Product Profile

Voydeya™ (danicopan) 50mg·100mg tablets

The US Food and Drug Administration (FDA) has approved the following product:

NOW APPROVED

VOYDEYA™ (danicopan) is indicated as add-on therapy to ravulizumab or eculizumab for the treatment of extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH).[1]

VOYDEYA has not been shown to be effective as monotherapy and should only be prescribed as an add-on to ravulizumab or eculizumab.

FDA Approval Date[1,2]: March 29, 2024

PNH DISEASE BACKGROUND & TREATMENT GOAL

PNH is a **progressive, life-threatening rare blood disorder,** which can cause **thrombosis, end-organ damage**, and **impaired health-related quality of life.**[3,4] The primary goal of treatment for patients with PNH is control of terminal complement activation and reduction of intravascular hemolysis.[5]

100% of PNH patients will experience **intravascular hemolysis[6,7]**

Intravascular hemolysis is the destruction of red blood cells within vessels.[8]

Intravascular hemolysis may result in:
- **Thrombosis[6]**
- **Chronic kidney disease[9]**
- **Pulmonary hypertension[8]**

Up to 35% of PNH patients die within 5 years of diagnosis.[10]

~10%-20% of PNH patients treated with a C5 inhibitor may experience **extravascular hemolysis[11,12,a]**

Extravascular hemolysis is the removal of red blood cells in the spleen or liver and is an ongoing, natural process.[7,11,12]

Extravascular hemolysis may result in[5,8,14,15,a]:
- **Anemia**
- **Transfusion burden**
- **Fatigue**

Extravascular hemolysis has not been shown to be associated with increased risk of mortality.[11,12]

ULTOMIRIS is recognized as the **standard of care[b]** for the treatment of adult patients with PNH in the US.[5,16]
ULTOMIRIS has demonstrated **long-term control of intravascular hemolysis** over 6 years.[17]

VOYDEYA, as an add-on to ULTOMIRIS or SOLIRIS, is designed to allow the **~10%-20%** of patients experiencing **extravascular hemolysis** to avoid potentially devastating consequences of intravascular hemolysis.[1,11,12,18]

a. Extravascular hemolysis is defined as anemia (hemoglobin [Hgb] ≤9.5 grams per deciliter [g/dL]) with absolute reticulocyte count (ARC) ≥120 x 10^9/liter (L) with or without transfusion support. **b.** Based on US PNH market share as of March 2024.

Please see page 5 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal infections, and accompanying full Prescribing Information for VOYDEYA, page 6 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, and the full Prescribing Information for ULTOMIRIS, and page 7 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, and the full Prescribing Information for SOLIRIS.

VOYDEYA™ (DANICOPAN) PRODUCT INFORMATION

Route of Administration[1]	Mechanism of Action[1]	Dosage Form and Strength[1]	Dosing and Administration[1]
Oral	Small-molecule complement factor D inhibitor	50 mg and 100 mg film-coated tablets	Starting dose of 150 mg TID, with an increase to 200 mg TID dose based on clinical response

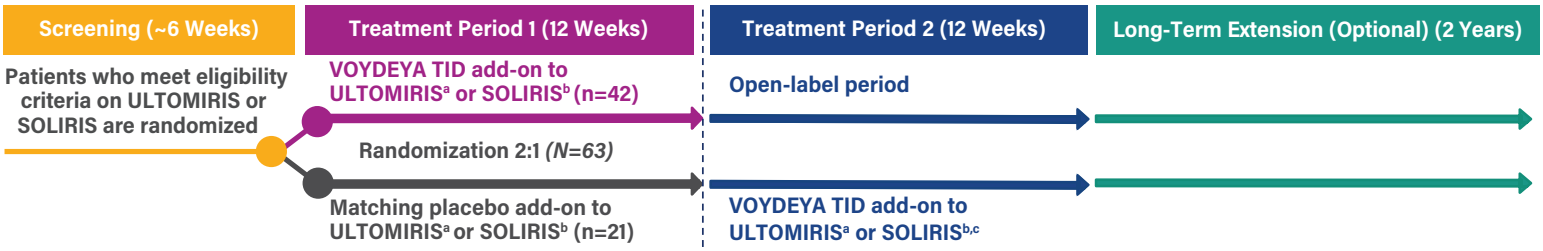
Note: The dose can be increased to 200 mg three times a day if the patient's hemoglobin (Hgb) level has not increased by greater than 2 g/dL after 4 weeks of therapy, if the patient required a transfusion during the previous 4 weeks, or to achieve an appropriate Hgb response based on clinical judgment.

