Ocrelizumab

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Codes ATC: L04AG08

Indication	Multiple sclerosis Code ICD11: 8A40
INN	Ocrelizumab
Type de médicament	Biological agent
Type de liste	Liste complémentaire
Formulations	Parenteral > General injections > IV: 30 mg per mL in 10 vial concentrate for solution
Historique des statuts LME	Demande refusée en 2023 (TRS 1049)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Balises	Biological
Wikipédia	Ocrelizumab
DrugBank	Ocrelizumab

Recommandation du comité d'experts

The Expert Committee noted that MS is the most common non-traumatic cause of neurological disability in young adults. About 2.8 million people are living with MS worldwide, with women affected 2–3 times more than men. The most common form is relapsing-remitting MS, characterized by relapses and remissions of neurological symptoms. Over time, most people with relapsing-remitting MS develop a secondary progressive course of the disease (secondary progressive MS) marked by gradual worsening with or without additional inflammatory events. Currently, there are no medicines specifically for the treatment MS included on the Model List. However, rituximab is included for other conditions, is widely available and is listed on many national essential medicines lists. The Committee acknowledged the benefits of ocrelizumab in the management of relapsing-remitting and primary progressive forms of MS. However, there was no compelling evidence of its superiority over alternative treatments, specifically rituximab, which has the same molecular target (CD20). The Committee considered the option of listing ocrelizumab as alternative to rituximab, but also recognized the difference in current prices of the two products and the fact that off-label use of medicines is allowed in many countries, when robust evidence exists. The Committee concluded that including ocrelizumab as a therapeutic alternative to rituximab could result in considerable additional expenditure at the country level for patients and health systems, without offering additional clinical benefit. The Committee considered that inclusion only of the less expensive rituximab on the EML might serve to facilitate its use (albeit off-label) for MS. The Committee recalled and reiterated the views expressed by the 2015 Expert Committee on consideration of medicines for inclusion on the Model Lists for off-label uses or indications: that is, labelling is the responsibility of national regulatory authorities and there may consequently be different labels for the same

product in different countries, and there is thus no global standard for what is considered off-label. Furthermore, updating approved labels for older products may not be pursued by market authorization holder(s) if doing so is not considered commercially viable, and there are many examples of older products whose regulatory labels are inconsistent with current clinical evidence and current clinical practice. Consequently, the Expert Committee reaffirmed that off-label status of a medicine need not be a reason to exclude it from the Model Lists if it otherwise meets the criteria for inclusion. The Committee considered that the Model List can play an important role in identifying those medicines for which off-label use is supported by convincing evidence, complementing the assessment and labelling by jurisdictional authorities. The Committee therefore did not recommend the inclusion of ocrelizumab as an individual medicine, or as a therapeutic alternative to rituximab under a square box listing, on the EML for the treatment of MS.

Contexte

In 2019, the Expert Committee reviewed an application from the Multiple Sclerosis International Federation requesting the addition of glatiramer acetate, fingolimod and ocrelizumab on the Model Lists for use in the treatment of MS. The Committee acknowledged the important public health burden of MS and the need for effective and affordable treatments. However, the Committee noted that the superiority of the proposed medicines over other therapeutic options in terms of benefits, harms and affordability did not clearly emerge from the application. The Committee noted that some commonly used treatments were not included in the application (e.g. azathioprine, natalizumab, dimethyl fumarate, cladribine), or were not given full consideration (e.g. rituximab), with reasons for their exclusion being unclear. In particular, the Committee noted the evidence presented in the application in relation to rituximab and considered that rituximab could have a relevant clinical role in the treatment of MS and recommended that any future application include evidence for rituximab versus active comparators, not just placebo. The Committee therefore did not recommend listing of glatiramer acetate, fingolimod or ocrelizumab at the time, and requested a revised application which comprehensively reviewed the relative roles of relevant available medicines for MS (2).

