

Iptacopan (FABHALTA) in Paroxysmal Nocturnal Hemoglobinuria (PNH) National Drug Mini-monograph SEPT 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION	Description / MOA	Iptacopan binds to Factor B of the alternative complement pathway
	Indication Under Review¹	Paroxysmal Nocturnal Hemoglobinuria (PNH)
	Dosage Regimen	Iptacopan 200mg twice daily
	Dosage Forms Under Review	Iptacopan 200mg oral capsules

EFFICACY CONSIDERATIONS	Trial	APPLY-PNH²	APPOINT-PNH²
	Design	Open-label randomized trial	Single-arm study
	Population	Adult patients (n=97) who had confirmed PNH with Hgb <10g/dL despite stable treatment (>6 months) with anti-C5 therapy (e.g. either IV eculizumab or ravulizumab)	Adult patients (n=40) with PNH with Hgb <10g/dL and who had NOT received anti-C5 treatment
	Intervention	Patients were randomized 8:5 to 24 weeks of iptacopan 200mg bid followed by a 24 week extension period	Patient provided 24 weeks of treatment with iptacopan 20mg bid followed by a 24 week extension period
	Comparator Results	Continuation of anti-C5 therapy	Baseline Hgb levels
	Results	Co-primary endpoints of Hgb increase of >2 g/dL and achieving Hgb >12g/dL without need for red cell transfusions. A total of 51 of 60 evaluable patients had Hgb increase >2g/dL and 42 of 60 evaluable pts had final Hgb >12g/dL (82% and 62%, respectively) compared to none of the patients continued on eculizumab or ravulizumab	Primary endpoint was increase in Hgb>2g/dL, secondary endpoint was final Hgb>12g/dL without need for red cell transfusions. Thirty-one of 33 evaluable patients had 2g/dL Hgb increase (92%) and 19 of 33 pts achieved a Hgb >12 g/dL. No pts needed transfusions (baseline 70% in 6 months prior to enrollment)

SAFETY CONSIDERATIONS	Boxed Warnings	Serious infections caused by encapsulated bacteria. Complete or update vaccination for encapsulated bacteria at least 2 weeks prior to the first dose of iptacopan, unless the risks of delaying therapy with iptacopan outweigh the risk of developing a serious infection.
	Contraindications	Hypersensitivity to iptacopan Unresolved serious infection caused by encapsulated bacteria, including: Strep. Pneumoniae, Niesseria meningitidis, or H. influenzae type B.
	Other Warnings	Use not recommended in severe renal (eGFR<30mL/min) or severe hepatic impairment (Child-Pugh class C) Insufficient data to make recommendation regarding risk of birth defects in pregnancy. Cessation of breastfeeding recommended during treatment with iptacopan and for 5 days after final dose Monitor for hemolysis after cessation of therapy
	Top 5 AEs	Headache (16%), Diarrhea (15%), Nasopharyngitis (11%), Nausea (10%), Arthralgia (8%)
	Drug Interactions	Strong CYP2C8 inducers (e.g. rifampin) or inhibitors (e.g. gemfibrozil) can significant decrease or increase iptacopan exposure

	DRUG	VANF	CFU	FDA	GUIDELINES
PLACE IN THERAPY	Ravulizumab	No	Yes	Yes	CFU Ravulizumab Ultomiris CFU Rev March 2023.pdf (va.gov)
	Eculizumab	No	Yes	Yes	CFU Eculizumab Soliris for PNH CFU rev June 2023.pdf (va.gov)
	Iptacopan	TBD	TBD	Yes	TBD

VHA PLACE IN THERAPY	<p>Potential Use in VHA</p> <ol style="list-style-type: none"> 1. PNH is a rare condition (1 to 10 per million) with primary treatment for past 2 decades being C5 inhibitors (e.g. eculizumab or ravulizumab). However, 20-30% of patients treated with anti-C5 therapy will have breakthrough hemolysis and/or extravascular hemolysis which iptacopan addressed in the APPLY-PNH trial. While iptacopan has also been studied in anti-C5 naïve patients, long-term effects are unknown in context of 2 decades of experience with anti-C5 inhibitors. There have been multiple drugs recently released for PNH (iptacopan, danicopan, pegcetacoplan) which all fill a similar niche. All treatments cost \$300-400k per year (see table below)
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Prepared Ian Pace, PharmD.

Contact person: Bernadette heron, PharmD, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

References

- 1 FABHALTA (iptacopan) 200mg oral capsules [prescribing information online]. East Hanover, New Jersey: Novartis. Available at: [fabhalta.pdf \(novartis.com\)](#). Accessed June 2024.
- 2 Peffault de Latour R, et al.,. Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. N Engl J Med. 2024 Mar 14;390(11):994-1008. doi: 10.1056/NEJMoa2308695. PMID: 38477987.