Dose Strength[1]	150 mg carton		200 mg carton
Tablet Strength[1]	50 mg	100 mg	100 mg
Package Size[1]	One 90-count bottle of 50 mg tablets	One 90-count bottle of 100 mg tablets	Two 90-count bottles of 100 mg tablets
NDC Code[1]	25682-046-92		25682-043-92
Annual WAC[16]	$50,261		$67,014
ICD-10-CM[19]	D59.5, D59.4, D64.9, R53.82, R53.83		

CLINICAL TRIAL OVERVIEW[1,20]

VOYDEYA safety and efficacy were evaluated in a phase III, randomized, double-blind, placebo-controlled, multi-dose clinical trial (ALPHA) in patients with PNH currently treated with ULTOMIRIS® (ravulizumab-cwvz) or SOLIRIS® (eculizumab) who experience extravascular hemolysis (NCT04469465).

Study Design



Note: There were no major differences between the arms in baseline demographics.

Key Inclusion Criteria[20]

- Diagnosis of PNH
- Extravascular hemolysis defined by:
  - Anemia (Hgb ≤9.5 g/dL) with ARC ≥120 x 10^9/L
- Receiving an approved C5i for at least 6 months prior to Day 1
- Platelet count ≥30,000/µL
- Absolute neutrophil counts ≥500/µL without the need for platelet transfusions
- Vaccination for *Neisseria meningitidis* within 3 years before or at enrollment

Key Exclusion Criteria[20]

- History of a major organ transplant or HSCT
- Participants with known aplastic anemia or other bone marrow failure that requires HSCT or other therapies including anti-thymocyte globulin and/or immunosuppressants
- Laboratory abnormalities at screening, including:
  - Alanine aminotransferase >2x ULN (>3x ULN in case of patients with documented liver iron overload defined by serum ferritin values 500 ng/mL)
  - Direct bilirubin >2x ULN (unless due to extravascular hemolysis or documented Gilbert's syndrome)
- Evidence of human immunodeficiency virus, hepatitis B, or active hepatitis C infection at screening

µL, microliters; **ARC,** absolute reticulocyte count; **C5i,** C5 inhibitor; **g/dL,** grams per deciliter; **Hgb,** hemoglobin; **HSCT,** hematopoietic stem cell transplantation; **ICD-10-CM,** International Classification of Diseases, Tenth Revision, Clinical Modification; **L,** liter; **NDC,** national drug code; **ng/mL,** nanograms per milliliter; **PNH,** paroxysmal nocturnal hemoglobinuria; **TID,** three times daily; **ULN,** upper limit of normal; **WAC,** wholesale acquisition cost.

a. ULTOMIRIS maintenance dosing schedule every 8 weeks. **b.** SOLIRIS maintenance dosing schedule every 2 weeks. **c.** Participants could not switch between ULTOMIRIS and SOLIRIS therapy during the first 24 weeks but may do so during the long-term extension (LTE) period. The only switch allowed during the LTE period was from ULTOMIRIS to SOLIRIS.

