapping pharmacodynamic effects must be taken into consideration (see “Mechanism of action/pharmacodynamics”). Caution should be exercised when prescribing Ocrevus, taking into consideration the pharmacodynamics of other disease-modifying MS therapies. Ocrevus has not been studied in combination with other disease-modifying MS therapies.

## Vaccinations

Physicians should review the immunization status of patients, follow the current regional vaccination recommendations and administer important booster shots before starting treatment with Ocrevus. Vaccinations should be completed at least 6 weeks prior to first administration of Ocrevus.

The safety of immunization with live or live-attenuated vaccines following Ocrevus therapy has not been studied. Such vaccination is not recommended during treatment and until B-cell repletion (the median time to B‑cell repletion was 72 weeks; see “Mechanism of action/pharmacodynamics”).

After treatment with Ocrevus over 2 years, the proportion of patients with positive antibody titers against *S. pneumoniae,* mumps, rubella and varicella was similar to the proportions at baseline.

In a randomized, open-label, parallel-group study of Ocrevus vs no or other immunomodu-latory therapy, RMS patients treated with Ocrevus mounted sometimes markedly reduced humoral immune responses to tetanus toxoid (positive IgG response in 23.9% vs 54.5%), 23-valent pneumococcal polysaccharide (up to two-thirds reduction in positive immune response, with a further booster resulting in no relevant increase), keyhole limpet hemocyanin neoantigen and seasonal influenza vaccines (with seroprotective titers for seasonal influenza vaccines of 55.6-80% vs 75-97%).

It is recommended that all vaccinations other than live or live-attenuated should follow the local vaccination recommendations (including inactivated seasonal influenza vaccination). Measurement of vaccine-induced immune titers should be considered in order to check whether vaccinees can mount a protective immune response, because the efficacy of the vaccination may be decreased.

*In utero exposure to ocrelizumab and vaccination of neonates and infants with live or live-attenuated vaccines*

Due to potential B-cell depletion in neonates and infants of mothers who have received Ocrevus during pregnancy, infants must be monitored for B-cell depletion. CD19-positive B-cell counts should be determined in neonates and infants prior to vaccination. Vaccination with live or live-attenuated vaccines should be delayed until B-cell counts have fully recovered. The safety and timing of immunization should be discussed with the attending pediatrician.

## Malignancies

Cases of malignancy were reported in clinical trials (including 6 cases of breast cancer on Ocrevus, no cases in the control arms [Rebif® or placebo] of the controlled trials). The incidence was within the background rate expected in MS patients.

Except for patients with cutaneous basal cell carcinoma, patients with existing active malignancies (including patients being actively monitored for recurrence of a malignancy) must not be treated with Ocrevus (see “Contraindications”). In patients with known risk factors for malignancies, the risk-benefit balance of Ocrevus should be carefully considered and appropriate cancer surveillance undertaken before and during treatment.

# Interactions

No formal drug interaction studies have been performed. A risk of interactions with concomitantly used medicinal products cannot be excluded.

# Pregnancy, lactation

## Women of childbearing potential

Treatment must not be initiated during pregnancy (see “Contraindications”). Women of childbearing potential should use reliable contraception during Ocrevus treatment and for 6 months after the last Ocrevus infusion (see “Pharmacokinetics, Elimination”).

## Pregnancy

Ocrevus is a humanized monoclonal antibody of the immunoglobulin G1 subtype, and immunoglobulins are known to cross the placental barrier. Animal studies have shown no teratogenic effects, although reproductive toxicity has been observed (see “Preclinical data”).

There are no adequate and well-controlled data from studies in pregnant women; however, transient peripheral B‑cell depletion and lymphopenia have been reported in infants born to mothers given other anti-CD20 antibodies during pregnancy.

In neonates and infants exposed to Ocrevus in utero, it is recommended that vaccination with live or live-attenuated vaccines be postponed. B-cell counts in human neonates and infants exposed to Ocrevus in utero have not been studied in clinical trials. The potential duration of B cell depletion in neonates and infants is unknown (see “Warnings and precautions, Vaccinations”).

In neonates exposed *in utero* with B‑cell counts outside the normal range, deferral of immunization with live or live-attenuated vaccines should be considered.