Pertinence pour la santé publique

MS is a chronic autoimmune disease characterized by inflammation of the central nervous system that leads to demyelination, axonal loss and progressive neuronal degeneration, resulting in irreversible disability and cognitive impairment (3,4). Common symptoms include pain, fatigue, mood and cognitive changes, mobility and sensory impairment, visual disturbances, and elimination dysfunction. Symptoms can vary in severity and can result in significant disability, and reduction in quality and length of life. Data on the global prevalence of MS vary. The Global Burden of Disease study reported that globally, about 1.8 million people (23 per 100 000) had MS in 2019. Age-standardized prevalence per 100 000 population shows large variability across WHO regions, ranging from 4 cases per 100 000 in the Western Pacific Region to 60 per 100 000 in the European Region (5). The atlas of MS estimated that globally, about 2.8 million people (36 per 100 000) had MS in 2020 (6). The number of people with MS per 100 000 population also showed large variability across WHO regions, ranging from 5 per 100 000 in the African and Western Pacific regions to 133 per 100 000 in the European Region (6). MS is most often diagnosed between the ages of 20 and 50 years, but the disease may also first manifest in older adults and children. Women are affected 2–3 times more than men (7,8). MS is broadly divided into relapsing and progressive forms, classified in three different clinical phenotypic patterns based on the presence of transient attacks of neurological symptoms and/or a progressive worsening of the neurological function: relapsing-remitting MS, secondary progressive MS and primary progressive MS (9). Relapsing-remitting MS is characterized by relapses and remissions of neurological symptoms, with relapses associated with new areas of inflammation in the central nervous system. Over time, most people with relapsing-remitting MS will transition to secondary progressive MS, marked by gradual worsening of neurological function with or without additional inflammatory events. Primary progressive MS is characterized by the absence of clearly defined relapses (9,10). The course of MS is highly variable and unpredictable, and patients may have a broad range of neurological symptoms or signs, depending on the location and degree of central nervous system inflammation. Life expectancy for patients with MS is 5–10 years shorter than for the general population (3,11,12). Exposure to any disease-modifying therapy for MS is associated with a lower risk of death compared with no exposure (13). MS has a substantial negative impact on health-related quality of life (14–16). People with MS have significantly lower health-related quality of life scores than people who have other chronic diseases, such as chronic ischaemic heart disease, gastro-oesophageal reflux disease, non-insulin-dependent diabetes mellitus, or inflammatory bowel disease (17). People with MS are less likely to be employed, more likely to take time off work when they are employed, and more likely to retire early than the general population (18–20). Globally, an estimated 1 million people (unpaid spouses, partners, children, family members or friends) are involved in the overall care of people living with MS (21).

Caregivers often stop working to care for the person with MS, further increasing the societal burden of the disease (22). Caregivers of people with MS also experience high levels of distress and reduced quality of life (23, 24).