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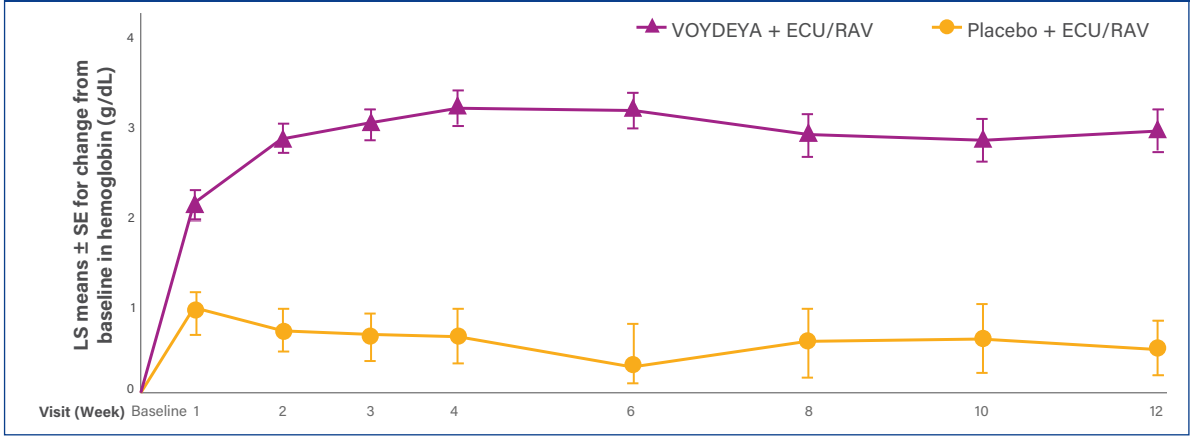
Primary Endpoint Results[1,18]

VOYDEYA™ (danicopan) as an add-on to ravulizumab-cwvz or eculizumab was superior to placebo as an add-on to ravulizumab-cwvz or eculizumab and resulted in a statistically significant increase in Hgb from baseline to Week 12. Mean change in hemoglobin level over time is considered exploratory in nature. The intermediate visits between baseline and Week 12 were not alpha controlled.

Mean Change From Baseline in Hemoglobin Level at Week 12



LS means change from baseline to week 12 in Hgb for VOYDEYA and placebo groups was **+2.9** and **+0.5 g/dL** (p<0.0007), respectively.

LS mean change from baseline to week 24 was **consistent** with those at **week 12**.[21]

Secondary Endpoint Results[1]

Secondary Endpoints at Week 12	VOYDEYA	Placebo	*P*-value
Proportion of patients with Hgb increase of ≥2 g/dL in the absence of transfusion	59.5%	0.0%	<0.0001
Proportion of patients with transfusion avoidance	83.3%	38.1%	0.0004
Mean change from baseline in FACIT-Fatigue Score	8.0	1.9	0.002
Mean change from baseline in ARC (10^9/L)	-84	4	<0.0001

Safety Results[1]

Adverse reactions reported in ≥5% of VOYDEYA-treated patients with PNH and greater than placebo through 12 weeks:

Body System	Adverse Reaction	Number of Patients	
		VOYDEYA (add-on with RAV or ECU) N=57 n (%)	**Placebo** (RAV or ECU only) N=29 n (%)
Gastrointestinal disorders	Vomiting	4 (7)	0 (0)
General disorders and administration site conditions	Pyrexia	4 (7)	0 (0)
Investigations	Hepatic enzyme increased[b]	3 (5)	1 (3)
Musculoskeletal and connective tissue disorders	Pain in extremity	3 (5)	0 (0)
Nervous system disorders	Headache	6 (11)	3 (10)
Vascular disorders	Hypertension	3 (5)	1 (3)

Key Safety Details

- Serious adverse reactions were reported in 3 (5%) patients with PNH receiving VOYDEYA
  - The serious adverse reactions in patients treated with VOYDEYA included pancreatitis, cholecystitis, and increased blood bilirubin
  - No serious adverse reaction was reported in more than 1 patient treated with VOYDEYA
  - The 24-week data reported TEAEs (≥10%) consisting of COVID-19, diarrhea, headache, pyrexia, nausea, and fatigue[21]

ARC, absolute reticulocyte count; **ECU,** eculizumab; **FACIT-Fatigue,** Functional Assessment of Chronic Illness Therapy-Fatigue; **g/dL,** grams per deciliter; **Hgb,** hemoglobin; **L,** liter; **LS,** least squares; **PNH,** paroxysmal nocturnal hemoglobinuria; **RAV,** ravulizumab; **SE,** standard error; **TEAE,** treatment-emergent adverse event.

b. Hepatic enzyme increased includes Preferred Terms alanine aminotransferase increased, hepatic function abnormal, and hepatic enzyme increased.