Ocrevus should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.

## Labor and delivery

The safe use of Ocrevus during labor and delivery has not been studied.

## Lactation

It is not known whether Ocrevus is excreted in human milk or has any effect on the breastfed child or on milk production. Animal studies have shown excretion of ocrelizumab in the milk (see “Preclinical data”). Because human IgG is excreted in breast milk, and the potential for B-cell depletion due to Ocrevus absorption is unknown, women should be advised to discontinue breastfeeding during ocrelizumab therapy.

## Fertility

Preclinical data reveal no special hazards for humans based on studies of male and female fertility in cynomolgus monkeys.

# Effects on ability to drive and use machines

Ocrevus itself has no or negligible influence on the ability to drive or use machines. Nevertheless, the influence of premedication with antihistamines should be noted. After infusion reactions, the patient’s condition should be allowed to stabilize before the patient drives vehicles or operates machines.

# Undesirable effects

## Clinical trials

The safety of Ocrevus has been evaluated in 1311 patients in MS clinical trials, including 825 patients with relapsing multiple sclerosis (RMS) in two identical active-controlled clinical trials and 486 patients in a placebo-controlled study in patients with primary progressive multiple sclerosis (PPMS) (see “Properties/Effects, Clinical efficacy”). The most frequently reported adverse drug reactions (ADRs) were IRRs and respiratory tract infections.

The frequency categories are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000). Adverse reactions are presented in order of decreasing frequency.

## Summary of ADRs occurring with Ocrevus in RMS or PPMS

## Blood and lymphatic system disorders

*Common*: Neutropenia.

Infections and infestations

*Very common*: Upper respiratory tract infection (RMS: 15.2%; PPMS: 12.1%), nasopharyngitis (PPMS: 24.1%; RMS: 14.9%), influenza (PPMS: 11.7%; RMS: 4.6%).

*Common*: Bronchitis, sinusitis, gastroenteritis, viral infection, oral herpes, respiratory tract infection, cellulitis, herpes zoster, conjunctivitis.

## Respiratory, thoracic and mediastinal disorders

*Common*: Cough, catarrh.

## General disorders and administration site conditions

*Very common*: Infusion-related reactions (PPMS: 40.1%; RMS: 34.3%) (symptoms reported as IRRs within 24 hours of infusion are described below as “Infusion-related reactions”).

## Investigations

*Very common*: IgM serum levels decreased (RMS: 16.5%, PPMS: 15.5%).

*Common*: IgG serum levels decreased.

## Description of selected undesirable effects from clinical trials

Infusion-related reactions

Symptoms occurring as part of an IRR in the RMS and PPMS trials included, but were not limited to: pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, nausea, tachycardia. In the controlled clinical trials there were no fatal IRRs.

In the active-controlled (RMS) clinical trials, IRRs were the most common adverse event in patients treated with Ocrevus 600 mg, with an overall incidence of 34.3% compared to an incidence of 9.9% in the interferon beta-1a treatment group (placebo infusion). The incidence of IRRs was highest during the initial dose/dose 1 at infusion 1 (27.5%) and decreased over time to <10% at dose 4. The majority of IRRs in both treatment groups were mild to moderate; 2.4% had severe IRRs and 0.1% life-threatening IRRs (see “Warnings and precautions, Infusion-related reactions”).

In the placebo-controlled (PPMS) clinical trial, IRRs were the most common ADRs, with an incidence of 40.1% compared to 25.5% in the placebo group. The incidence of IRRs was highest during the initial dose/dose 1 at infusion 1 (27.4%) and decreased with subsequent doses to <10% at dose 4. A greater proportion of patients in each group experienced IRRs with the first infusion of each dose than with the second infusion of that dose. The majority of IRRs with Ocrevus were mild (26.7%) to moderate (11.9%); 1.4% had severe, and no one had life-threatening IRRs (see “Warnings and precautions, Infusion-related reactions”).

### Infections

Ocrevus treatment was not associated with an increase in severe infections (in RMS patients the rate of severe infections was lower [Ocrevus 1.3%] than with interferon beta-1a [2.9%], and in PPMS patients the rate was similar to placebo [6.2% vs 6.7%]).

