# PROFESSIONAL INFORMATION

**SCHEDULING STATUS:** S4

## 1 NAME OF MEDICINE

ULTOMIRIS® 300 mg Concentrate for solution for infusion

ULTOMIRIS® 1100 mg Concentrate for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ultomiris 300 mg: each ml contains 100 mg ravulizumab.

Ultomiris 1100 mg: each ml contains 100 mg ravulizumab.

After dilution, the final concentration of the solution to be infused is 50 mg/ml.

Contains sugar: Sucrose 50 mg/ml

For full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Translucent, clear to yellowish colour, practically free from particles.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

ULTOMIRIS is indicated for:

- the treatment of adult and paediatric patients one month of age and older with paroxysmal nocturnal haemoglobinuria (PNH).

- the treatment of adults and paediatric patients one month of age and older with atypical haemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

- the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

- the treatment of adult patients with anti-aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD).

**4.2 Posology and method of administration**

**Posology**

***Adult and paediatric patients with PNH or aHUS with body weight greater than or equal to 5 kg***

The recommended ULTOMIRIS maintenance dosing in adult and paediatric patients with PNH or aHUS with a body weight greater than or equal to 5 kg is based on the patient's body weight, as shown in Table 1, with maintenance doses administered every 4 or 8 weeks, starting 2 weeks after loading dose.

Refer to Table 2 or treatment initiation instructions in patients who are complement inhibitor treatment-naïve or switching treatment from eculizumab.

Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS), but the subsequent dose should be administered according to the original schedule.

***Adult patients with gMG or NMOSD with body weight greater than or equal 40 kg***

The recommended ULTOMIRIS maintenance dosing in adult patients with gMG or NMOSD with a body weight greater than or equal to 40 kg is based on the patient's body weight, as

shown in Table 1, with maintenance doses administered every 8 weeks, starting 2 weeks after loading dose.

Refer to Table 2 for treatment initiation instructions in patients who are complement inhibitor treatment-naïve or switching treatment from eculizumab.

Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS) but the subsequent dose should be administered according to the original schedule.

**Table 1: ULTOMIRIS weight-based dosing regimen**

| **Body Weight Range (kg)** | **Loading Dose (mg)*** | **Maintenance Dose (mg)** | **Dosing Interval** |
|---|---|---|---|
| ≥ 5 to < 10** | 600 | 300 | Every 4 weeks |
| ≥ 10 to < 20** | 600 | 600 | Every 4 weeks |
| ≥ 20 to < 30** | 900 | 2100 | Every 8 weeks |
| ≥ 30 to < 40** | 1200 | 2700 | Every 8 weeks |
| ≥ 40 to < 60 | 2400 | 3000 | Every 8 weeks |
| ≥ 60 to < 100 | 2700 | 3300 | Every 8 weeks |
| ≥ 100 | 3000 | 3600 | Every 8 weeks |

*See Table 2 for ULTOMIRIS loading dose instructions prior to maintenance dosing.
**For PNH and aHUS indications only.

**Table 2: ULTOMIRIS treatment initiation instructions**

| **Population** | **Weight-based ULTOMIRIS Loading Dose** | **Time of First ULTOMIRIS Weight-based Maintenance Dose** |
|---|---|---|
| Not currently on ULTOMIRIS or eculizumab treatment | At treatment start | 2 weeks after ULTOMIRIS loading dose |
| Currently treated with eculizumab | At time of next scheduled eculizumab dose | 2 weeks after ULTOMIRIS loading dose |

***Supplemental dosing following treatment with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg)***

Plasma exchange (PE), plasmapheresis (PP), and intravenous immunoglobulin (IVIg) have been shown to reduce ULTOMIRIS serum levels. A supplemental dose of ULTOMIRIS is required in the setting of PE, PP, or IVIg (Table 3).

**Table 3: Supplemental dose of ULTOMIRIS dose after PE, PP, or IVIg**

| Body Weight Group (kg) | Most Recent ULTOMIRIS Dose (mg) | Supplemental Dose (mg) following Each PP or PE Session | Supplemental Dose (mg) following Complete IVIg Cycle |
|---|---|---|---|
| ≥ 40 to < 60 | 2400 | 1200 | 600 |
| | 3000 | 1500 | |
| ≥ 60 to < 100 | 2700 | 1500 | 600 |
| | 3300 | 1800 | |
| ≥ 100 | 3000 | 1500 | 600 |
| | 3600 | 1800 | |
| **Timing of ULTOMIRIS Supplemental Dose** | | Within 4 hours following each PE or PP intervention | Within 4 hours following completion of an IVIg cycle |

**Method of Administration**

This medicinal product must be administered through a 0.2 µm filter and should not be administered as an intravenous push or bolus injection.

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

ULTOMIRIS must be diluted to a final concentration of 50 mg/ml.

Following dilution, ULTOMIRIS is to be administered by intravenous infusion based on body weight as shown in Table 4 and Table 5.

