IOWA | Health and Human Services

PDL DRUG REVIEW

Proprietary Name: Voydeya®
Common Name: danicopan
PDL Category: Complement Inhibitors

Comparabl	
Fabhalta	Non-Preferred
Soliris (eculizumab)	Medical Benefit
Ultomiris (ravulizumab)	Medical Benefit

Pharmacology/Usage: Danicopan, the active ingredient of Voydeya®, is a small molecule complement Factor D inhibitor. It binds reversibly to complement Factor D and selectively inhibits the alternative complement pathway. Danicopan prevents the cleavage of complement Factor B into the Ba and Bb fragments, which are required for the formation of the alternative pathway (AP) complement component C3 convertase (C3bBb), the generation of downstream effectors including C3 fragment opsonization, and the amplification of the terminal pathway.

In PNH, intravascular hemolysis (IVH) is mediated by the terminal membrane attack complex (MAC), while extravascular hemolysis (EVH) is facilitated by C3 fragment opsonization. Danicopan acts proximally in the alternative pathway of the complement cascade to control preferentially C3 fragment-mediated EVH, while co-administered ravulizumab or eculizumab is anticipated to maintain control over MAC-mediated IVH.

Indication: As add-on therapy to ravulizumab or eculizumab for the treatment of extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH). A limitation of use includes that Voydeya® has not been shown to be effective as monotherapy and should only be prescribed as an add-on to ravulizumab or eculizumab.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant individuals to assess 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. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 50mg, 100mg.

Recommended Dosage: Vaccinate against encapsulated bacteria, including *Neisseria meningitidis* (serogroups A, C, W, Y, and B) and *Streptococcus pneumoniae* per current Advisory Committee on Immunization Practices (ACIP) recommendations at least 2 weeks prior to the start of Voydeya®. If urgent Voydeya® treatment is indicated in a patient who is not up to date with vaccines for *Neisseria meningitidis* and *Streptococcus pneumoniae* per ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible.

Healthcare professionals who prescribe Voydeya® must enroll in the Voydeya® REMS.

The recommended dosage is 150mg PO TID, with or without food. The dose can be increased to 200mg PO TID if the patient's hemoglobin (Hgb) level has not increased by greater than 2g/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.

A patient who misses a dose should take it as soon as they remember unless it is within 3 hours prior to their next dose, in which case the patient should skip the missed dose and take Voydeya® at the next regularly scheduled time. Patients should not take two or more doses of Voydeya® at the same time.

Dose adjustments are not required with mild to moderate hepatic impairment. Studies have not been conducted in patients with severe hepatic impairment; thus, avoid Voydeya® use with severe hepatic impairment.

Drug Interactions: 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. If used together, monitor patients more frequently for adverse reactions associated with the BCRP substrate, and consider dose reduction of the BCRP substrate per its prescribing information.

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

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

Box Warning: Voydeya® has a box warning regarding serious infections caused by encapsulated bacteria. Voydeya® increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenza* type B. 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 ACIP recommendations for vaccinations against encapsulated bacteria in patients receiving a complement inhibitor.
- 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 assess 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.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Voydeya®) minus reported % incidence for placebo, both taken with ravulizumab or eculizumab. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included headache (1%), vomiting (7%), pyrexia (7%), alanine aminotransferase increased (2%), hypertension (2%), and pain in extremity (5%).

As discussed in the box warning, Voydeya® is available only through a restricted program under a REMS, called the Voydeya® REMS, because of the risk of serious infections caused by encapsulated bacteria. Notable requirements of the Voydeya® REMS include the following:

- Prescribers must enroll in the REMS.
- Prescribers must counsel patients about the risk of serious infections caused by encapsulated bacteria.
- Prescribers must provide patients with the REMS educational materials.
- Prescribers must assess patient vaccination status for vaccines against encapsulated bacteria and vaccinate if needed per current ACIP recommendations two weeks prior to the first Voydeya® dose.

- Prescribers must provide a prescription for antibacterial drug prophylaxis if treatment must be started urgently, and the patient is not up to date with vaccines against encapsulated bacteria per current ACIP recommendations at least 2 weeks prior to the first Voydeya® dose.
- 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, the need to take antibiotics as directed by the prescriber, and the early signs and symptoms of serious infection.
- Patients must be instructed to carry the Patient Safety Card with them at all times during treatment and for 1 week following the last Voydeya® dose.
- Further information is available by calling 1-888-765-4747 or online at www.VoydeyaREMS.com.

Hepatic enzyme elevations have been observed in patients treated with Voydeya®. 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.