In the active-controlled (RMS) and placebo-controlled (PPMS) clinical trials, respiratory tract infections and herpes infections (both predominantly mild to moderate) were more frequently reported in the Ocrevus treatment arm.

The overall proportion of patients with serious infection on Ocrevus was comparable to the corresponding frequencies in the control arms (placebo and IFN). Life-threatening (grade 4) infections on treatment with Ocrevus were low, but more common than in the control arms (0.2% on OCR compared to 0% on IFN in RMS, and 1.6% on OCR compared to 0.4% on placebo in PPMS). These infections did not result in any limitation of treatment. PPMS patients with dysphagia are at increased risk of aspiration pneumonia. Treatment with Ocrevus may further increase the risk of severe pneumonia in these patients. Physicians should immediately institute appropriate measures in patients with pneumonia.

### Respiratory tract infections

The proportion of respiratory tract infections was higher in the Ocrevus treated patients than in those treated with interferon beta-1a or placebo. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections (including nasopharyngitis) and bronchitis. Fatal pneumonia has occurred with Ocrevus. The incidence of fatal pneumonia reported during treatment with Ocrevus is within the incidence of fatal pneumonia reported for placebo-treated patients in other MS studies.

### Herpes

In the active-controlled (RMS) clinical trials, herpes infections were reported more frequently in Ocrevus treated patients than in those treated with interferon beta-1a; they included herpes zoster (2.1% vs 1.0%), herpes simplex (0.7% vs 0.1%) and oral herpes (3.0% vs 2.2%), genital herpes (0.1% vs 0%) and generalized herpes virus infections (0.1% vs 0%). The infections were predominantly mild to moderate, and the patients recovered on standard treatments. There were no reports of disseminated herpes.

In the placebo-controlled (PPMS) clinical trial, a higher proportion of patients with herpes simplex was observed in the Ocrevus treatment arm (2.7% vs 0.8%).

##### Severe infections from clinical studies of autoimmune conditions other than MS

Ocrevus in combination with concomitant immunosuppressive medications (e.g. chronic steroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclo­phosphamide, azathioprine) has been studied in other autoimmune conditions.

The majority of available data is from studies in patients with rheumatoid arthritis (RA), where an imbalance in serious infections was observed, including, but not limited to, atypical pneumonia, *Pneumocystis jirovecii* pneumonia, varicella pneumonia, tuberculosis and histoplasmosis in the Ocrevus immunosuppressant group. In rare cases, some of these infections were fatal. Serious infections were reported more frequently in the 1000 mg dose group than in the 400 mg dose group or immunosuppressant-placebo group.

Risk factors for serious infections in these trials included: other comorbidities, chronic use of immunosuppressants/steroids and Asian ethnicity.

## Laboratory abnormalities

Immunoglobulins

Treatment with Ocrevus resulted in a decrease in total immunoglobulins over the controlled-study period, mainly driven by a reduction in IgM.

In the active-controlled (RMS) studies, the proportions of patients in the Ocrevus arm with IgG, IgA and IgM below the lower limit of normal (<LLN) at baseline were 0.5%, 1.5% and 0.1%, respectively. After 96 weeks of treatment, the proportions of Ocrevus treated patients with IgG, IgA and IgM <LLN were 1.5%, 2.4% and 16.5%, respectively.

In the placebo-controlled (PPMS) study, the proportions of patients in the Ocrevus arm with IgG, IgA and IgM <LLN at baseline were 0.0%, 0.2% and 0.2%, respectively. After 120 weeks of treatment, the proportions of Ocrevus treated patients with IgG, IgA and IgM <LLN were 1.1%, 0.5% and 15.5%, respectively.

The pooled data of the Ocrevus pivotal clinical studies (RMS and PPMS) and their open-label extensions (up to approximately seven years of exposure) appear to show an association between decreased immunoglobulin levels and serious infections (SIs), most clearly for IgG (0.5% of patients had an SI during a period with IgG < lower limit of normal [LLN]). The type, severity, latency, duration and outcome of SIs observed during episodes with immunoglobulins below LLN were consistent with the data observed generally for SIs in patients treated with Ocrevus.