**Table 4: Loading and maintenance dose administration rate for ULTOMIRIS**

| Body Weight Range (kg)[a] | Loading Dose (mg) | Minimum Infusion Duration Minutes (hours) | Maintenance Dose (mg) | Minimum Infusion Duration Minutes (hours) |
|---|---|---|---|---|
| ≥ 5 to < 10[*] | 600 | 85 (1.4) | 300 | 45 (0.8) |
| ≥ 10 to < 20[*] | 600 | 45 (0.8) | 600 | 45 (0.8) |
| ≥ 20 to < 30[*] | 900 | 35 (0.6) | 2100 | 75 (1.3) |
| ≥ 30 to < 40[*] | 1200 | 31 (0.5) | 2700 | 65 (1.1) |
| ≥ 40 to < 60 | 2400 | 45 (0.8) | 3000 | 55 (0.9) |
| ≥ 60 to < 100 | 2700 | 35 (0.6) | 3300 | 40 (0.7) |
| ≥ 100 | 3000 | 25 (0.4) | 3600 | 30 (0.5) |

[*] For PNH and aHUS indications only.
[a] Body weight at time of treatment.

**Table 5: Supplemental dose administration rate for ULTOMIRIS**

| Body Weight Range (kg)[a] | Supplemental Dose (mg) | Minimum Infusion Duration Minutes (h) |
|---|---|---|
| ≥ 40 to < 60 | 600 | 15 (0.25) |
| | 1200 | 25 (0.42) |
| | 1500 | 30 (0.5) |
| ≥ 60 to < 100 | 600 | 12 (0.20) |
| | 1500 | 22 (0.36) |
| | 1800 | 25 (0.42) |
| ≥ 100 | 600 | 10 (0.17) |
| | 1500 | 15 (0.25) |
| | 1800 | 17 (0.28) |

[a] Body weight at time of treatment.

**Special populations**

***Use in the elderly***

ULTOMIRIS may be administered to patients aged 65 years and over. There is no evidence indicating any special precautions are required for treating a geriatric population.

***Patients with aplastic anaemia***

ULTOMIRIS may be administered to patients with PNH treated with concomitant medications for aplastic anaemia (including immunosuppressive therapies). There is no evidence indicating any special precautions are required in patients with aplastic anaemia.

***Renal and hepatic impairment***

Studies have not been conducted to examine the effects of hepatic impairment; however, pharmacokinetic data suggest that no dose adjustment is required in patients with hepatic impairment.

No dose adjustment is required for patients with renal impairment, see section 5.2.

The clinical trials of ULTOMIRIS in patients with aHUS included patients with other complement-mediated TMA conditions (patients with renal impairment, some of whom were receiving dialysis). No dose adjustment is required in this population, see section 5.2

**Paediatric population**

Use of ULTOMIRIS in paediatric patients for treatment of PNH is supported by evidence from a paediatric clinical study (13 patients aged 9 to 17 years). The safety and efficacy of ULTOMIRIS for the treatment of paediatric and adult patients with PNH appear similar. See section 5.1.

Use of ULTOMIRIS in paediatric patients for treatment of aHUS is supported by evidence from a paediatric clinical study (14 patients aged 10 months to 17 years). The safety and efficacy of ULTOMIRIS for the treatment of aHUS is consistent in paediatric and adult patients.

ULTOMIRIS has not been studied in PNH patients below 9 years of age.

The posology to be used in paediatric patients with PNH is identical to the weight-based dosing recommendations provided for paediatric patients with aHUS, with maintenance dosing

starting 2 weeks after loading dose administration. Based on the PK/PD data available in aHUS and PNH patients treated with ULTOMIRIS, this dosing regimen is expected to result in an efficacy and safety profile similar to that in adults, for all paediatric patients starting at 5 kg. ULTOMIRIS has not been evaluated in paediatric patients with gMG or NMOSD.

**4.3 Contraindications**

Hypersensitivity to ravulizumab or to any of the excipients of ULTOMIRIS.

ULTOMIRIS is contraindicated in patients:

- with unresolved *Neisseria meningitidis* infection.
- who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

**4.4 Special warnings and precautions for use**

**Serious meningococcal infection**

Due to its mechanism of action, the use of ULTOMIRIS increases the patient's susceptibility to meningococcal infection/sepsis (*Neisseria meningitidis*). Meningococcal disease due to any serogroup may occur. To reduce this risk of infection, all patients must be vaccinated against meningococcal infection at least 2 weeks prior to initiating ULTOMIRIS unless the risk of delaying ULTOMIRIS outweighs the risks of developing a meningococcal infection. Patients who initiate ULTOMIRIS 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 guidelines for vaccination use.

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 or fatal meningococcal infections/sepsis have been reported in patients treated with ULTOMIRIS and other terminal complement inhibitors. 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. Health care providers should provide patients with a patient information leaflet.

**Immunisation**

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.

**Other systemic infections**

ULTOMIRIS therapy should be administered with caution to patients with active systemic infections. ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially infections caused by Neisseria species. Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported in patients treated with ULTOMIRIS. Patients should be provided with information from the patient information leaflet to increase their awareness of potential serious infections and their signs and symptoms. Health care providers should advise patients about gonorrhoea prevention. Patients below the age of 18 years old must be vaccinated against *Haemophilus influenz*ae and pneumococcal infections and need to adhere strictly to the national vaccination recommendations for their age group.