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KEY CONSIDERATIONS

1 ULTOMIRIS® (ravulizumab-cwvz) is recognized as the standard of care[a] for the treatment of adult patients with PNH in the US.[5,16] ULTOMIRIS and SOLIRIS® (eculizumab) have demonstrated control of IVH, the leading cause of morbidity and early mortality in PNH[6,22,23]

2 VOYDEYA™ (danicopan) is an oral complement factor D inhibitor indicated for use in combination with ULTOMIRIS or SOLIRIS for adult patients with PNH who experience EVH (~10%-20%)[1,11,12]

3 VOYDEYA, in combination with ULTOMIRIS or SOLIRIS, demonstrated statistically significant improvements compared to placebo from baseline to week 12 and maintained improvements through week 24 across mean hemoglobin, transfusion avoidance, FACIT-Fatigue score, and ARC endpoints[1,18,21]

References:

1. VOYDEYA. Prescribing information. Alexion Pharmaceuticals, Inc.
2. Voydeya approved in the US as add-on therapy to ravulizumab or eculizumab for treatment of extravascular haemolysis in adults with the rare disease PNH. News release. AstraZeneca. April 1, 2024. https://www.astrazeneca.com/media-centre/press-releases/2024/voydeya-approved-in-us.html
3. Sharma VR. Paroxysmal nocturnal hemoglobinuria: pathogenesis, testing, and diagnosis. *Clin Adv Hematol Oncol*. 2013;11(suppl 13):2-8.
4. Jalbert JJ, Chaudhari U, Zhang H, et al. Epidemiology of PNH and real-world treatment patterns following an incident PNH diagnosis in the US. *Blood*. 2019;134(suppl 1):3407.
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6. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121(25):4985-4996.
7. Lee JW, Brodsky RA, Nishimura JI, Kulasekararaj AG. The role of the alternative pathway in paroxysmal nocturnal hemoglobinuria and emerging treatments. *Expert Rev Clin Pharmacol*. 2022;15(7):851-861.
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9. Hillmen P, Elebute M, Kelly R, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. *Am J Hematol*. 2010;85(8):553-559.
10. Kelly RJ, Hill A, Arnold LM, et al. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. *Blood*. 2011;117:6786-6792.
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13. Risitano AM, Marotta S, Ricci P, et al. Anti-complement treatment for paroxysmal nocturnal hemoglobinuria: time for proximal complement inhibition? A position paper from the SAAWP of the EBMT. *Front Immunol*. 2019;10:1157.
14. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804-2811.
15. Berentsen S, Hill A, Hill QA, Tvedt THA, Michel M. Novel insights into the treatment of complement-mediated hemolytic anemias. *Ther Adv Hematol.* 2019;10:2040620719873321.
16. Data on file. Alexion Pharmaceuticals, Inc.; 2024.
17. Kulasekararaj AG, Schrezenmeier H, Usuki K, et al. Ravulizumab provides durable control of intravascular hemolysis and improves survival in patients with paroxysmal nocturnal hemoglobinuria: long-term follow-up of study 301 and comparisons with patients of the International PNH Registry. Presented at: 65th Annual Meeting and Exposition of the American Society of Hematology (ASH); December 9-12, 2023; San Diego, CA, USA. Poster #2714.
18. Lee JW, Griffin M, Kim JS, et al. Addition of danicopan to ravulizumab or eculizumab in patients with paroxysmal nocturnal haemoglobinuria and clinically significant extravascular haemolysis (ALPHA): a double-blind, randomised, phase 3 trial. *Lancet Haematol*. 2023;10(12):e955-e965.
19. CDC. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Last Reviewed June 29, 2023. Accessed March 5, 2024. https://www.cdc.gov/nchs/icd/icd-10-cm.htm
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22. SOLIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.
23. ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.