### Neutrophils

Overall, the decrease in neutrophil count was transient in most cases (observed only once in a patient treated with Ocrevus) and grade 1 or 2 in severity.

In the active-controlled (RMS) treatment period, the neutrophil count decreased in 14.7% of Ocrevus patients compared to 40.9% of patients treated with interferon beta-1a. In the placebo-controlled (PPMS) clinical trial, the proportion of Ocrevus patients with decreased neutrophils was slightly higher (12.9%) than placebo patients (10.0%); of these, approximately 1% of patients in the Ocrevus group had grade 4 neutropenia compared to 0% in the placebo group.

Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

# Overdose

### Signs and symptoms

There is limited clinical trial experience with doses higher than the approved IV dose of Ocrevus. The highest dose tested to date in MS patients was 2000 mg, as two 1000 mg IV infusions 2 weeks apart (phase II dose-finding study in RRMS). The adverse drug reactions were consistent with the safety profile for Ocrevus in the pivotal clinical studies.

### Treatment

There is no specific antidote in the event of an overdose. The infusion must be immediately stopped, and the patient observed for IRRs (see “Warnings and precautions, Infusion-related reactions”).

# Properties/Effects

**ATC code:** L04AA36

## Mechanism of action

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-cells.

CD20 is a surface antigen found on pro-B-cells, mature and memory B-cells, but not expressed on lymphoid stem cells or plasma cells.

The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but are presumed to involve immunomodulation through the reduction in the number and function of CD20-expressing B-cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis. The capacity of B-cell reconstitution and pre-existing humoral immunity are preserved. In addition, innate immunity and total T‑cell numbers are not affected.

## Pharmacodynamics

Treatment with Ocrevus leads to rapid depletion of CD19-expressing B-cells in blood by 14 days post-treatment (first time point of assessment), which is an expected pharmacological effect. This was sustained throughout the treatment period. CD19 is used for the B‑cell counts because the presence of Ocrevus interferes with the detection of CD20 by the assay.

The phase III studies showed B-cell repletion (>lower limit of normal [LLN] or baseline) occurring between each dose of Ocrevus in up to 5% of patients, at least at one time point. The extent and duration of B-cell depletion was consistent in the PPMS and RMS trials.

The longest follow-up time after the last Ocrevus IV infusion (phase II WA21493, n=51) indicates that the median time to B‑cell repletion (return to baseline/LLN, whichever occurred first) was 72 weeks (range 27–175 weeks). Ninety percent of all patients had their B‑cell population repleted to LLN or baseline by approximately two-and-a-half years after the last IV infusion.

## Clinical efficacy

Relapsing forms of MS

The efficacy and safety of Ocrevus were evaluated in two randomized, double-blind, double-dummy, active comparator-controlled clinical trials (WA21092, WA21093) with identical design in patients with relapsing forms of MS (in accordance with McDonald criteria 2010). Study design and baseline characteristics of the study population are summarized in Table 2.

Demographic and baseline characteristics were well balanced across the two treatment groups. Patients in group A received Ocrevus 600 mg every 6 months (dose 1 as 2 × 300 mg IV infusions 2 weeks apart), and subsequent doses were administered as a single 600 mg IV infusion. Patients in group B received interferon beta-1a (Rebif®) 44 µg via subcutaneous (SC) injection 3 times per week.

The results of these studies show that Ocrevus significantly reduces relapses, subclinical disease activity as measured by MRI and disease progression compared to interferon beta‑1a 44 µg SC.

The key clinical findings and the effects in the MRI are presented in Table 3 and Figure 1.

