ファビハルタカプセル 200 mg
に関する資料

ノバルティスファーマ株式会社

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1 起原又は発見の経緯

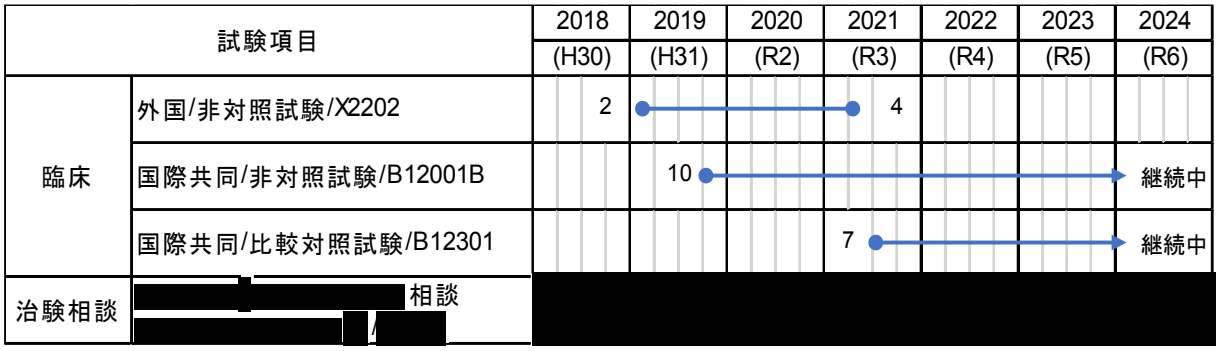
起原又は発見の経緯は「2.5-1.1.3 項」参照。

2 開発の経緯

開発の経緯図を Figure 2-1 に示す。開発の経緯図を除く当該内容については，「2.5-1.2 項」に記載した。なお，C3 腎症の小児に係る LNP023 の開発については，本申請の評価資料とした国際共同比較対照試験（B12301 試験）に，成人とは別コホートとして 12 歳～17 歳の青少年患者を登録中であり，試験デザインの妥当性については，医薬品医療機器総合機構と[redacted]相談（20[redacted] 年[redacted] 月[redacted] 日，受付番号：[redacted]）にて協議，合意している。なお，本試験の青少年コホートは日本及び欧米を含む国々で組入れ中である。

また，[redacted]。

Figure 2-1 開発の経緯図



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1 外国における使用状況等

イプタコパンは，発作性夜間ヘモグロビン尿症の適応で 2023 年 12 月に米国で初めて承認され，2025 年 1 月末時点において，欧米を含む 48 ヵ国で承認されている。また，国内においてはファビハルタカプセル 200 mg の販売名で 2024 年 6 月に承認された。

今回効能追加する「C3 腎症」については，国際共同第 III 相試験（B12301 試験）の結果に基づき，承認申請が世界的に予定されており，欧州で 2024 年 7 月，中国で 2024 年 8 月，米国で 2024 年 9 月に承認申請した。また，米国では 2025 年 3 月，欧州及び中国では 2025 年 4 月に承認された。

2 外国の添付文書等の概要

ノバルティス社の企業中核データシート（CCDS / Basic Prescribing Information version [redacted]，20[redacted] 年[redacted] 月[redacted] 日改訂）を添付する。また，米国の添付文書（2025 年 3 月改訂）の概略を 2.1 項に，欧州の添付文書（2025 年 4 月改訂）の概略を 2.2 項に示す。

2.1 米国の添付文書の概略

販売名

FABHALTA® (iptacopan) capsules, for oral use

1. 効能・効果

1.1 発作性夜間ヘモグロビン尿症

FABHALTA は，成人発作性夜間ヘモグロビン尿症（PNH）患者の治療を適応とする。

1.2 IgA 腎症

FABHALTA は，急速な疾患進行のリスクがあり，一般に尿蛋白/クレアチニン比（UPCR）が 1.5 g/g 以上である成人原発性 IgA 腎症患者における蛋白尿の減少を適応とする。

本適応症は，蛋白尿の減少に基づき迅速承認された。FABHALTA が IgA 腎症患者の腎機能低下を遅延させるかどうかは確立されていない。本適応症に対する承認の継続は，検証的臨床試験における臨床的ベネフィットの検証及び説明を条件とする。