ARC, absolute reticulocyte count; **EVH,** extravascular hemolysis; **FACIT-Fatigue,** Functional Assessment of Chronic Illness Therapy-Fatigue; **IVH,** intravascular hemolysis; **PNH,** paroxysmal nocturnal hemoglobinuria; **US,** United States.
a. Based on US PNH market share as of March 2024.

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INDICATION & IMPORTANT SAFETY INFORMATION FOR VOYDEYA™ (danicopan)

INDICATION

VOYDEYA is indicated as an add-on therapy to ravulizumab or eculizumab for the treatment of extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH).

Limitation of Use:
VOYDEYA has not been shown to be effective as monotherapy and should only be prescribed as an add-on to ravulizumab or eculizumab.

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

VOYDEYA, a complement inhibitor, increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B [*see Warnings and Precautions (5.1)*]. Life-threatening and fatal infections with encapsulated bacteria have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for encapsulated bacteria specifically, *Neisseria meningitidis* and *Streptococcus pneumoniae* at least 2 weeks prior to the first dose of VOYDEYA, unless the risks of delaying therapy with VOYDEYA outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by encapsulated bacteria.**
- **Patients receiving VOYDEYA are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and evaluate immediately if infection is suspected.**

Because of the risk of serious infections caused by encapsulated bacteria, VOYDEYA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the VOYDEYA REMS [*see Warnings and Precautions (5.2)*].

CONTRAINDICATIONS

Initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae*, or *Haemophilus influenzae* type B.

WARNINGS AND PRECAUTIONS

Serious Infections Caused by Encapsulated Bacteria
VOYDEYA, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria, including *Neisseria meningitidis* (caused by any serogroup, including non-groupable strains), *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B. Life-threatening and fatal infections with encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Complete, update, or revaccinate patients in accordance with ACIP recommendations considering the duration of VOYDEYA therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent VOYDEYA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria according to ACIP recommendations, provide antibacterial drug prophylaxis and administer these vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including VOYDEYA. The benefits and risks of treatment with VOYDEYA, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by encapsulated bacteria.

Vaccination does not eliminate the risk of serious encapsulated bacterial infections, despite development of antibodies following vaccination. Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of VOYDEYA in patients who are undergoing treatment for serious infections.

VOYDEYA REMS
Due to the risk of serious infections caused by encapsulated bacteria, VOYDEYA is available only through a restricted program called VOYDEYA REMS. Per the REMS requirements:

Prescribers must enroll in the REMS, counsel patients about the risk of serious infections caused by encapsulated bacteria, provide patients with the REMS educational materials, assess patient vaccination status for vaccines against encapsulated bacteria, and vaccinate if needed according to current ACIP recommendations 2 weeks prior to the first dose of VOYDEYA. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently and the patient is not up to date with vaccines against encapsulated bacteria according to current ACIP recommendations at least 2 weeks prior to the first dose of VOYDEYA.

Pharmacies that dispense VOYDEYA must be certified in the VOYDEYA REMS and must verify prescribers are certified.

Patients must receive counseling from the prescriber about the need to receive vaccinations against encapsulated bacteria per ACIP recommendations, to take antibiotics as directed, the early signs and symptoms of serious infection, and be instructed to carry the Patient Safety Card at all times during and for 1 week following the last dose of VOYDEYA.

Further information is available at www.voydeyarems.com or 1-888-765-4747.

Hepatic Enzyme Increases
Hepatic enzyme elevations have been observed in patients treated with VOYDEYA. A total of 14% of patients receiving VOYDEYA had elevations in serum alanine aminotransferase (ALT). ALT elevations >3× the upper limit of normal (ULN) and ≤5× ULN occurred in 9% of VOYDEYA-treated patients, and ALT elevations >5× ULN and ≤10× ULN occurred in 5% of VOYDEYA-treated patients.

Assess liver enzyme test results prior to the initiation of VOYDEYA and periodically during treatment. Consider treatment interruption or discontinuation if elevations are clinically significant or if the patient becomes symptomatic. VOYDEYA has not been studied in patients with severe hepatic impairment.