Table 2: Study design and demographic characteristics

|  |  |  |
| --- | --- | --- |
|  | **Study 1** | **Study 2** |
| **Study name** | **WA21092 (OPERA I) (n=821)** | **WA21093 (OPERA II) (n=835)** |
| **Study design** |
| Study population | Patients with relapsing forms of MS |
| Disease history at screening | At least two relapses within the prior two years or one relapse within the prior year; EDSS between 0 and 5.5, inclusive |
| Study duration | 2 years (96 weeks) |
| Treatment groups | Group A: Ocrevus 600 mg every 24 weeks IVGroup B: interferon beta-1a (Rebif®), 44 µg 3 times/week SC (IFN) |
| **Baseline characteristics** | Ocrevus600 mg(n=410) | IFN44 µg(n=411) | Ocrevus600 mg(n=417) | IFN44 µg(n=418) |
| Mean age (years) | 37.1 | 36.9 | 37.2 | 37.4 |
| Age range (years) at inclusion in the study | 18–56 | 18–55 | 18–55 | 18–55 |
| Gender distribution (% male / % female) | 34.1/65.9 | 33.8/66.2 | 35.0/65.0 | 33.0/67.0 |
| Mean/median duration since onset of MS symptoms (years) | 6.74/4.88 | 6.25/4.62 | 6.72/5.16 | 6.68/5.07 |
| Mean/median duration since diagnosis (years) | 3.82/1.53 | 3.71/1.57 | 4.15/2.10 | 4.13/1.84 |
| Mean number of relapses in the last year | 1.31 | 1.33 | 1.32 | 1.34 |
| Mean EDSS\* | 2.82 | 2.71 | 2.73 | 2.79 |
| Patients naïve to prior disease-modifying MS therapies (%)\*\* | 73.4 | 71.0 | 72.7 | 74.9 |
| Mean number of Gd-enhancing T1 lesions | 1.69 | 1.87 | 1.82 | 1.95 |
| Mean number of hyperintense T2 lesions | 51.04 | 51.06 | 49.26 | 51.01 |

\* Expanded Disability Status Scale.

\*\* Patients who had not received a specific MS medication in the 2 years before randomization.

Table 3: Key clinical findings and MRI end points in studies WA21092 and WA21093

|  |  |  |
| --- | --- | --- |
|  | **Study 1: WA21092(OPERA I)** | **Study 2: WA21093(OPERA II)** |
| **End points** | Ocrevus600 mg(n=410) | IFN44 µg(n=411) | Ocrevus600 mg(n=417) | IFN44 µg(n=418) |
| **Clinical end points** |  |  |  |  |
| Annualized relapse rate (primary end point) | 0.156 | 0.292 | 0.155 | 0.290 |
| Relative reduction | 46%(p<0.0001) | 47%(p<0.0001) |
| Proportion of patients with 12-week Confirmed Disability Progression3 | 9.8% Ocrevus vs 15.2% IFN |
| Risk reduction (pooled analysis1) | 40%(p=0.0006) |
| Risk reduction (individual studies2) | 43%(p=0.0139) |  | 37%(p=0.0169) |  |
| Proportion of patients with 24-week Confirmed Disability Progression3 | 7.6% Ocrevus vs 12.0% IFN |
| Risk reduction (pooled analysis1) | 40%(p=0.0025) |
| Risk reduction (individual studies2) | 43%(p=0.0278) | 37%(p=0.0370) |
| Proportion of patients with at least 12-weeks confirmed disability improvement4 (pooled) | 20.7% Ocrevus vs 15.6% IFN |
| Relative improvement (pooled analysis1) | 33% (p=0.0194) |
| Relative improvement (individual studies2) | 61%(p=0.0106) | 14%(p=0.4019) |
| Mean change from baseline in Multiple Sclerosis Functional Composite (MSFC) | 0.213 | 0.174 | 0.276 | 0.169 |
| Difference | 0.039(p=0.3261) | 0.107(p=0.0040) |
| Proportion of patients with no evidence of disease activity (NEDA)5 | 48% | 29% | 48% | 25% |
| Relative improvement2 | 64%(p<0.0001) | 89%(p<0.0001) |
| **MRI end points** |  |  |  |  |
| Mean number of T1 Gd-enhancing lesions in MRI scan | 0.016 | 0.286 | 0.021 | 0.416 |
| Relative reduction | 94%(p<0.0001) | 95%(p<0.0001) |
| Mean number of new and/or enlarged T2 hyperintense lesions in MRI scan | 0.323 | 1.413 | 0.325 | 1.904 |
| Relative reduction | 77%(p<0.0001) | 83%(p<0.0001) |
| Mean number of new T1 hypointense lesions (chronic black holes) in MRI scan | 0.420 | 0.982 | 0.449 | 1.255 |
| Relative reduction | 57%(p<0.0001) | 64%(p<0.0001) |
| Percentage change in brain volume from week 24 to week 96 | –0.572 | –0.741 | –0.638 | –0.750 |
| Relative reduction in brain volume loss | 22.8%(p=0.0042)2 | 14.9%(p=0.0900) |
| **Quality of life** |  |  |  |  |
| Mean change from baseline in SF-36 Physical Component Summary | 0.036 | –0.657 | 0.326 | –0.833 |
| Difference | 0.693(p=0.2193) | 1.159(p=0.0404)6 |