1.3 C3 腎症

FABHALTA は，成人 C3 腎症患者の治療を適応とし，蛋白尿を減少させる。

2. 用法及び用量

2.1 推奨される莢膜形成細菌感染症に対するワクチン接種及び予防

肺炎球菌及び髄膜炎菌（血清型 A，C，W，Y 及び B）を含む莢膜形成細菌に対し，最新の ACIP の勧告に従い，FABHALTA の投与開始の 2 週間以上前にワクチンを接種すること［警告及び使用上の注意（5.1 項）参照］。

肺炎球菌及び髄膜炎菌に対するワクチン接種を ACIP の勧告に従って受けていない患者に FABHALTA の緊急投与が適応となる場合は，抗菌薬の予防投与を行い，可能な限り速やかにこれらのワクチンを接種すること［警告及び使用上の注意（5.1）参照］。

FABHALTA を処方する医療従事者は，FABHALTA の REMS に登録しなければならない［警告及び使用上の注意（5.2）を参照］。

2.2 推奨用量

FABHALTA の推奨用量は，食事の有無にかかわらず 200 mg を 1 日 2 回経口投与である。カプセルはそのまま飲み込むこと。カプセルを開けたり，割ったり，噛んだりしないこと。飲み忘れた場合は，可能な限り速やかに FABHALTA 1 回分を服用し（予定されている次の服用の直前であっても），その後通常の投与スケジュールで再開するよう患者に助言すること。

2.3 抗 C5 抗体薬（エクリズマブ，ラブリズマブ）から FABHALTA に切り替える PNH 患者

その他の PNH 治療薬投与の突然の中止に伴う溶血の潜在的リスクを軽減するため：

- エクリズマブから切り替える患者では，エクリズマブの最終投与後 1 週間以内に FABHALTA の使用を開始すること。
- ラブリズマブから切り替える患者では，ラブリズマブの最終投与から 6 週間以内に FABHALTA の投与を開始すること。

他の PNH 治療薬投与後の FABHALTA の開始時期に関する情報は得られていない。

3. 剤形・含量

Iptacopan 200 mg カプセル：淡黄色不透明の硬カプセル剤で，本体に「LNP200」，キャップに「NVR」と印字されている。

4. 禁忌

FABHALTA の使用は以下に対し禁忌である：

- Iptacopan 又はその添加物に対して重篤な過敏症のある患者。
- 肺炎球菌，髄膜炎菌又はインフルエンザ菌 b 型などの莢膜形成細菌による重篤な感染症が未回復の患者。

5. 警告及び使用上の注意

5.1 莢膜形成細菌による重篤な感染症

補体阻害剤の FABHALTA は，肺炎球菌，髄膜炎菌（いずれかの血清型に起因する，グループ化されていない株を含む）及びインフルエンザ菌 b 型を含む莢膜形成細菌による重篤な感染症，生命を脅かす又は致死的な感染症に対する患者の感受性を高める。莢膜形成細菌による生命を脅かす又は致死的な感染症は，補体阻害剤を投与されたワクチン接種患者及びワクチン未接種患者のいずれにおいても発現している。莢膜形成細菌による重篤な感染症が未回復の患者には，FABHALTA の投与を開始しないこと。

補体阻害剤の投与を受けている患者に対する最新の ACIP 勧告に従い，FABHALTA の初回投与の少なくとも 2 週間前に莢膜形成細菌に対するワクチン接種を完了又は更新すること。FABHALTA の投与期間を考慮した ACIP の推奨事項に従ってワクチンを再接種すること。なお，ACIP は，補体阻害剤の投与を受けている患者では，ワクチンの添付文書の投与スケジュールとは異なる投与スケジュールを推奨している。莢膜形成細菌に対するワクチン接種を ACIP の勧告に従って受けていない患者に緊急の FABHALTA 療法が適応となる場合は，抗菌薬の予防投与を行い，可能な限り速やかにこれらのワクチンを接種すること。抗菌薬予防の様々な期間及びレジメンが検討されているが，ワクチン未接種又はワクチン接種を受けた FABHALTA を含む補体阻害剤投与患者における最適な予防期間及び薬剤レジメン並びにその有効性は検討されていない。莢膜形成細菌による重篤な感染症の既知のリスクに対して，FABHALTA による治療のベネフィットとリスク，並びにワクチン接種を受けていない又は受けている患者における抗菌薬の予防投与のベネフィットとリスクを考慮しなければならない。

