Prescribing Information

Please refer to the SmPC for further information before prescribing

▼**ULTOMIRIS® (ravulizumab)** 300 mg concentrate for solution for infusion. This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Presentation: 30 ml vial containing 300 mg ravulizumab (10 mg/ml). **Indication:** Treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH): (1) patients with haemolysis with clinical symptom(s) indicative of high disease activity, (2) patients who are clinically stable after having been treated with eculizumab for at least the past 6 months. Treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

Dosage and method of administration: *Adult patients with PNH and aHUS*: The loading dose is followed by maintenance doses, both based on the patient's body weight and administered by intravenous infusion. Maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration. Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ravulizumab) but the subsequent dose should be administered according to the original schedule. For patients with body weight ≥ 40kg to < 60kg, the loading dose is 2400mg and the maintenance dose is 3000mg. For patients with body weight ≥ 60kg to < 100kg, the loading dose is 2700mg and the maintenance dose is 3300mg. For patients with body weight ≥ 100kg, the loading dose is 3000mg and the maintenance dose is 3600mg. For adult patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, and then maintenance doses are administered once every 8 weeks, starting 2 weeks after loading dose administration. *Paediatric population*: Ultomiris has not been evaluated in paediatric patients with PNH. Paediatric patients with aHUS with body weight ≥ 40kg are treated in accordance with the adult dosing recommendations. For aHUS paediatric patients with body weight ≥ 10kg to <20kg both the loading and maintenance doses are 600mg, administered once every 4 week interval. For aHUS patients with body weight ≥ 20kg to < 30kg loading dose is 900mg and the maintenance dose is 2100mg. For aHUS patients with body weight ≥ 30kg to < 40kg loading dose is 1200mg and the maintenance dose is 2700mg. For aHUS patients with body weight > 20kg maintenance dose is administered once every 8 weeks interval. Data to support safety and efficacy of ravulizumab for body weight below 10 kg are limited. No recommendation on a posology can be made for patients below 10 kg body weight (please refer to the SmPC for currently available data). The safety and efficacy of ravulizumab in children with PNH aged 0 to < 18 years have not been established. No data are available. *Elderly:* No dose adjustment is required for patients with PNH and aHUS aged 65 years and over. There is no evidence indicating any special precautions are required for treating a geriatric population – although experience with ravulizumab in elderly patients is limited. *Renal impairment:* In aHUS clinical trials, patients with renal impairment including on dialysis were included. No dose adjustment. *Hepatic impairment:* Not studied, however pharmacokinetic data suggest that no dose adjustment is required in patients with hepatic impairment. Recommended to continue Ultomiris treatment unless discontinuation is medically justified. *Administration:* Dilute to a concentration of 5 mg/ml. Administer through a 0.2µm filter via an intravenous infusion (not push or bolus injection). The infusion time varies according to patient body weight (refer to SmPC for details). There is no experience of concomitant PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion) use with ravulizumab. Administration of PE/PI may reduce ravulizumab serum levels. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in SmPC. Patients with unresolved *Neisseria meningitidis* infection at treatment initiation (refer to SmPC for details). Patients who are not currently vaccinated against *N. meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (refer to SmPC for details).