1 Data prospectively pooled from studies 1 and 2.

2 Non-confirmatory p‑value analysis; not part of the prespecified testing hierarchy.

3 Defined as an increase of ≥1.0 points from the baseline Expanded Disability Status Scale (EDSS) score for patients with a score of 5.5 or less, or ≥0.5 when the baseline score was >5.5; Kaplan-Meier estimates at week 96.

4 Defined as a decrease of ≥1.0 points from the baseline EDSS score for patients with baseline EDSS score ≥2 and ≤5.5, or ≥0.5 when the baseline score was >5.5. Patients with baseline score <2 were not included in the analysis.

5 NEDA defined as absence of protocol-defined relapses, Confirmed Disability Progression (CDP) and any MRI activity (either Gd-enhancing T1 lesions or new or enlarging T2 lesions) during the whole 96-week treatment.

6 Exploratory results based on complete ITT population.

**Figure 1: Kaplan-Meier plot of time to onset of Confirmed Disability Progression sustained for at least 24 weeks, with the initial event of neurological worsening occurring during the double-blind treatment period (pooled ITT population)\***



\* Prespecified pooled analysis of OPERA I and II.

The results of the prespecified pooled analyses of time to onset of Confirmed Disability Progression sustained for at least 24 weeks showed that treatment with ocrelizumab resulted in a 40% risk reduction compared to interferon beta‑1a (p=0.0025).

##### Primary progressive form of MS

The efficacy and safety of Ocrevus were also evaluated in a randomized, double-blind, placebo-controlled clinical trial in patients with primary progressive MS (study WA25046). Study design and baseline characteristics of the study population are presented in Table 4.

Demographic and baseline characteristics were well balanced across the two treatment groups.

Patients with Ocrevus (group A) received 600 mg every 6 months (as 2 × 300 mg IV infusions 2 weeks apart), whereas patients in group B received a placebo. The 600 mg infusions in RMS and the 2 × 300 mg infusions in PPMS demonstrated consistent PK and PD profiles. IRR profiles per infusion were also similar, regardless of whether the 600 mg dose was administered as a single 600 mg infusion or as separate 300 mg infusions 2 weeks apart (see “Undesirable effects, Infusion-related reactions” and “Pharmaco­kinetics”). As more 300 mg infusions were administered overall, the total number of IRRs was higher in this group. After dose 1 (initial dose) it is therefore recommended to subsequently administer Ocrevus only as a 600 mg single infusion (see Table 1) to reduce the total number of infusions and associated infusion reactions (with concurrent exposure to prophylactic methylprednisolone).

Table 4: Study design and baseline characteristics of study WA25046

|  |  |
| --- | --- |
| **Study name** | **Study WA25046 ORATORIO (n=732)** |
| **Study design** |
| Study population | Patients with primary progressive form of MS |
| Study duration | Event-driven (*minimum 120 weeks and 253 Confirmed Disability Progression events*)*Median follow-up time: Ocrevus 3.0 years, placebo 2.8 years* |
| Disease history at screening | Age 18–55 years,EDSS 3.0–6.5,including score of ≥2 in pyramidal functional system due to lower extremity findings. |
| Treatment groups | Group A: Ocrevus 600 mgGroup B: placebo, randomized 2:1 |
| **Baseline characteristics** | Ocrevus 600 mg (n=488) | Placebo (n=244) |
| Mean age (years) | 44.7 | 44.4 |
| Age range (years) at inclusion in the study | 20–56 | 18–56 |
| Gender distribution (% male / % female) | 51.4/48.6 | 49.2/50.8 |
| Mean/median duration since onset of MS symptoms (years) | 6.7/6.0 | 6.1/5.5 |
| Mean/median disease duration since PPMS diagnosis (years) | 2.9/1.6 | 2.8/1.3 |
| Mean EDSS | 4.7 | 4.7 |

The clinical end points and effects in the MRI are presented in Table 5 and Figure 2.

