Voydeya™
(danicopan) 50mg·100mg tablets

Not an actual patient.

Identifying extravascular hemolysis in patients managing PNH with a C5 inhibitor

Explore one patient's journey from diagnosis to effective management

PNH=paroxysmal nocturnal hemoglobinuria.

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)*].

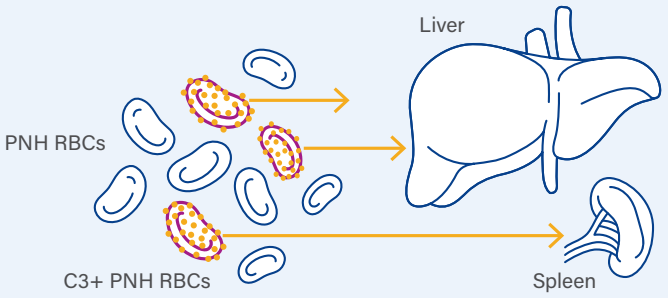
Please see Important Safety Information throughout and full Prescribing Information for VOYDEYA, including Boxed WARNING regarding serious and life-threatening or fatal infections.

Understanding EVH

A subset of patients treated with a C5 inhibitor may experience EVH[1,2]

For patients with PNH, the standard of care—C5 inhibition—controls intravascular hemolysis (IVH) of PNH red blood cells (RBCs) and reduces the risk of life-threatening vascular events.[3-6] The PNH RBCs remaining in circulation are susceptible to C3 fragment deposition that may lead to extravascular hemolysis (EVH).[4,6-8]

EVH occurs when PNH RBCs are cleared by the liver and spleen prematurely, which may lead to anemia[7]



Patients with EVH may experience persistent signs and symptoms of anemia (with or without the need for transfusion) that impacts a patient's ability to accomplish daily tasks.[2,7]

- **EVH is not considered life-threatening**[7]
- Patients with EVH **are not at increased risk of thrombosis**, the most common cause of death in PNH[7,9]
- A diagnosis of EVH **does not indicate inadequate C5 inhibition**, but patients may need help managing symptoms[6]

Indication

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

Select Important Safety Information for ULTOMIRIS® (ravulizumab-cwvz)

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)*].

Please see Important Safety Information on pages 8 and 9 and full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

How to identify EVH

Clinical observations and hematological indicators are key[1,2,7,10-12]

A subset of patients with a confirmed treatment response (LDH <1.5 x ULN) to a C5 inhibitor may experience persistent signs and symptoms of anemia. There are multiple causes,[a] one of which may be EVH.[1-4,11,13,14]

EVH could be the cause if your patients have[1,2,4,6,10-12,15,16,b]:

- Persistent anemia with or without the need for transfusion while on a C5 inhibitor
- **+**
- Low hemoglobin[c] and increased absolute reticulocyte count[d]

WHEN

- Other causes of persistent anemia, such as BMF (AA, MDS, bone marrow disorders requiring transfusions), are eliminated[a]

To confirm if persistent anemia is due to EVH, other causes should be eliminated by checking key hematological indicators.[11]

Explore Julia's journey[e] with PNH, including the impact of EVH and its treatment.

Click to meet Julia

Not an actual patient.

[a]Other causes of persistent anemia include low folate levels, relative erythropoietin deficiency, breakthrough intravascular hemolysis, hypersplenism, iron overload, and/or the presence of alloantibodies.[11,16]
[b]Based on a clinical trial for a treatment used as an add-on treatment to ULTOMIRIS or SOLIRIS® (eculizumab).[1]
[c]Low levels of hemoglobin are considered to be ≤9.5 g/dL.[1,2]
[d]An increased absolute reticulocyte count is considered to be ≥120 x 10^9/L.[1,2]
[e]Hypothetical data based on a typical EVH patient profile.

AA=aplastic anemia; BMF=bone marrow failure; LDH=lactate dehydrogenase; MDS=myelodysplastic syndromes; ULN=upper limit of normal.

Please see Important Safety Information throughout and full Prescribing Information for VOYDEYA, including Boxed WARNING regarding serious and life-threatening or fatal infections.