**Infusion related reactions**

Intravenous administration of ULTOMIRIS may result in systemic infusion-related reactions that cause allergic or hypersensitivity reactions (including anaphylaxis).

In case of a systemic infusion-related reaction, if signs of cardiovascular instability or respiratory compromise occur, administration of ULTOMIRIS should be interrupted and appropriate supportive measures should be instituted.

**Immunogenicity**

Treatment with any therapeutic protein may induce an immune response.

In ULTOMIRIS studies in PNH (N = 488), aHUS (N = 89), gMG (N = 86), and NMOSD (N = 58), treatment-emergent anti-drug antibodies were reported in 2 patients (0.28%), one with PNH and one with aHUS. These anti-drug antibodies were transient in nature with low titre and did not correlate with clinical response or adverse events.

**Treatment discontinuation**

***Treatment discontinuation in PNH***

Paroxysmal Nocturnal Haemoglobinuria (PNH) is a chronic disease, and treatment with ULTOMIRIS is recommended to continue for the patient's lifetime.

If patients with PNH discontinue treatment with ULTOMIRIS, they should be closely monitored for signs and symptoms of haemolysis, identified by elevated lactate dehydrogenase (LDH) along with sudden decrease in PNH clone size or haemoglobin, or re-appearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Any patient who discontinues ULTOMIRIS should be monitored for at least 16 weeks to detect haemolysis and other reactions. If signs and symptoms of haemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

***Treatment discontinuation in aHUS***

ULTOMIRIS treatment to resolve aHUS should be a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually. Patients who

are at higher risk for TMA recurrence, as determined by the treating healthcare provider (or clinically indicated), may require chronic therapy.

There are no specific data on ravulizumab discontinuation. In a long-term prospective observational study, discontinuation of complement C5 inhibitor treatment (eculizumab) resulted in a 13.5-fold higher rate of TMA recurrence and showed a trend toward reduced renal function compared to patients who continued treatment.

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.

TMA complications post-discontinuation can be identified if any of the following is observed:

(i) At least two of the following laboratory results observed concurrently:

- a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ravulizumab treatment;
- an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ravulizumab treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ravulizumab treatment; (results should be confirmed by a second measurement 28 days apart).

Or

(ii) any one of the following symptoms of TMA: a change in mental status or seizures or other extra renal TMA manifestations including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/diarrhoea; or thrombosis.

If TMA complications occur after ravulizumab discontinuation, consider reinitiating ravulizumab treatment beginning with the loading dose and maintenance dose described in section 4.2.

***Treatment discontinuation in gMG***

Considering that gMG is a chronic disease, patients benefiting from ULTOMIRIS treatment who discontinue treatment should be monitored for symptoms of the underlying disease. If symptoms of gMG occur after discontinuation, consider restarting treatment with ULTOMIRIS.

**Treatment Discontinuation in NMOSD**

Considering that NMOSD is a chronic disease, patients benefiting from ULTOMIRIS treatment who discontinue treatment should be monitored for symptoms of NMOSD relapse. If symptoms of NMOSD relapse occur after discontinuation, consider restarting treatment with ULTOMIRIS.

**4.5 Interaction with other medicines and other forms of interaction**

No drug-drug interaction studies have been performed.

Concomitant use of ULTOMIRIS with neonatal Fc receptor (FcRn) blockers may lower systemic exposures and reduce effectiveness of ULTOMIRIS. Closely monitor for reduced effectiveness of ULTOMIRIS.

See section 4.2 for guidance in case of concomitant PE, PP, or IVIg treatment.

**4.6 Fertility, pregnancy and lactation**

**Woman of childbearing potential/Contraception in males and females**

Women of childbearing potential should use effective contraception methods during treatment and up to 8 months after treatment.

**Pregnancy**

No clinical data on exposed pregnancies are available.

Nonclinical reproductive toxicology studies were not conducted with ULTOMIRIS. Reproductive toxicology studies were conducted in mice using the murine surrogate molecule BB5.1, which assessed effect of C5 blockade on the reproductive system. No specific test-article related reproductive toxicities were identified in these studies. Human IgG are known to

cross the human placental barrier, and thus ULTOMIRIS may potentially cause terminal complement inhibition in foetal circulation.

**Breastfeeding**

It is unknown whether ULTOMIRIS is excreted into human milk. 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 and up to 8 months after treatment.

Nonclinical reproductive toxicology studies conducted in mice with the murine surrogate molecule BB5.1 identified no adverse effect to pups resulting from consuming milk from treated dams.

**Fertility**

No specific non-clinical study on fertility has been conducted with ULTOMIRIS.

Nonclinical reproductive toxicology studies conducted in mice with a murine surrogate molecule (BB5.1) identified no adverse effect on fertility of the treated females or males.

**4.7 Effects on ability to drive and use machines**

ULTOMIRIS has no or negligible influence on the ability to drive and use machines. ULTOMIRIS may cause dizziness.