ワクチン接種後に抗体が産生されるにもかかわらず，ワクチン接種によって重篤な莢膜形成細菌による感染症のリスクを取り除くことはできない。重篤な感染症の初期徴候及び症状について患者を注意深く観察し，感染症が疑われる場合は直ちに患者を評価すること。これらの徴候及び症状について患者に説明し，これらの徴候及び症状が発現した場合は直ちに受診するよう患者を指導すること。既知の感染症を速やかに治療すること。重篤な感染症は，早期に発見して治療しなければ，急速に生命を脅かしたり死に至ることがある。重篤な感染症の治療を受けている患者では，治療対象の疾患における投与中断のリスクに応じて，FABHALTA の投与中断を検討すること。

FABHALTA は，REMS　のプログラムの枠組み内での使用に限られる［警告及び使用上の注意（5.2）参照］。

5.2 FABHALTA REMS

FABHALTA は，莢膜形成細菌による重篤な感染症のリスクがあるため FABHALTA REMS と呼ばれる REMS によるプログラムの枠組み内での使用に限られる［警告及び使用上の注意（5.1）参照］。

FABHALTA REMS の注目すべき要件は以下のとおりである。

- 処方医は，REMS に登録しなければならない。
- 処方医は，莢膜形成細菌による重篤な感染症のリスクについて患者に説明しなければならない。
- 処方医は，患者に REMS 教育資料を提供しなければならない。
- 処方医は，莢膜形成細菌に対するワクチンについて患者のワクチン接種状況を評価し，必要に応じて，FABHALTA の初回投与の 2 週間前に最新の ACIP 勧告に従ってワクチン接種を行わなければならない。

- 処方医は，治療を緊急に開始しなければならず，かつ患者が FABHALTA の初回投与の 2 週間以上前に最新の ACIP 勧告に従った莢膜形成細菌に対するワクチン接種を受けていない場合，処方医は予防の抗菌薬を処方しなければならない。
- FABHALTA を調剤する薬局は，FABHALTA REMS で認定されていなければならず，処方医が認定されていることを確認しなければならない。
- 患者は，ACIP の推奨に従って莢膜形成細菌に対するワクチン接種を受ける必要性，処方医の指示に従って抗菌薬を服用する必要性，並びに重篤な感染症の初期徴候及び症状について，処方医からカウンセリングを受けなければならない。
- 患者には，投与期間中及び FABHALTA の最終投与後 2 週間は患者安全性カードを常に携帯するよう指導すること。

詳細な情報は，電話 1-833-99FABHA（1-833-993-2242）又はオンライン www.FABHALTA-REMS.com で入手できる。

5.3 FABHALTA 投与中止後の PNH 症状のモニタリング

PNH 患者では，FABHALTA の投与中止後少なくとも 2 週間は溶血の徴候及び症状について患者を注意深く観察すること。これらの徴候には，ヘモグロビン又は PNH クローンサイズの突然の減少を伴う乳酸脱水素酵素（LDH）値の上昇，疲労，ヘモグロビン尿，腹痛，呼吸困難，主要血管事象（血栓症，脳卒中，心筋梗塞など），嚥下障害又は勃起不全などがある。FABHALTA の中止が必要な場合は，代替療法を検討すること。

FABHALTA の投与中止後に溶血が発現した場合は，必要に応じて本剤の投与再開又は PNH に対する別の治療の開始を検討すること。

5.4 高脂血症

FABHALTA は，総コレステロール，LDL コレステロール及び血清トリグリセリドを増加させる可能性がある［副作用（6.1）参照］。

APPLY-PNH のベースライン時に総コレステロール値が正常であった FABHALTA 投与患者 54 例のうち，43%がランダム化投与期間中にグレード 1 の高コレステロール血症を発現した。APPLY-PNH の FABHALTA 投与患者 1 例に総コレステロール増加が発現し，ベースライン時のグレード 1 からグレード 2 に悪化した。

APPOINT-PNH のベースライン時にコレステロール値が正常であった FABHALTA 投与患者 34 例のうち，24%がコア投与期間中にグレード 1 の高コレステロール血症を発現した。

APPLY-PNH のベースライン時に LDL コレステロールが 130 mg/dL 以下であった FABHALTA 投与患者 60 例のうち，ランダム化投与期間中に 17%が LDL コレステロール＞130~160 mg/dL，8%が LDL コレステロール＞160~190 mg/dL，7%が LDL コレステロール＞190 mg/dL を発現した。APPOINT-PNH のベースライン時に LDL コレステロールが 130 mg/dL 以下であった FABHALTA 投与患者 36 例のうち，11%が LDL コレステロール＞130~160 mg/dL，3%が LDL コレステロール＞160~190 mg/dL を発現した。