Meet Julia: A patient living with PNH and EVH

While **ULTOMIRIS® (ravulizumab-cwvz)**[a] has kept Julia's[b] PNH symptoms reliably under control, hematological indicators identified that Julia was experiencing EVH.[1,2,7,10-12,17]

Explore Julia's treatment journey

Normal measures[18-20,c]

Hb, g/dL:	12-16
LDH, U/L:	122-222
ARC, x 10^9 cells/L:	23-90
PLT, x 10^9 cells/L:	150-350
WBC, x 10^9 cells/L:	4.5-11
ANC, x 10^9 cells/L:	2.6-8.5
Total bilirubin, mg/dL:	0.3-1.2
D-dimer, ng/dL:	≤500
FACIT-Fatigue score, points[d]:	43.5

Not an actual patient.

Baseline at diagnosis of PNH

Age: 39

Diagnosis: PNH

Treatment: None

Clinical presentation
Hemoglobinuria, fatigue, dyspnea, abdominal pain, occasional dysphagia.

- **Symptom management with frequent RBC transfusions**

Lab values

Hb, g/dL:	**6.2**
LDH, U/L:	**1790**
ARC, x 10^9 cells/L:	**150**
PLT, x 10^9 cells/L:	30
WBC, x 10^9 cells/L:	2.4
ANC, x 10^9 cells/L:	0.8
Total bilirubin, mg/dL[21]:	2.0
D-dimer, ng/dL:	2300
Coombs test:	Negative

PNH monitoring

Neutrophil clone:	82.5%
Monocyte clone:	83.2%
Erythrocyte clone:	39.8%

FACIT-Fatigue score, points: 27.3

Management

- Counseling and meningococcal vaccination[17]
- **ULTOMIRIS initiated**

5 years after diagnosis of PNH and initiation of ULTOMIRIS

Age: 44

Diagnosis: PNH

Treatment: ULTOMIRIS

Clinical presentation
No new symptoms reported but had talked about ongoing fatigue.

- **No BTH or MAVEs in past 2 years**

Lab values

Hb, g/dL:	**8.7**	!
LDH, U/L:	**198**	✓
ARC, x 10^9 cells/L:	**160**	!
PLT, x 10^9 cells/L:	110	
WBC, x 10^9 cells/L:	4.8	
ANC, x 10^9 cells/L:	2.7	
Total bilirubin, mg/dL[21]:	1.8	
D-dimer, ng/dL:	450	

PNH monitoring

Neutrophil clone:	85.6%
Monocyte clone:	86.2%
Erythrocyte clone:	70.6%

FACIT-Fatigue score, points: 35.7 ↑

Management

- **ULTOMIRIS**
- **Reduced but ongoing need for RBC transfusions**
  - Explored potential causes of persistent anemia

6-month follow-up and diagnosis of EVH

Age: 45

Diagnosis: PNH, EVH

Treatment: ULTOMIRIS

Clinical presentation
Reports of ongoing fatigue. Hematology workup indicated possible EVH, which was confirmed by differential diagnosis.

Lab values

Hb, g/dL:	**8.6**	!
LDH, U/L:	**205**	✓
ARC, x 10^9 cells/L:	**180**	!
PLT, x 10^9 cells/L:	115	
WBC, x 10^9 cells/L:	5.0	
ANC, x 10^9 cells/L:	2.9	
Total bilirubin, mg/dL[21]:	2.0	
D-dimer, ng/dL:	435	

Differential tests included: *CBC, Coombs test, peripheral blood smear, and bone marrow biopsy.*

PNH monitoring

Neutrophil clone:	85.8%
Monocyte clone:	86.8%
Erythrocyte clone:	71.0%

FACIT-Fatigue score, points: 33.4 ↓

Management

- **ULTOMIRIS**
- Counseling and additional vaccine (*Streptococcus pneumoniae*)[1]
- **VOYDEYA initiated at 150 mg TID**

7-month follow-up after initiating treatment with VOYDEYA™

Age: 45

Diagnosis: PNH, EVH

Treatment: ULTOMIRIS + VOYDEYA

Clinical presentation
EVH resolved; reported less fatigue.