**4.8 Undesirable effects**

**Summary of safety profile**

The most common adverse drug reactions (≥ 10%) across all clinical trials are headache, nasopharyngitis, upper respiratory tract infection, diarrhoea, pyrexia, nausea, arthralgia, fatigue, back pain, abdominal pain which occurred with administration of ULTOMIRIS.

The most serious adverse reactions in patients in clinical trials are meningococcal infections**.**

**Tabulated list of adverse reactions**

Table 6 lists the adverse reactions observed from clinical trials and post-marketing experience. Adverse reactions with ULTOMIRIS are listed by System Organ Class and preferred term using MedDRA frequency convention very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 6: Adverse reactions from clinical trials & post-marketing experience**

| **MedDRA System Organ Class** | **Very Common** | **Common** | **Uncommon** |
|---|---|---|---|
| **Infections and infestations** | Upper respiratory tract infection, Nasopharyngitis | | Meningococcal infection[b], Gonococcal infection[c] |
| **Immune system disorders** | | Hypersensitivity[d] | Anaphylactic reaction[a] |
| **Nervous system disorders** | Headache | Dizziness | |
| **Gastrointestinal disorders** | Diarrhoea, Nausea, Abdominal pain | Vomiting, Dyspepsia | |
| **Skin and subcutaneous tissue disorders** | | Urticaria, Rash Pruritus | |
| **Musculoskeletal and connective tissue disorders** | Back pain, Arthralgia | Myalgia, Muscle spasms | |

| MedDRA System Organ Class | Very Common | Common | Uncommon |
|---|---|---|---|
| **General disorders and administration site conditions** | Pyrexia, Fatigue | Influenza like illness, Chills, Asthenia, | |
| **Injury, poisoning and procedural complications** | | Infusion-related reaction | |

[a] Estimated post-marketing experience based on 2020-Dec-31 cut-off from Periodic Safety Update Report (PSUR).

[b] Meningococcal infection is a group term that includes Preferred Terms meningococcal infection, meningococcal sepsis, and encephalitis meningococcal.

[c] Gonococcal infection includes disseminated gonococcal infection; data based on 2021-Dec-31 cut-off date from Development Safety Update Report (DSUR).

[d] Hypersensitivity is a group term for Preferred Term drug hypersensitivity with related causality and Preferred Term hypersensitivity.

**Description of selected adverse reactions**

***Meningococcal infections/sepsis***

In clinical studies, the most serious adverse reactions from ULTOMIRIS were meningococcal infections, which were uncommon in frequency (0.5%). Meningococcal infections in patients treated with ULTOMIRIS have presented as meningococcal sepsis. Patients should be informed of the signs and symptoms of meningococcal septicaemia and advised to seek medical care immediately.

***Infusion-related reactions***

In clinical trials, infusion-related reactions were common (1.8%). They were mild to moderate in severity and transient (e.g., lower back pain, abdominal pain, muscle spasms, drop in blood pressure, elevation in blood pressure, rigors, limb discomfort, drug hypersensitivity [allergic reaction], dysgeusia [bad taste], and drowsiness). These reactions did not require discontinuation of ULTOMIRIS.

**Paediatric population**

*Paroxysmal nocturnal haemoglobinuria (PNH)*

In children and adolescent PNH patients (aged 9 to 17 years old) included in the paediatric PNH Study (ALXN1210-PNH-304), the safety profile of ULTOMIRIS was consistent with that observed in adult PNH patients. The most common adverse reaction reported in paediatric PNH patient was abdominal pain and nasopharyngitis.

*Atypical haemolytic uremic syndrome (aHUS)*

In paediatric aHUS patients (aged 10 months to 17 years old) included in Study ALXN1210-aHUS-312, the safety profile of ULTOMIRIS was consistent with that observed in adult patients with evidence of aHUS. The safety profile was also consistent for paediatric patients in the different age-group subsets. The safety data for patients below 2 years of age are limited to four patients. The most common adverse reaction reported in paediatric patients was pyrexia.

*Generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD)*

ULTOMIRIS has not been evaluated in paediatric patients with gMG or NMOSD.

**Other special populations**

*Geriatric population*

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years) with ULTOMIRIS.

**Reporting suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

### 4.9 Overdose

No case of overdose has been reported to date.

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

## 5 PHARMACOLOGICAL PROPERTIES

Ravulizumab is a humanised monoclonal antibody (mAb) consisting of 2 identical 448 amino acid heavy chains and 2 identical 214 amino acid light chains and has a molecular weight of approximately 148kDa. The constant regions of ravulizumab include the human kappa light chain constant region, and the protein engineered "IgG2/4" heavy chain constant region.

The heavy chain CH1 domain, hinge region, and the first 5 amino acids of the CH2 domain match the human IgG2 amino acid sequence, residues 6 to 36 in the CH2 region (common to both human IgG2 and IgG4 amino acid sequences), while the remainder of the CH2 domain and the CH3 domain match the human IgG4 amino acid sequence. The heavy and light chain variable regions that form the human C5 binding site consist of human framework regions grafted to murine complementarity-determining regions.

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA43

**Mechanism of action**

Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) and preventing the generation of the C5b-9. By binding specifically to C5, ravulizumab antagonizes terminal complement-mediated inflammation, and cell lysis while preserving the early components of complement activation that are essential for opsonization of microorganisms and clearance of immune complexes.