Table 5: Clinical and MRI end points in study WA25046 (PPMS)

|  |  |
| --- | --- |
|  | **Study 3** |
|  | **WA25046 (ORATORIO)** |
| **End points** | Ocrevus 600 mg(n=488) | Placebo(n=244) |
| **Clinical end points** |  |  |
| **Primary efficacy end point**Proportion of patients with 12-week Confirmed Disability Progression1 (primary end point) | 30.2% | 34.0% |
| Risk reduction | 24%(p=0.0321) |
| Proportion of patients with 24-week Confirmed Disability Progression1 | 28.3% | 32.7% |
| Risk reduction | 25%(p=0.0365) |
| Percentage change in timed 25-foot walk from baseline to week 120 | 38.9 | 55.1 |
| Relative reduction in progression rate of walking time | 29.4%(p=0.0404) |
| **MRI end points** |  |  |
| Percentage change in T2 hyperintense lesion volume from baseline to week 120 | –3.4 | 7.4 |
|  | (p<0.0001) |
| Percentage change in brain volume from week 24 to week 120 | –0.902 | –1.093 |
| Relative reduction in rate of brain volume loss | 17.5%(p=0.0206) |
| **Quality of life** |  |  |
| Mean change from baseline in SF-36 Physical Component Summary | –0.731 | –1.108 |
| Difference | 0.377(p=0.6034) |

1 Defined as an increase of ≥1.0 points from the baseline EDSS score for patients with a baseline score of 5.5 or less, or ≥0.5 if the baseline score is >5.5; Kaplan-Meier estimates at week 120.

**Figure 2: Kaplan-Meier plot of time to onset of Confirmed Disability Progression sustained for at least 12 weeks, with the initial event of neurological worsening occurring during the double-blind treatment period (ITT population)\***



\* All patients in this analysis had a minimum of 120 weeks of follow-up. The primary analysis is based on all events that occurred.

## Immunogenicity

The patients in the MS trials (WA21092, WA21093 and WA25046) were tested at multiple time points (baseline and then every 6 months until after completion of treatment and the trial) for anti-drug antibodies (ADAs). Of the 1311 patients treated with ocrelizumab, 12 (~1%) tested positive for treatment-emergent ADAs, including 2 patients with neutralizing antibodies. The impact of treatment-emergent ADAs on safety and efficacy cannot be assessed given the low incidence of ADAs associated with Ocrevus. Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to Ocrevus with the incidence of antibodies to other products may be misleading.

# Pharmacokinetics

In the MS trials, the pharmacokinetics of Ocrevus were assessed in a population pharmacokinetic analysis. At low doses, Ocrevus clearance was concentration dependent. Its pharmacokinetics are linear in the therapeutic dose range.

Overall exposure (area under the curve [AUC] over the 24-week dosing intervals) was similar in the study with 2 × 300 mg in PPMS and that with 1 × 600 mg in RMS, as was expected since identical doses were administered. The AUC after the fourth dose of 600 mg Ocrevus was 3510 mcg/mL•day, and the mean maximum concentration (Cmax) was 212 µg/mL in RMS (600 mg infusion) and 141 µg/mL in PPMS (300 mg/infusion).

## Absorption

Ocrevus is administered as an IV infusion. No studies have been performed with other routes of administration.

## Distribution

The population pharmacokinetic estimate of the central volume of distribution was 2.78 L. Peripheral volume and inter-compartment clearance were estimated at 2.68 L and 0.294 L/day, respectively.

## Metabolism

The metabolism of Ocrevus has not been specifically studied, as antibodies are cleared principally by catabolism.

## Elimination

Constant clearance was estimated at 0.17 L/day. The terminal half-life was 26 days.

## Kinetics in specific patient groups

Hepatic impairment

No formal pharmacokinetic study has been conducted in this regard. Patients with mild hepatic impairment were included in clinical trials, and no changes in the pharmacokinetics of Ocrevus were observed in those patients.