Bénéfices

The application presented a summary of evidence from pivotal studies of ocrelizumab in relapsing and primary progressive MS. Relapsing MS Two identically designed industry-sponsored, randomized, multicentre, active-controlled, double-blind, phase III studies (OPERA I and OPERA II) evaluated the efficacy and safety of ocrelizumab in 1651 adults with relapsing MS (25). Participants received ocrelizumab 600 mg by intravenous infusion every 6 months or subcutaneous interferon beta-1a 44 micrograms three times a week. The primary efficacy endpoint was annualized relapse rate over 96 weeks. Ocrelizumab treatment was associated with a statistically significant and clinically meaningful improvement in annualized relapse rate, compared with interferon. • OPERA I: annualized relapse rate 0.16 versus 0.29 (rate ratio (RR) 0.54, 95% confidence interval (CI) 0.40 to 0.72; relative reduction 46%); • OPERA II: annualized relapse rate 0.16 versus 0.29 (RR 0.53, 95% CI 0.40 to 0.71; relative reduction 47%). Ocrelizumab treatment was also associated with statistically significant and clinically meaningful improvements compared with interferon for several secondary endpoints, including the proportion of patients with confirmed disability progression at 12 and 24 weeks and proportion of patients with no evidence of disease activity. Patients receiving ocrelizumab also had significantly lower mean numbers of T1 gadolinium-enhancing lesions and new and/or enlarging T2 lesions on magnetic resonance imaging (MRI). Periodic analyses of efficacy data from patients in the OPERA I and II trials who continued on to the open-label extension phase reported that: the benefits of earlier initiation of ocrelizumab were maintained compared with patients switching from interferon (26–28); the risk of requiring a walking aid was lower (29, 30); and rates of upper- and lower-limb disability were lower (31). In the phase IIIb ENSEMBLE study (1225 participants), most treatment-naïve patients with early-stage relapsing-remitting MS treated with ocrelizumab over 2 years showed minimal disease activity based on clinical and MRI measures – 86.5% had no evidence of clinical activity and 88.9% had no evidence of MRI activity. Expanded Disability Status Scale scores remained stable or showed improvements in most patients (87.4%) (32). In an analysis of 7-year open-label extension data from the OPERA I and II studies, 81% of treatment-naive patients with early MS had no disability progression over 7 years on treatment with ocrelizumab (33). Progressive MS The industry-funded phase III randomized, multicentre, double-blind, parallel-group, placebo-controlled ORATORIO trial evaluated the efficacy of ocrelizumab in the treatment of 732 patients with primary progressive MS (34). Participants were randomized 2:1 to receive ocrelizumab 600 mg by intravenous infusion every 6 months or placebo. The primary efficacy endpoint was the proportion of patients with 12-week confirmed disability progression. Secondary endpoints included 24-week confirmed disability progression, timed 25-foot walk, T2 lesion volume and total brain volume loss. The percentage of patients with 12-week confirmed disability progression was 32.9% with ocrelizumab versus 39.3% with placebo (hazard ratio (HR) 0.76, 95% CI 0.59 to 0.98). The percentage of patients with 24-week confirmed disability progression was 29.6% with ocrelizumab versus 35.7% with placebo (HR 0.75, 95% CI 0.58 to 0.98). By week 120, performance on the timed 25-foot walk worsened by 38.9% with ocrelizumab versus 55.1% with placebo; the total volume of brain lesions on T2-weighted MRI decreased by 3.4% with ocrelizumab and increased by 7.4% with placebo; and the percentage of brain volume loss was 0.90% with ocrelizumab versus 1.09% with placebo. The ongoing CONSONANCE trial is a single-arm phase IIIb trial to evaluate the effectiveness and safety of ocrelizumab across the spectrum of progressive MS (i.e. in patients with either primary progressive MS or secondary progressive MS) (35). Primary outcomes are proportion of patients with no evidence of progression, and the proportion of patients with no evidence of progression and no active disease. In the 2-year interim analysis, treatment with ocrelizumab was associated with comparable rates of no evidence of progression and no evidence of progression and no active disease in patients with secondary progressive MS and primary progressive MS and with functional improvement in about one third of patients.

Torts

Pooled results for adverse events reported during the controlled treatment period of the pivotal phase III studies in relapsing MS (OPERA I and OPERA II (25)) are presented in Table 10 (refer TRS 1049). Adverse events reported during the controlled treatment period of the phase III ORATORIO study (34) on primary progressive MS are presented in Table 11 (refer TRS 1049). A phase II, randomized placebo-controlled trial of ocrelizumab in relapsing-remitting MS found that treatment with 2 x 300 mg or 2 x 1000 mg of ocrelizumab was generally well tolerated (37). The adverse event profile of ocrelizumab during the open-label treatment period up to week 96 and during follow-up and monitoring/observation periods up to week 144 was consistent with observations during the first 24 weeks. The single most common adverse event was infusion-related reactions, reported more often in patients treated with ocrelizumab compared with patients given placebo (9.3% in placebo arm, 34.5% in the 300-mg x 2 arm and