This mechanism of action provides the therapeutic rationale for the use of ravulizumab in PNH, complement-mediated TMA, gMG, and NMOSD in which uncontrolled complement activation is involved. In patients with PNH, complement-mediated intravascular hemolysis is blocked with ULTOMIRIS treatment. Ravulizumab resolves complement-mediated TMA. In gMG patients, ravulizumab inhibits terminal complement activation, which otherwise leads to MAC deposition at the neuromuscular junction resulting in impairment of neuromuscular transmission. In patients with NMOSD, ravulizumab inhibits terminal complement activation, thus preventing MAC formation and C5a-dependent inflammation, and limiting astrocyte necrosis and damage to surrounding glial cells and neurons.

Ravulizumab was specifically engineered to dissociate from C5 and associate with human neonatal Fc receptor (FcRn) at pH 6.0 (with minimal impact in binding to C5 in intravascular space where the normal pH is 7.4). As a result, dissociation of antibody:C5 complexes in the acidified environment of the early endosome after pinocytosis is increased. Therefore, free antibody is recycled from the early endosome back into the vascular compartment by FcRn, resulting in an extended ravulizumab terminal elimination half-life.

Ravulizumab dosing has been optimized to achieve therapeutic steady state concentrations following the first dose, resulting in immediate onset of action and complete terminal complement inhibition by the end of infusion, that is sustained throughout the dosing interval. This dosing regimen provides prolonged pharmacologic activity, based on the half-life of ravulizumab in serum, and allows dosing once every 8 weeks (or once every 4 weeks for patients weighing less than 20 kg).

**Pharmacodynamic effects**

Following ULTOMIRIS treatment in both adult and pediatric complement-inhibitor naïve patients and eculizumab-experienced patients with PNH in Phase 3 studies, immediate and

complete inhibition of serum free C5 (concentration of < 0.5 µg/ml) was observed by the end of the first infusion and sustained throughout the entire 26-week treatment period in all patients. In contrast, serum free C5 concentrations did not consistently remain < 0.5 µg/ml following eculizumab treatment.

Following ULTOMIRIS treatment, immediate and complete inhibition of serum free C5 was also observed in adult and pediatric patients with complement-mediated TMA and adult patients with gMG or NMOSD by the end of the first infusion and was sustained throughout the primary treatment period.

The extent and duration of the pharmacodynamic response were exposure-dependent in patients with PNH, complement-mediated TMA, gMG, or NMOSD following ULTOMIRIS treatment. Free C5 levels of < 0.5 µg/ml were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition.

**Clinical efficacy and safety**

***Paroxysmal nocturnal haemoglobinuria.***

*Adults:*

Phase 3 studies (ALXN1210-PNH-301 and ALXN1210-PNH-302) were conducted in 2 distinct and complementary populations: a complement inhibitor-naïve population of patients with active haemolysis to establish the magnitude of the efficacy response with ravulizumab, and a population of patients stable on eculizumab therapy that allowed the assessment of the maintenance of efficacy and safety in a population switching to ravulizumab.

The efficacy of ravulizumab was evaluated across a continuum of inter-related endpoints (lactate dehydrogenase [LDH] levels, transfusion avoidance [TA], breakthrough haemolysis [BTH], haemoglobin stabilisation and Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue) that reflected the pathophysiology of PNH.

Both Phase 3 studies achieved their primary objectives of statistically significant noninferiority compared to eculizumab. Treatment with ravulizumab in both complement inhibitor-naïve and eculizumab-experienced patients was associated with immediate, complete and sustained reductions in C5 resulting in clinically meaningful benefits across a continuum of inter-related endpoints that reflect the pathophysiology of PNH. In both populations, ravulizumab treatment resulted in decreased incidence of breakthrough haemolysis compared to eculizumab, addressing an identified medical need in the PNH patient population.

*Paediatrics:*

Study ALXN1210-PNH-304 was a Phase 3, open-label, single-arm, multicentre study that evaluated the PK, PD, safety, and efficacy of ravulizumab in paediatric patients with PNH. Patients who completed the 26-week Primary Evaluation Period were to be followed for up to 4 years in the long-term Extension Period.

Due to the high similarity of disease characteristics and efficacy response in the paediatric and adult patients with PNH on ravulizumab treatment, results observed in the 26-week Primary Evaluation Period in paediatric patients can be expected to be durable based on the efficacy results through a 52-week data cut-off in adults (ALXN1210-PNH-301 52-week data and ALXN1210-PNH-302 52-week data).

The overall efficacy extrapolation concept confirmed the following results:

• Mean percent change in LDH from baseline showed consistent response across the paediatric and adult PNH patient populations.

• A high percentage of patients achieved transfusion avoidance (TA) in both paediatric and adult PNH patient populations.

• Mean improvements in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores in the paediatric patients were consistent with those in the adult patients.

• Results of haemoglobin stabilisation in the paediatric patients were consistent with those in the adult patients.