APPLY-PNH のベースライン時にトリグリセリド値が正常であった 52 例のうち，23%がランダム化投与期間中に Grade 1 のトリグリセリド増加を発現した。APPLY-PNH において，FABHALTA の投与を受けた 3 例の患者で，グレード 1 からグレード 2 へのトリグリセリド増加が認められた。

APPOINT-PNH のベースライン時にトリグリセリド値が正常であった FABHALTA 投与患者 37 例のうち，27%がコア投与期間にグレード 1 のトリグリセリド増加を発現した。

APPLY-PNH 及び APPOINT-PNH で FABHALTA の投与を受けた患者 102 例のうち，2 例がコレステロール低下薬を必要とした。

FABHALTA の投与中は血清脂質パラメータを定期的にモニタリングし，必要に応じてコレステロール低下薬の投与を開始すること。

2.2 欧州の添付文書の概略

販売名

FABHALTA 200 mg hard capsules

4.1 効能・効果

発作性夜間ヘモグロビン尿症

FABHALTA は，単剤療法として溶血性貧血を伴う成人発作性夜間ヘモグロビン尿症（PNH）患者の治療を適応とする。

C3 腎症

FABHALTA は，レニン-アンジオテンシン系（RAS）阻害薬との併用，又は RAS 阻害薬に不耐容である患者，又は RAS 阻害薬が禁忌である成人 C3 腎症（C3G）患者の治療を適応とする（5.1 項参照）。

4.2 用法・用量

用量

推奨用量は 200 mg の 1 日 2 回経口投与である。

医療従事者は，投与スケジュールの遵守の重要性について患者に助言すること。PNH 患者では，溶血のリスクを最小限に抑えるために服薬遵守が重要である（4.4 項参照）。

服用を忘れた場合は，（次の服用予定の直前であっても）できるだけ早く 1 回分を服用し，その後は通常の投与スケジュールで再開するよう患者に指導すること。PNH 患者が複数回連続して服用しなかった場合は，溶血の徴候及び症状がないかモニタリングすること。

PNH は長期治療を必要とする疾患である。臨床的に必要な場合（4.4 項参照）を除き，本剤の投与中止は推奨されない。

抗 C5 抗体薬（エクリズマブ，ラブリズマブ）又は他の PNH 治療から iptacopan に切り替えた PNH 患者

突然の投与中止による溶血の潜在的リスクを軽減するため：

- エクリズマブから切り替えた患者では，エクリズマブの最終投与後 1 週間以内に iptacopan の投与を開始すること。
- ラブリズマブから切り替えた患者では，ラブリズマブの最終投与後 6 週間以内に iptacopan の投与を開始する。

エクリズマブ及びラブリズマブ以外の補体阻害薬からの切替えは検討されていない。

腎移植後に C3G が再発した患者（再発 C3G）

再発 C3G の診断は，移植腎の糸球体における組織学的 C3 沈着に基づいて行う。C3 沈着は，移植後の定期的な生検で確認されることがある。それ以外では，臨床徴候から C3G の再発が示唆される場合に生検を実施する。X2202 試験（5.1 項参照）で実施したように，推定糸球体濾過率（eGFR）減少又は尿蛋白/クレアチニン比（UPCR）増加などの臨床徴候が発現する前に iptacopan の投与を開始することができる。臨床試験における移植後の再発 C3G 患者に対する iptacopan の使用経験は限られている（5.1 項参照）。

特別な集団

高齢者

65 歳以上の患者に対する用量調節は不要である（5.2 項参照）。

腎機能障害

軽度（eGFR が 60 mL/min 以上 90 mL/min 未満）又は中等度（eGFR が 30 mL/min 以上 60 mL/min 未満）の腎機能障害を有する患者に対する用量調節は不要である。現在のところ，重度の腎機能障害を有する患者又は透析を受けている患者におけるデータは得られておらず，推奨用量は得られていない（5.2 項参照）。

肝機能障害

重度の肝機能障害（Child-Pugh 分類 C）を有する患者への iptacopan の使用は推奨されない。軽度（Child-Pugh 分類 A）又は中等度（Child-Pugh 分類 B）の肝機能障害を有する患者に対する用量調節は不要である（5.2 項参照）。