Renal impairment

No formal pharmacokinetic study has been conducted. Patients with mild renal impairment were included in clinical trials, and no changes in the pharmacokinetics of Ocrevus were observed in those patients.

Elderly patients

No studies have been conducted to investigate the pharmacokinetics of Ocrevus in elderly patients (≥58 years).

### Children and adolescents

No studies have been conducted to investigate the pharmacokinetics of Ocrevus in children and adolescents (<18 years).

# Preclinical data

## Safety pharmacology

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology and acute and repeated-dose toxicity.

## Mutagenicity

No mutagenicity studies have been performed

## Carcinogenicity

No carcinogenicity studies have been performed.

## Reproductive toxicity

Preclinical data reveal no special hazards for humans based on studies of male and female fertility in monkeys.

In an embryo-fetal development study in monkeys, there was no evidence of maternal toxicity, teratogenicity or embryo toxicity following Ocrevus administration at 75/100 mg/kg (loading dose/study dose). As IgG molecules cross the placental barrier, Ocrevus causes depletion of B-cells in the fetuses of treated monkeys.

In a pre- and postnatal development study in monkeys, administration of Ocrevus (15/20 and 75/100 mg/kg loading/study doses, corresponding to human equivalent doses of approximately 3000 mg [approximately 5 × clinical dose] and 15,000 mg [approximately 25 × clinical dose], respectively) was associated with glomerulopathy (7/24 animals), lymphoid follicle formation in bone marrow (9/24 animals) and lymphoplasmacytoid inflammation in the kidney (2/24 animals). Testicular weight of the neonates was significantly reduced in the 75/100 mg/kg group compared to controls. There were two deaths (2/24 animals) in the study. One case was attributed to weakness due to premature birth accompanied by opportunistic infection, and the other to infective meningo­encephalitis of the newborn with cerebellar involvement due to active infection (mastitis) of the dam. The course of both neonatal infections may have been influenced by B-cell depletion. Newborn offspring of maternal animals exposed to Ocrevus showed depleted B-cell populations during the postnatal phase.

Measurable amounts of Ocrevus (approximately 0.2% of steady-state trough serum level) were detected in milk during the lactation period.

# Other information

## Incompatibilities

No incompatibilities have been observed between Ocrevus and polyvinyl chloride (PVC) or polyolefin bags or IV administration sets.

No diluents other than those mentioned under “Instructions for handling” should be used for Ocrevus, as their use has not been studied.

## Stability

Do not use this medicine after the expiry date (“EXP”) stated on the container.

### Stability of the prepared infusion solution

The product contains no preservatives and is intended for single use only.

The prepared infusion solution should be used immediately. If not used immediately, it can be stored for up to 24 hours at 2–8°C and 8 hours at room temperature at 25 °C. If an IV infusion solution is not all used on the same day, the remaining solution must be discarded.

## Special precautions for storage

Keep out of the sight and reach of children.

Store in a refrigerator (2–8°C). Keep the vial in its outer carton to protect the contents from light.

Do not freeze. Do not shake.

## Instructions for handling

Ocrevus infusions must be prepared by a healthcare professional under aseptic conditions.

Ocrevus may contain fine translucent and/or reflective particles with enhanced opalescence. The solution must not be used if it is discolored or contains discrete foreign particulate matter.

Ocrevus must be diluted before administration. Solutions of Ocrevus for IV administration are prepared by dilution of the drug product in an infusion bag containing 0.9% sodium chloride (300 mg/250 mL or 600 mg/500 mL) to a final drug concentration of approximately 1.2 mg/mL.

The diluted infusion solution must be administered as an infusion equipped with a 0.2 or 0.22 micrometer in-line filter.

Before the start of the IV infusion, the contents of the infusion bag must reach room temperature to avoid an infusion reaction due to the low solution temperature.

### Disposal of unused and expired medicinal product

The release of medicinal products into the environment should be minimized. The medicinal product must not be disposed of in wastewater or through household waste. Use established “collection systems,” if available at your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medical sharps:

* Needles and syringes should never be reused.
* Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product and/or waste material should be disposed of in accordance with local requirements. Needles and syringes should never be reused.

## Packs

Vial 300 mg/10 ml 1

**This is a medicament**

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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