Special warnings and precautions: *Traceability:* To improve traceability of biological medicinal products, the batch number of Ultomiris should be recorded. *Serious meningococcal infection:* Due to its mechanism of action, the use of ravulizumab increases the patient's susceptibility to meningococcal infection/sepsis (*N. meningitidis*). Meningococcal disease due to any serogroup may occur. To reduce this risk of infection, all patients must be vaccinated against meningococcal infections at least two weeks prior to initiating ravulizumab unless the risk of delaying ravulizumab therapy outweighs the risk of developing a meningococcal infection. Patients who initiate ravulizumab treatment less than 2 weeks after receiving a meningococcal vaccine, must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W135 and B where available, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current national immunization guidelines. Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. Cases of serious meningococcal infections/sepsis have been reported in patients treated with ravulizumab. All patients should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and steps should be taken to seek medical care immediately. Physicians should provide patients with a patient information brochure and a patient safety card. *Immunization:* Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination. Patients below the age of 18 years old must be vaccinated against Haemophilus influenzae and pneumococcal infections. *Other systemic infections:* Ravulizumab therapy should be administered with caution to patients with active systemic infections. Ravulizumab blocks terminal complement activation; therefore, patients may have increased susceptibility to infections caused by *Neisseria* species and encapsulated bacteria. Serious infections with *Neisseria* species (other than *N. meningitidis*), including disseminated gonococcal infections, have been reported. Physicians should advise patients about gonorrhoea prevention. *Infusion reactions:* Administration of ravulizumab may result in mild and transient infusion reactions (refer to SmPC for details). In case of infusion reaction, infusion of ravulizumab should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur. *Treatment discontinuation for PNH:* PNH is a chronic disease and treatment with ravulizumab is recommended to continue for the patient's lifetime, unless the discontinuation of ravulizumab is clinically indicated. If patients with PNH discontinue treatment with ravulizumab, they should be closely monitored for signs and symptoms of serious intravascular haemolysis (refer to SmPC for details) for at least 16 weeks. *Treatment discontinuation for aHUS*: The discontinuation of ravulizumab in aHUS patients can result in the recurrence complement-mediated TMA. Ravulizumab treatment to resolve TMA manifestations should be for a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually. There are no specific data on ravulizumab discontinuation. If patients must discontinue treatment with ravulizumab, they should be monitored closely for signs and symptoms of TMA on an on-going basis. However, monitoring may be insufficient to predict or prevent severe TMA complications. *Excipients:* When diluted with sodium chloride (0.9 %) solution for injection, Ultomiris contains 2.65 g sodium per 720 mL at the maximal dose, equivalent to 133 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. **Pregnancy:** Women of childbearing potential should use effective contraception methods during treatment and up to 8 months after treatment. There are no clinical data from the use of ravulizumab in pregnant women. Human IgG are known to cross the human placental barrier, and thus ravulizumab may potentially cause terminal complement inhibition in the foetal circulation. In pregnant women the use of ravulizumab may be considered following an assessment of the risks and benefits. **Breast-feeding:** It is unknown whether ravulizumab is excreted into human milk. A risk to infants cannot be excluded. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in nursing infants, breast-feeding should be discontinued during treatment with ravulizumab and up to 8 months after treatment. **Undesirable effects:** The most common adverse drug reactions (very common frequency) are diarrhoea, nausea, vomiting, nasopharyngitis and headache. Serious adverse reactions: The most serious adverse reactions in patients in clinical trials are meningococcal infection and meningococcal sepsis (refer to SmPC for details). Very common side effects (≥1/10): Upper respiratory tract infection, Nasopharyngitis, Headache, Diarrhoea, Nausea, Pyrexia, Fatigue Common side effects (≥1/100 to <1/10): Dizziness, Abdominal pain, Vomiting, Dyspepsia, Rash, Pruritus, Arthralgia, Back pain, Myalgia, Muscle spasms, Influenza like illness, Asthenia. Uncommon side effects (>1/,1000 to < 1/100): Meningococcal infection and/or meningococcal sepsis, Chills. Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Please refer to SmPC for information on prevention and treatment of suspected meningococcal infection. Treatment with any therapeutic protein may induce an immune response. In paediatric patients with evidence of aHUS (aged 10 months to <18 years) included in ALXN1210-aHUS-312 study, the safety profile of ravulizumab appeared similar to that observed in adult patients with evidence of aHUS. The safety data for patient below 2 years of age is limited to four patients. The most common adverse reaction reported in paediatric patients was pyrexia. The safety of ravulizumab in children with PNH aged 0 to < 18 years have not been established. No data are available. **MA number:** EU/1/19/1371/001 **MAH:** Alexion Europe SAS, 103-105 rue Anatole France, 92300 Levallois-Perret, FRANCE. Further information available from Alexion Pharma UK, 3 Furzeground Way, Stockley Park, Uxbridge, Middlesex, UB11 1EZ. Tel (UK):0800 028 4394, tel (IE): 1800 882 840. **Date of Authorisation:** 02 July 2019. **Legal Category**: POM. **UK Cost**: £4,533 per vial. **Irish Cost**: €4,936.18 per vial**. Last revised**: August 2020.

UK: Adverse events should be reported.
Reporting forms and information can be found at
https://yellowcard.mhra.gov.uk/
Adverse events should also be reported to Alexion Pharma UK Ltd on uk.adverseevents@alexion.com,
Freephone (UK): 0800 321 3902

Ireland: Adverse events should be reported.
Information on reporting adverse events can be found at www.hpra.ie.
Adverse event should also be reported to Alexion Pharma UK Ltd on uk.adverseevents@alexion.com,
Freephone (Ireland): 1 800 936 544