43.6% in the 1000-mg x 2 arm, after the first infusion of day 1 of the study). Safety data were pooled up to a clinical cut-off date of November 2020 from the phase II study and three pivotal phase III studies, and the "all-exposure population" including the same studies plus an additional seven phase IIIb studies. Safety findings, excluding coronavirus disease 2019 (COVID-19) infections, remain generally consistent with the controlled treatment period in the pooled relapsing MS/primary progressive MS population from the phase II study and pivotal phase III studies. Very common (frequency ≥ 1/10) adverse drug reactions reported in association with the use of ocrelizumab in the pivotal phase III studies were infusion-related reactions, upper respiratory tract infections, nasopharyngitis and influenza. Common (frequency (≥ 1/100 to < 1/10) adverse drug reactions reported were sinusitis, bronchitis, cough, gastroenteritis, oral herpes, respiratory tract infection, viral infection herpes zoster, conjunctivitis and cellulitis. The application reported that suspected or confirmed COVID-19 cases were identified from 10 ongoing Roche/Genentech clinical trials, as of 28 May 2021. Symptomatic COVID-19 was reported in 406 (9.9%) of 4089 patients treated with ocrelizumab across 10 clinical trials. Most cases of COVID-19 were non-serious (274/406, 67.5%) and most patients had recovered or were recovering at the time of the analysis (347/406, 85.5%). Eighteen patients (out of 406; 4.4%) had not recovered from COVID-19 and in 32/406 cases (7.9%), there was a fatal outcome. Most of the symptomatic COVID-19 cases (265/406, 65.3%) had a mild/moderate presentation, with 86 (21.2%) cases being classified as severe, 13 (3.2%) life-threatening and 32 (7.9%) fatal; information on severity was missing for 10 patients (2.5%).

Rapport coût/efficacité

The application reported that in France, Germany, Italy, Spain and the United Kingdom, ex-factory prices for ocrelizumab range from €5125 to €6250 per vial, or €20 500 to €25 000 per patient per year. In upper and lower middle-income countries and low-income countries, excluding countries with high foreign and exchange market rate fluctuations, the average ocrelizumab list price is €4450 per vial with the lowest list price starting at €1495 per vial. Roche has implemented an international differential pricing model which is reported to apply in 75 upper and lower middle-income countries and low-income countries, either through public funding or the out-of-pocket paying sector, where pricing is added to non-pricing support in the form of patient assistance programmes. These programmes include components such as medicine doses, donations, patient awareness educational campaigns involving health care practitioners, patient assistance to treatment adherence, and health service delivery improvements. To date, and with the implementation of a greater price flexibility, as part of its international differential pricing model, Roche reports to have supported governments and private institutions in more than 30 upper and lower middle-income countries and low-income countries in providing access to patients for ocrelizumab in MS, including Argentina, Armenia, Belarus, Bosnia and Herzegovina, Brazil, Bulgaria, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, Egypt, El Salvador, Georgia, Ghana, Guatemala, Honduras, Jordan, Kazakhstan, Kenya, Kosovo, Lebanon, Libya, Malaysia, Mexico, Montenegro, Morocco, Namibia, Nicaragua, Nigeria, North Macedonia, Pakistan, Paraguay, Peru, South Africa, Tunisia, Türkiye, Ukraine, Uzbekistan and Venezuela (Bolivarian Republic of). The use of ocrelizumab to treat MS was evaluated in health technology assessments and eventually resulted in positive reimbursement decisions in several high-income countries, following price negotiations and (confidential) pricing agreements (38-43). The application did not present a review of published economic evaluations of ocrelizumab or other disease-modifying therapies for MS, arguing that comparability of results across studies and generalizability of conclusions are limited and affected by many factors, including different study parameters, inputs and modelling assumptions.

Directives de l'OMS

WHO guidelines for the treatment of MS are not currently available.

Disponibilité

Ocrelizumab has marketing approval in more than 100 countries worldwide. Regulatory applications are currently being submitted in Asia. Approved indications are for treatment of adults with relapsing forms of MS and treatment of adults with primary progressive MS.

Autres considérations

A separate application submitted by the Multiple Sclerosis International Federation, requesting individual listings for cladribine and glatiramer acetate, and a square box listing for rituximab, specifying ocrelizumab as a therapeutic alternative, was also considered by the Expert Committee at this meeting. The Department of Mental Health and Substance Use provided comments on

two applications submitted for Expert Committee consideration for disease-modifying therapies for MS – this application and an application for inclusion of three disease-modifying therapies for MS submitted by the Multiple Sclerosis International Federation. The technical department supported the inclusion of disease-modifying therapies for MS on the EML, highlighting that the proposals were well aligned with the mandate of the intersectoral global action plan on epilepsy and other neurological disorders (1), which includes a strategic objective to "provide effective, timely and responsive diagnosis, treatment, and care" for people with neurological disorders such as MS.

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