小児集団

18 歳未満の小児における iptacopan の安全性及び有効性は確立していない。データは得られていない。

投与方法

経口投与用。

本剤は食事の有無にかかわらず服用できる（5.2 項参照）。

4.3 禁忌

- 本剤の有効成分又は 6.1 項に記載されている添加剤のいずれかに対する過敏症。
- 髄膜炎菌及び肺炎球菌に対するワクチン接種を現在受けていない患者。ただし，治療を遅らせるリスクがこれらの莢膜形成細菌による感染症の発現リスクを上回る場合を除く（4.4 項参照）。
- 投与開始時に髄膜炎菌，肺炎球菌又はインフルエンザ菌 B 型を含む莢膜形成細菌による感染症が未回復の患者。

4.4 警告及び使用上の注意

莢膜形成細菌による重篤な感染症

Iptacopan などの補体阻害剤を使用すると，莢膜形成細菌に起因する重篤な，生命を脅かす又は致死的な感染症に罹患しやすくなる可能性がある。感染のリスクを軽減するため，すべての患者に髄膜炎菌及び肺炎球菌を含む莢膜形成細菌に対するワクチン接種を行わなければならない。ワクチンが入手可能であれば，インフルエンザ菌 B 型に対するワクチン接種が推奨される。医療従事者は各国のワクチン接種ガイドラインの推奨事項を参照すること。

Iptacopan 初回投与の 2 週間以上前にワクチンを接種すること。ワクチン接種前に投与を開始しなければならない場合は，可能な限り速やかにワクチン接種を行い，ワクチン接種後 2 週間まで抗菌薬の予防投与を行うこと。

必要であれば，各国のワクチン接種ガイドラインの推奨事項に従って患者に再接種してもよい。

ワクチン接種によって重篤な感染症のリスクは軽減されるものの，完全に取り除くことはできない。重篤な感染症は，早期に発見して治療しなければ，急速に生命を脅かしたり死に至ったりする可能性がある。重篤な感染症の初期徴候及び症状について患者に説明し，モニタリングすること。感染が疑われる場合は，直ちに患者を評価し，治療すること。リスクとベネフィットを評価した上で，重篤な感染症の治療中に iptacopan の使用を検討してもよい（4.8 項参照）。

PNH 臨床検査モニタリング

Iptacopan の投与を受けている PNH 患者では，乳酸脱水素酵素（LDH）値の測定を含め，溶血の徴候及び症状を定期的にモニタリングすること。

投与中止後の PNH 症状のモニタリング

投与を中止しなければならない場合，PNH 患者では最終投与後少なくとも 2 週間は溶血の徴候及び症状を注意深くモニタリングすること。これらの徴候及び症状には，ヘモグロビン又は PNH クローンサイズの突然の減少を伴う LDH 値上昇，疲労，ヘモグロビン尿，腹痛，呼吸困難，嚥下障害，勃起不全，静脈血栓症又は動脈血栓症を含む主要な有害血管事象（MAVE）が含まれるが，これらに限定されない。投与中止が必要な場合は，代替療法を検討すること。

Iptacopan の投与中止後に溶血が発現した場合は，投与再開を考慮すること。

他の医薬品との併用

Iptacopan と CYP2C8，UGT1A1，PgP，BCRP 及び OATP1B1/3 の強力な誘導剤との併用は臨床試験で検討されていない。したがって，iptacopan の有効性が低下する可能性があるため，併用は推奨されない（4.5 項参照）。代替の併用薬が特定できない場合は，PNH 患者で溶血の徴候及び症状がないかモニタリングすること。

C3G 患者の治療

免疫抑制剤の投与を受けている C3G 患者では，iptacopan による蛋白尿の減少の程度が小さい可能性があり，これはこれらの患者がより治療抵抗性の C3G であることに関連している可能性が高い。

治療開始時に尿蛋白が 1 g/g 未満である自己腎を有する C3G 患者における iptacopan の使用経験はない。

教育資料

FABHALTA を処方しようとするすべての医師は，医師向け教育資料を受領し，熟知していなければならない。医師は，FABHALTA 療法のベネフィット及びリスクについて患者に説明し，患者情報パックを提供しなければならない。重篤な感染症又は投与中止後の重篤な溶血（PNH 患者）の徴候又は症状が認められた場合には，速やかに医療機関を受診するよう患者を指導すること。

NOVARTIS

[redacted]

FABHALTA™ (iptacopan)
200 mg Hard capsules

Core Data Sheet (CDS)

[redacted]

P2-28は非公表とするため削除

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FABHALTA safely and effectively. See full prescribing information for FABHALTA.

FABHALTA® (iptacopan) capsules, for oral use
Initial U.S. Approval: 2023

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

See full prescribing information for complete boxed warning.

FABHALTA increases the risk of serious and life-threatening infections caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b.