Monitoring of PNH Manifestations After VOYDEYA Discontinuation
After discontinuing treatment with VOYDEYA, closely monitor patients for at least 2 weeks after the last dose for signs and symptoms of hemolysis. If discontinuation of VOYDEYA is necessary, continue background treatment with ravulizumab or eculizumab or consider alternative therapy if necessary. The signs and symptoms of hemolysis may include sudden decrease in hemoglobin or fatigue.

If hemolysis occurs after discontinuation of VOYDEYA, consider restarting treatment with VOYDEYA, if appropriate.

Hyperlipidemia
VOYDEYA increases total cholesterol and LDL-cholesterol. Of the 50 VOYDEYA-treated patients who had a normal total cholesterol level at baseline, 30% developed Grade 1 hypercholesterolemia. Of the 6 VOYDEYA-treated patients who had Grade 1 hypercholesterolemia at baseline, 1 patient experienced increased total cholesterol that worsened to Grade 2. Of the 54 VOYDEYA-treated patients who had LDL-cholesterol ≤130 mg/dL at baseline, 13% developed LDL-cholesterol >130-160 mg/dL, and 9% developed LDL-cholesterol >160-190 mg/dL.

Some patients required cholesterol-lowering medications. Monitor serum lipid parameters periodically during treatment with VOYDEYA and initiate cholesterol-lowering medication, if indicated.

ADVERSE REACTIONS

The most common adverse reaction reported in ≥10% of patients treated with VOYDEYA was headache. Serious adverse reactions were reported in 5% of patients who received VOYDEYA and included pancreatitis, cholecystitis, and increased blood bilirubin. No specific serious adverse reaction was reported in more than 1 patient treated with VOYDEYA. Adverse reactions reported in ≥5% of patients treated with VOYDEYA and greater than placebo in the randomized, controlled period included vomiting, pyrexia, increased alanine aminotransferase, hypertension, and pain in the extremities. Clinically relevant adverse reactions in <5% of patients included increased serum triglycerides.

DRUG INTERACTIONS

BCRP Substrates
Danicopan is a Breast Cancer Resistance Protein (BCRP) inhibitor. Concomitant use of VOYDEYA with a BCRP substrate increases the plasma concentrations of the BCRP substrate, which may increase the risk for adverse reactions associated with the BCRP substrate. If used together, monitor patients more frequently for adverse reactions associated with the BCRP substrate and consider dose reduction of the BCRP substrate according to its prescribing information.

Rosuvastatin
Danicopan significantly increased rosuvastatin exposure. The dose of rosuvastatin should not exceed 10mg once daily when concomitantly used with VOYDEYA.

P-glycoprotein Substrates
Danicopan is an inhibitor of P-glycoprotein (P-gp). Concomitant administration of VOYDEYA with P-gp substrates may increase the plasma concentrations of the P-gp substrates. Dose adjustment might be necessary for P-gp substrates where minimal concentration changes may lead to serious adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy
There are no available data on VOYDEYA use in pregnant individuals to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH in pregnancy. The use of VOYDEYA in pregnant women or women planning to become pregnant may be considered following an assessment of the risks and benefits.

Lactation
There are no data on the presence of VOYDEYA in human milk, the effects on the breastfed child, or the effect on milk production. VOYDEYA is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Because of the potential for serious adverse reactions in the breastfed child, including serious infections with encapsulated bacteria and liver enzyme increases, advise patients not to breastfeed during treatment with VOYDEYA and for 3 days after the last dose.

Hepatic Impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment. Studies have not been conducted in patients with severe hepatic impairment, therefore, avoid use of VOYDEYA in this patient population.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information for VOYDEYA (danicopan), including Boxed WARNING regarding serious and life-threatening or fatal infections.

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INDICATION & IMPORTANT SAFETY INFORMATION for ULTOMIRIS® (ravulizumab-cwvz)

INDICATION

ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1)*]. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.**

Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [*see Warnings and Precautions (5.2)*].

CONTRAINDICATIONS

- Initiation in patients with unresolved serious *Neisseria meningitidis* infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

ULTOMIRIS, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent ULTOMIRIS therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including ULTOMIRIS. The benefits and risks of treatment with ULTOMIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis*.

Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection depending on the risks of interrupting treatment in the disease being treated.

ULTOMIRIS and SOLIRIS REMS

Due to the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program called ULTOMIRIS and SOLIRIS REMS.

Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with the REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of ULTOMIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently, and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of ULTOMIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card at all times during and for 8 months following ULTOMIRIS treatment.

Further information is available at www.UltSolREMS.com or 1-888-765-4747.

Other Infections

Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. Children treated with ULTOMIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP recommendations. Patients receiving ULTOMIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues ULTOMIRIS for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

Thromboembolic Event Management

The effect of withdrawal of anticoagulant therapy during treatment with ULTOMIRIS has not been established. Treatment should not alter anticoagulant management.

Infusion-Related Reactions

Intravenous administration may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1 to 7% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.

ADVERSE REACTIONS

Adverse reactions reported in ≥10% or more of patients with PNH were upper respiratory tract infection and headache. Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS. One fatal case of sepsis was identified in a patient treated with ULTOMIRIS. In clinical studies, clinically relevant adverse reactions in 1% of adult patients include infusion-related reactions.

Adverse reactions reported in ≥10% of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced were anemia (20% vs. 25%), abdominal pain (0% vs. 38%), constipation (0% vs. 25%), pyrexia (20% vs. 13%), upper respiratory tract infection (20% vs. 75%), pain in extremity (0% vs. 25%), and headache (20% vs. 25%).

DRUG INTERACTIONS

Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins

Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS.

Neonatal Fc Receptor Blockers

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

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Please see page 5 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal infections, and accompanying full Prescribing Information for VOYDEYA, page 6 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, and the full Prescribing Information for ULTOMIRIS, and page 7 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, and the full Prescribing Information for SOLIRIS.

INDICATION & IMPORTANT SAFETY INFORMATION for SOLIRIS® (eculizumab)

INDICATION

SOLIRIS is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

SOLIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1)*]. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of SOLIRIS, unless the risks of delaying SOLIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. *See Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving SOLIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.**

Because of the risk of serious meningococcal infections, SOLIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [*see Warnings and Precautions (5.2)*].

CONTRAINDICATIONS

- SOLIRIS is contraindicated for initiation in patients with unresolved serious *Neisseria meningitidis* infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

SOLIRIS, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with SOLIRIS. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information.

If urgent SOLIRIS therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including SOLIRIS. The benefits and risks of treatment with SOLIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis*.

Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if these signs and symptoms occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of SOLIRIS in patients who are undergoing treatment for serious meningococcal infection, depending on the risks of interrupting treatment in the disease being treated.

ULTOMIRIS and SOLIRIS REMS

Due to the risk of serious meningococcal infections, SOLIRIS is available only through a restricted program called ULTOMIRIS and SOLIRIS REMS.

Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of SOLIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of SOLIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, the signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card with them at all times during and for 3 months following SOLIRIS treatment.

Further information is available at www.UltSolREMS.com or 1-888-765-4747.

Other Infections

Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

SOLIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections with *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. Additionally, *Aspergillus* infections have occurred in immunocompromised and neutropenic patients. Children treated with SOLIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP recommendations. Patients receiving SOLIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

Monitoring Disease Manifestations After SOLIRIS Discontinuation

Monitor patients after discontinuing SOLIRIS for at least 8 weeks to detect hemolysis.

Thrombosis Prevention and Management

The effect of withdrawal of anticoagulant therapy during SOLIRIS treatment has not been established. Therefore, treatment with SOLIRIS should not alter anticoagulant management.

Infusion-Related Reactions

Administration of SOLIRIS may result in infusion-related reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion-related reaction which required discontinuation of SOLIRIS. Interrupt SOLIRIS infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) were: headache, nasopharyngitis, back pain, and nausea.

To report SUSPECTED ADVERSE REACTIONS contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full prescribing information for SOLIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Please see page 5 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal infections, and accompanying full Prescribing Information for VOYDEYA, page 6 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, and the full Prescribing Information for ULTOMIRIS, and page 7 for Important Safety Information, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, and the full Prescribing Information for SOLIRIS.

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