• Overall, response to ravulizumab treatment in adolescents with PNH (≥ 12 to < 18 years of age) and children with PNH (< 12 years of age) aligns with that observed in adult patients with PNH.

**Atypical Haemolytic Uremic Syndrome (aHUS)**

Two Phase 3, single-arm, multicentre studies of ravulizumab were conducted in complement inhibitor treatment-naïve populations of paediatric (< 18 years of age, Study ALXN1210-aHUS-312) and adult (≥ 18 years of age, Study ALXN1210-aHUS-311) patients with aHUS. Study ALXN1210-aHUS-312 also included a cohort of adolescent (12 to < 18 years of age) patients who were stable on eculizumab therapy to assess maintenance of response following a switch to ravulizumab.

The primary endpoint was complete TMA response and secondary endpoints included improved kidney function.

Results across all efficacy endpoints consistently demonstrated improvement in the hematologic and renal parameters characteristic of complement-mediated TMA activity in paediatric and adult patients with aHUS, who represent the targeted population. The clinical relevance of ravulizumab treatment was also evident in the improvement reported by patients in the quality of life endpoints. The long-term efficacy of ravulizumab in complement inhibitor-naïve adult and paediatric patients with aHUS was demonstrated and the proportion of patients with complete TMA response after 52 weeks of treatment was increased compared to Week 26 (from 54% to 61% in adults and from 78% to 94% in children).

Patients who switched from eculizumab to ravulizumab showed stable and sustained improvement in hematologic parameters and renal function.

**Generalized Myasthenia Gravis (gMG)**

Study ALXN1210-MG-306 was a Phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre study with an Open-Label Extension Period to evaluate the efficacy and safety of ravulizumab for the treatment of adult patients with gMG.

The primary efficacy endpoint was change from baseline in the clinician-administered, patient-reported Myasthenia Gravis Activities of Daily Living (MG-ADL) total score. The MG-ADL assesses the important, relevant functional activities affected by specific signs and symptoms of MG (eg, ocular, bulbar, respiratory, gross motor or limb).

The change from baseline in Quantitative Myasthenia Gravis score for disease severity (QMG) total score was selected as the first secondary endpoint, because it is a validated, objective, clinician-reported assessment tool for muscle weakness in gMG.

Treatment with ravulizumab resulted in a rapid and sustained improvement from baseline to Week 26 that was superior to placebo for the MG-ADL total score and QMG total score in adult patients with gMG. The treatment effect of ravulizumab was demonstrated as early as week 1 and sustained through week 26.

After switching to ravulizumab treatment during the open-label extension period, patients previously randomized to placebo group showed a rapid onset of efficacy of a similar magnitude of improvement in MG-ADL total score and QMG total score to that observed in patients previously randomized to ravulizumab.

Results from the open-label extension period demonstrated a durable treatment effect with ravulizumab up to week 52.

***Neuromyelitis optica spectrum disorder (NMOSD)***

Phase 3 clinical Study ALXN1210-NMO-307 was conducted to evaluate the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD), and immunogenicity of ravulizumab in adult patients with NMOSD. Study ALXN1210-NMO-307 employed a single-arm treatment

design utilizing the placebo group from Study ECU-NMO-301 (conducted from 2014 to 2018) as an external placebo control.

The objective of the study was to demonstrate that ravulizumab treatment is superior to a placebo in reducing the risk of relapse in adult patients
with NMOSD.

The study met its primary objective by demonstrating the efficacy of ravulizumab for the treatment of adult patients with NMOSD. No patients in the ravulizumab group had an adjudicated On-trial Relapse during the Primary Treatment Period of Study ALXN1210-NMO-307, compared with 20 patients (42.6%) in the placebo group from Study ECU-NMO-301. A significant effect on the time to first adjudicated On-trial Relapse and relapse risk reduction was observed with ravulizumab treatment compared to placebo during the Primary Treatment Period ($p < 0.0001$).

Treatment with ravulizumab also demonstrated statistically significant and clinically meaningful benefits for the prevention of worsening in mobility-related neurologic disability over time, as assessed using Hauser Ambulation Index (HAI) score.

**Safety**

The most important risk associated with C5 complement inhibition is increased susceptibility to infections caused by *Neisseria meningitidis.* Meningococcal infection is an important identified risk for ravulizumab based on the mechanism of action, findings from the ravulizumab clinical studies, and long-term experience with eculizumab.

Overall safety evaluation of the cumulative data on the important identified risk/potential risks associated with ravulizumab treatment shows that the benefit-risk balance of ravulizumab is

positive and favourable for the chronic treatment of patients with complement-mediated disorders, including PNH, aHUS, gMG, and NMOSD, under the recommended conditions of use.

## 5.2 Pharmacokinetic properties

### Absorption

Ravulizumab doses are 100% bioavailable resulting from intravenous administration. The time to maximum observed concentration ($t_{max}$) is expected at the end of infusion (EOI) or soon after EOI. Over the studied dose and regimen range, ravulizumab exhibited dose proportional and time linear pharmacokinetics (PK).

### Distribution

The mean (standard deviation [SD]) central volume and volume of distribution at steady state in adult and paediatric patients with PNH or complement mediated-TMA treated with ravulizumab, adult patients with gMG or NMOSD treated with ravulizumab, are presented in Table 7.