Lab values

Hb, g/dL:	**13.2**	✓
LDH, U/L:	**188**	✓
ARC, x 10^9 cells/L:	**87**	✓
PLT, x 10^9 cells/L:	115	
WBC, x 10^9 cells/L:	4.8	
ANC, x 10^9 cells/L:	2.7	
Total bilirubin, mg/dL[21]:	1.1	
D-dimer, ng/dL:	435	

PNH monitoring

Neutrophil clone:	86.3%
Monocyte clone:	87.6%
Erythrocyte clone:	78.9%

FACIT-Fatigue score, points: 42.4 ↑

Management

- **ULTOMIRIS**
- Continues **VOYDEYA** TID
- **Has not needed a transfusion since initiating VOYDEYA**

Individual results may vary.

The impact of treatment:

- **LDH levels with ULTOMIRIS were maintained after adding VOYDEYA**, indicating continued control of IVH[1,3,9,e]
- **Low hemoglobin and elevated reticulocyte count associated with EVH resolved**[1,2]
- **FACIT-Fatigue scores increased**, helping Julia to do more of the activities she wants[1,7]

By adding VOYDEYA, Julia was able to manage EVH without disrupting the critical PNH control of ULTOMIRIS.[1,17]

[a]VOYDEYA may also be taken with SOLIRIS® (eculizumab).[1]
[b]Hypothetical data based on a typical EVH patient profile.
[c]This is the normal hemoglobin range for females. The normal hemoglobin range for males is 14-17 g/dL.[18]
[d]FACIT-Fatigue score of the general population. Scores can range from 0 to 52, with higher scores indicating less fatigue.[1,20]
[e]LDH outcomes were not prespecified and are considered exploratory. All patients were on C5 inhibitor treatment at study entry and had control of IVH (LDH <1.5 x ULN).[1]

ANC=absolute neutrophil count; ARC=absolute reticulocyte count; BTH=breakthrough hemolysis; CBC=complete blood count; FACIT=Functional Assessment of Chronic Illness Therapy; Hb=hemoglobin; MAVE=major adverse vascular event; PLT=platelets; TID=3 times a day; WBC=white blood cell.

Select Important Safety Information for VOYDEYA

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.

Please see Important Safety Information throughout and full Prescribing Information for VOYDEYA, including Boxed WARNING regarding serious and life-threatening or fatal infections.

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 full Prescribing Information for VOYDEYA, including Boxed WARNING regarding serious and life-threatening or fatal infections.

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

Administration of ULTOMIRIS 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, including lower back pain, abdominal pain, muscle spasms, drop or elevation in blood pressure, rigors, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste). These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS 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.

USE IN SPECIFIC POPULATIONS

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ULTOMIRIS during pregnancy. Healthcare providers and patients may call 1-833-793-0563 or go to www.UltomirisPregnancyStudy.com to enroll in or to obtain information about the registry.

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

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When added to backbone therapy, ULTOMIRIS® (ravulizumab-cwvz),[a] VOYDEYA™:

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  - The most common adverse reaction (≥10%) with VOYDEYA was headache
  - No discontinuation due to hemolysis[b]
- Allows dosing to be adjusted based on patients' clinical response[1,c,d]
- Provides the same level of patient support and resources as ULTOMIRIS or SOLIRIS® (eculizumab)

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[a]VOYDEYA may also be taken with SOLIRIS.[1]
[b]Overall, there were 5 treatment-emergent adverse events of hemolysis (3 hemolysis and 2 breakthrough hemolysis) in 4 participants (all on a stable dose of ULTOMIRIS) based on the clinical judgment of the investigator. None of these events had LDH above 2.2 × ULN.[21]
[c]VOYDEYA should only be prescribed as an add-on to ULTOMIRIS or SOLIRIS and should NOT be administered as monotherapy.[1]
[d]The dosage can be increased to 200 mg TID if the patient's hemoglobin level has not increased by >2 g/dL after 4 weeks of therapy, if the patient required a transfusion during the previous 4 weeks, or to achieve an appropriate hemoglobin response based on clinical judgment.[1]

US/VOY-PNH/0143 V1 12/2024

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