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 needed. If hemolysis occurs after discontinuation of Voydeya®, consider restarting treatment with Voydeya® if appropriate.

Voydeya® increases total cholesterol and LDL-cholesterol. Some patients in clinical trials required cholesterol-lowering medications. Monitor serum lipid parameters periodically during treatment with Voydeya® and start cholesterol lowering medication, if indicated.

Contraindications: For initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae*, or *Haemophilus influenza* type B.

Manufacturer: Alexion Pharmaceuticals, Inc.

Analysis: The safety and efficacy of Voydeya® were assessed in adults with PNH and clinically significant EVH in a multiple-region, randomized, double-blind, placebo-controlled study. Clinically significant EVH was defined by anemia (Hgb ≤ 9.5g/dL) with absolute reticulocyte count ≥120 X 10^9/L with or without transfusion support. The study enrolled patients with PNH who had been treated with a stable dose of ravulizumab or eculizumab for at least the previous 6 months. Patients were vaccinated against meningococcal infection prior to or at the time of starting treatment if vaccination status within 3 years could not be verified.

Patients were randomized to Voydeya® or placebo for 12 weeks in addition to background ravulizumab or eculizumab treatment. After week 12, all patients received Voydeya® in combination with their background treatment up to week 24. After week 24, patients could enter a long-term extension period and continue to receive Voydeya® with background ravulizumab or eculizumab.

At baseline, the mean age of the Voydeya® and placebo groups were 55 years and 53 years, respectively, while 45.2% and 33.3% were male. The mean hemoglobin level was 7.7 with both groups. Background treatment included 64.3% on ravulizumab and 35.7% on eculizumab for the Voydeya® group and 47.6% on ravulizumab and 52.4% on eculizumab for the placebo group.

Efficacy was based on the change in Hgb level from baseline to week 12. Other efficacy measures included the proportion with Hgb increase of ≥2 g/dL at week 12 in the absence of transfusions, the proportion with transfusion avoidance through week 12, the change from baseline in Functional Assessment of Chronic

Illness Therapy (FACIT)-fatigue scores at week 12, and the change from baseline in absolute reticulocyte count at week 12. Note that transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol specified guidelines for transfusion from baseline through week 12.

A pre-specified interim analysis was performed when 63 subjects reached the end (either completed or discontinued) of week 12.

Efficacy was established based on demonstration of superiority of Voydeya® in combination with ravulizumab or eculizumab compared to placebo in combination with ravulizumab or eculizumab in all efficacy measures with statistically significant results. Results are presented in the table below, which was adapted from the prescribing information.

	Voydeya® add-on (N=42)	Placebo add-on (N=21)
Change in hemoglobin level		
Mean change from baseline to week 12 (g/dL)	2.9	0.5
Treatment difference	2.4	
p-value	0.0007	
Proportion with Hemoglobin increase of ≥2g/dL in the Absence of Transfusion		
At week 12 (%)	59.5	0
Treatment difference	46.9	
p-value	<0.0001	
Proportion with Transfusion Avoidance		
Through 12-week treatment period (%)	83.3	38.1
Treatment difference	41.7	
p-value	0.0004	
Change in FACIT-Fatigue Score		
Mean change from baseline to week 12	8.0	1.9
Treatment difference	6.1	
p-value	0.002	
Change in Absolute Reticulocyte Count		
Mean change from baseline to week 12 (10^9/L)	-84	4
Treatment difference	-87	
p-value	<0.0001	

Place in Therapy: Voydeya® is an oral complement factor D inhibitor indicated as add-on therapy to ravulizumab or eculizumab for the treatment of extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH). A limitation of use includes that Voydeya® has not been shown to be effective as monotherapy and should only be prescribed as an add-on to ravulizumab or eculizumab. It does have a box warning regarding serious infections caused by encapsulated bacteria. 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. Because of the risk of serious infections caused by encapsulated bacteria, Voydeya® is available only through a restricted program under a REMS called the Voydeya® REMS. The efficacy of Voydeya® was assessed in a randomized, double-blind, placebo-controlled study where Voydeya® was given three times day in addition to background therapy with either ravulizumab or eculizumab. The primary outcome measure was the change in Hgb level from baseline to week 12. Efficacy was established based on the demonstration of superiority of Voydeya® in combination with ravulizumab or eculizumab compared to placebo in combination with ravulizumab or eculizumab in all efficacy measures, with statistically significant results.

Summary

It is recommended that Voydeya® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use. Note that it has not been shown to be effective as monotherapy and should only be prescribed as an add-on to ravulizumab or eculizumab.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Voydeya® [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc; 2024.