### Biotransformation and elimination

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) terminal elimination half-life and clearance of ravulizumab in adult and paediatric patients with PNH or complement-mediated TMA treated with ravulizumab, adult patients with gMG or NMOSD treated with ravulizumab, are presented in Table 7.

**Pharmacokinetic Parameters**

A linear, 2-compartment PK model was developed that adequately described the observed ravulizumab PK following intravenous administration. The estimated mean (SD) clearance, central volume, volume at steady state and terminal elimination half-life following multiple dosing of ravulizumab in adult and paediatric patients with PNH or complement-mediated TMA treated with ravulizumab, adult patients with gMG or NMOSD treated with ravulizumab are presented in Table 7.

**Table 7: Estimated central volume, distribution, biotransformation and elimination parameters following ULTOMIRIS treatment**

| | **Adult and Pediatric Patients with PNH** | **Adult and Pediatric Patients with Complement-Mediated TMA (aHUS)** | **Adult Patients with gMG** | **Adult Patients with NMOSD** |
|---|---|---|---|---|
| Estimated central volume (litres) Mean (SD) | Adults: 3.44 (0.66) Paediatrics: 2.87 (0.60) | Adults: 3.25 (0.61) Paediatrics: 1.14 (0.51) | 3.42 (0.756) | 2.91 (0.571) |
| Volume of distribution at steady state (litres) Mean (SD) | 5.30 (0.9) | 5.22 (1.85) | 5.74 (1.16) | 4.77 (0.819) |
| Terminal elimination half-life (days) Mean (SD) | 49.6 (9.1) | 51.8 (16.2) | 56.6 (8.36) | 64.3 (11.0) |

| | **Adult and Pediatric Patients with PNH** | **Adult and Pediatric Patients with Complement-Mediated TMA (aHUS)** | **Adult Patients with gMG** | **Adult Patients with NMOSD** |
|---|---|---|---|---|
| Clearance (litres/day) Mean (SD) | 0.08 (0.022) | 0.08 (0.04) | 0.08 (0.02) | 0.05 (0.016) |

Therapeutic concentrations are achieved immediately following the first dose of ULTOMIRIS. In patients with PNH, complement-mediated TMA, gMG, or NMOSD, pharmacodynamic activity correlates directly with ravulizumab serum concentrations above the target exposure level and results in free C5 levels < 0.5 µg/ml, achieving immediate, complete and sustained terminal complement inhibition in all patients.

PK parameters for ULTOMIRIS are consistent across PNH, complement-mediated TMA, gMG, and NMOSD patient populations.

**Special Populations**

No formal trial of the effect of sex, race, age (geriatric), hepatic or renal impairment on the pharmacokinetics of ravulizumab was conducted. However, based on population-PK assessment, no impact of sex, age, race and hepatic or renal function on ravulizumab PK was identified in patients with PNH, complement-mediated TMA, gMG, or NMOSD, and as a result, no dosing adjustment is considered necessary (see section 4.2).

The pharmacokinetics of ravulizumab have been studied in complement-mediated TMA patients with a range of renal impairment and age including patients receiving dialysis. There have been no observed differences in pharmacokinetic parameters noted in these subpopulations including patients with proteinuria.

Body weight is a clinically significant covariate on the pharmacokinetics of ravulizumab.

### 5.3 Preclinical safety data

The tissue cross-reactivity of ravulizumab was evaluated by assessing binding to a panel of human tissues. C5 expression in the human tissue panel examined in this study is consistent with published reports of C5 expression. No unexpected tissue cross-reactivity was observed. In a 26-week toxicity study performed in mice with a surrogate antibody directed against murine C5, treatment did not affect any of the toxicity parameters examined. C5-induced haemolytic activity in an ex vivo assay was effectively blocked throughout the course of the study in both female and male mice.

Animal reproductive toxicology studies have not been conducted with ravulizumab but were conducted in mice with a murine surrogate complement inhibitory antibody, BB5.1. No clear treatment-related effects or adverse effects were observed in the murine surrogate reproductive toxicology studies in mice. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose (approximately 4 times the maximum recommended human ravulizumab dose, based on a body weight comparison); however, the exposure did not increase foetal loss or neonatal death.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of ravulizumab.

Non-clinical data reveal no special hazard for humans based on nonclinical studies using a murine surrogate molecule, BB5.1, in mice.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium phosphate, monobasic monohydrate

Sodium phosphate, dibasic heptahydrate

Polysorbate 80

L-arginine

Sucrose

Water for injection

**6.2 Incompatibilities**

Compatibility studies have not been conducted. ULTOMIRIS should not be mixed with other medicinal products.

ULTOMIRIS should only be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection as diluent.

**6.3 Shelf life**

18 months

After dilution, the medicinal product should be used immediately. However, chemical and physical stability of the diluted product using ULTOMIRIS have been demonstrated for up to 24 hours at 2°C – 8°C and up to 4 hours at room temperature.

**6.4 Special precautions for storage**

Store at 2°C – 8°C

After dilution see section 6.3.

**6.5 Nature and contents of container**

<u>ULTOMIRIS 300 mg/3 ml</u>

3 ml of sterile concentrate in a Type I clear glass vial with a grey butyl rubber stopper and aluminum seal with a polypropylene lavender coloured (3 ml) flip-off cap.

ULTOMIRIS 1,100 mg/11 ml:

11 ml of sterile concentrate in a Type I clear glass vial with a grey butyl rubber stopper and aluminium seal with a polypropylene aqua coloured (11ml) flip-off cap.

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**6.6 Special precautions for disposal and handling**

ULTOMIRIS requires dilution to a final concentration of 50 mg/ml.

***Aseptic technique must be used.***

Prepare ULTOMIRIS as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see section 4.2.
2. Prior to dilution, the solution in the vials should be visually inspected; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
3. The calculated volume of medicinal product is withdrawn from the appropriate number of vials and diluted in an infusion bag using sodium chloride 9 mg/ml (0.9%) solution for injection as diluent. Refer to the administration reference tables below. The product should be mixed gently. It should not be shaken.
4. After dilution, the final concentration of the solution to be infused is 50 mg/ml for ULTOMIRIS .
5. The prepared solution should be administered immediately following preparation. Do not administer as an intravenous push or bolus injection. Refer to the administration reference Table 4 and Table 5 in section 4.2 for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.
6. If the medicinal product is not used immediately after reconstitution, storage times at 2°C – 8°C must not exceed 24 hours taking into account the expected infusion time.

The loading, maintenance, and supplemental dose administration reference tables for ULTOMIRIS are provided in Table 8, Table 9 and Table 10, respectively.

**Table 8: Loading Dose Administration Reference Table for ULTOMIRIS**

| **Body Weight Range (kg)[a]** | **Loading Dose (mg)** | **ULTOMIRIS Volume (ml)** | **Volume of NaCl Diluent[b] (ml)** | **Total Volume (ml)** |
|---|---|---|---|---|
| ≥ 5 to < 10* | 600 | 6 | 6 | 12 |
| ≥ 10 to < 20* | 600 | 6 | 6 | 12 |
| ≥ 20 to < 30* | 900 | 9 | 9 | 18 |
| ≥ 30 to < 40* | 1200 | 12 | 12 | 24 |
| ≥ 40 to < 60 | 2400 | 24 | 24 | 48 |
| ≥ 60 to < 100 | 2700 | 27 | 27 | 54 |
| ≥ 100 | 3000 | 30 | 30 | 60 |

*For PNH and aHUS indications only.

[a] Body weight at time of treatment.

[b] ULTOMIRIS should only be diluted using sodium chloride 9 mg/ml (0.9 %) solution for injection.

**Table 9: Maintenance Dose Administration Reference Table for ULTOMIRIS**

| Body Weight Range (kg)[a] | Maintenance Dose (mg) | ULTOMIRIS Volume (ml) | Volume of NaCl Diluent[b] (ml) | Total Volume (ml) |
|---|---|---|---|---|
| ≥ 5 to < 10* | 300 | 3 | 3 | 6 |
| ≥ 10 to < 20* | 600 | 6 | 6 | 12 |
| ≥ 20 to < 30* | 2100 | 21 | 21 | 42 |
| ≥ 30 to < 40* | 2700 | 27 | 27 | 54 |
| ≥ 40 to < 60 | 3000 | 30 | 30 | 60 |
| ≥ 60 to < 100 | 3300 | 33 | 33 | 66 |
| ≥ 100 | 3600 | 36 | 36 | 72 |

*For PNH and aHUS indications only.

[a] Body weight at time of treatment.

[b] ULTOMIRIS should only be diluted using sodium chloride 9 mg/ml (0.9 %) solution for injection.

**Table 10: Supplemental Dose Administration Reference Table for ULTOMIRIS**

| Body Weight Range (kg)[a] | Supplemental Dose (mg) | ULTOMIRIS Volume (ml) | Volume of NaCl Diluent[b] (ml) | Total Volume (ml) |
|---|---|---|---|---|
| ≥ 40 to < 60 | 600 | 6 | 6 | 12 |
| | 1,200 | 12 | 12 | 24 |
| | 1,500 | 15 | 15 | 30 |
| ≥ 60 to < 100 | 600* | 6 | 6 | 12 |
| | 1,500 | 15 | 15 | 30 |
| | 1,800 | 18 | 18 | 36 |
| ≥ 100 | 600* | 6 | 6 | 12 |
| | 1,500 | 15 | 15 | 30 |
| | 1,800 | 18 | 18 | 36 |

[a] Body weight at time of treatment.

[b] ULTOMIRIS should be only diluted using sodium chloride 9 mg/ml (0.9 %) solution for injection.

Any unused medicinal product and waste material should be disposed of in accordance with local requirements.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg, 2191

South Africa

## 8 REGISTRATION NUMBERS

ULTOMIRIS 300 mg : 59/30.1/0014

ULTOMIRIS 1100 mg : 59/30.1/0015

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 JULY 2025

## 10 DATE OF REVISION OF THE TEXT

Not applicable