- **Complete or update vaccination for encapsulated bacteria at least 2 weeks prior to the first dose of FABHALTA, unless the risks of delaying FABHALTA 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. (5.1)**
- **Patients receiving FABHALTA 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. (5.1)**

FABHALTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called FABHALTA REMS. (5.2)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	8/2024
Indications and Usage (1.3)	3/2025
Dosage and Administration (2.1)	3/2024

----------INDICATIONS AND USAGE----------

FABHALTA is a complement factor B inhibitor, indicated for:

- the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH). (1.1)
- the reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥ 1.5 g/g. (1.2)
  This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FABHALTA slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.
- the treatment of adults with complement 3 glomerulopathy (C3G), to reduce proteinuria (1.3)

----------DOSAGE AND ADMINISTRATION----------

200 mg orally twice daily with or without food. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 200 mg (3)

----------CONTRAINDICATIONS----------

- Serious hypersensitivity to iptacopan or any of the excipients. (4)
- Initiation in patients with unresolved serious infection caused by encapsulated bacteria. (4)

----------WARNINGS AND PRECAUTIONS----------

- Monitoring of PNH Manifestations After FABHALTA Discontinuation: Monitor for signs of hemolysis after discontinuation. (5.3)
- Hyperlipidemia: Monitor serum lipid parameters periodically during treatment and initiate cholesterol-lowering medication, if indicated. (5.4)

----------ADVERSE REACTIONS----------

- Most common adverse reactions in adults with PNH (incidence ≥ 10%) were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea and rash. (6.1)
- Most common adverse reactions in adults with IgAN (incidence ≥ 5%) were upper respiratory tract infection, lipid disorder, and abdominal pain. (6.1)
- Most common adverse reactions in adults with C3G (incidence ≥ 10%) were nasopharyngitis and viral infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP2C8 inducers (e.g., rifampin): May decrease iptacopan exposure. Monitor for loss of efficacy. (7.1)
- Strong CYP2C8 inhibitors (e.g., gemfibrozil): May increase iptacopan exposure. Coadministration not recommended. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Severe hepatic impairment: Use not recommended. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

FABHALTA, a complement inhibitor, increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, 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 at least 2 weeks prior to the first dose of FABHALTA, unless the risks of delaying therapy with FABHALTA 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 FABHALTA 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, FABHALTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FABHALTA REMS *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria

FABHALTA is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

1.2 Immunoglobulin A Nephropathy

FABHALTA is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FABHALTA slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

1.3 Complement 3 Glomerulopathy

FABHALTA is indicated for the treatment of adults with complement 3 glomerulopathy (C3G), to reduce proteinuria.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis for Encapsulated Bacterial Infections

Vaccinate patients against encapsulated bacteria, including *Streptococcus pneumoniae* and *Neisseria meningitidis (serogroups A, C, W, Y and B),* according to current ACIP recommendations at least 2 weeks prior to initiation of FABHALTA *[see Warnings and Precautions (5.1)]*.

If urgent FABHALTA therapy is indicated in a patient who is not up to date with vaccines for *Streptococcus pneumoniae* and *Neisseria meningitidis* according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible *[see Warnings and Precautions (5.1)]*.

Healthcare providers who prescribe FABHALTA must enroll in the FABHALTA REMS *[see Warnings and Precautions (5.2)]*.

2.2 Recommended Dosage

The recommended dosage of FABHALTA is 200 mg orally twice daily without regard to food.

Swallow capsules whole. Do not open, break, or chew capsules.

If a dose or doses are missed, advise the patient to take one dose of FABHALTA as soon as possible (even if it is soon before the next scheduled dose) and then to resume the regular dosing schedule.

2.3 PNH Patients Switching From Anti-C5 (eculizumab, ravulizumab) to FABHALTA

To reduce the potential risk of hemolysis with abrupt discontinuation of other PNH therapies:

- For patients switching from eculizumab, initiate FABHALTA no later than 1 week after the last dose of eculizumab.
- For patients switching from ravulizumab, initiate FABHALTA no later than 6 weeks after the last dose of ravulizumab.

There is no available information regarding the timeframe for initiation of FABHALTA after other PNH therapies.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 200 mg of iptacopan in pale yellow, opaque, hard gelatin capsules imprinted with “LNP200” on the body and “NVR” on the cap.

4 CONTRAINDICATIONS

FABHALTA is contraindicated:

- in patients with serious hypersensitivity to iptacopan or any of the excipients.
- for initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type b.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections Caused by Encapsulated Bacteria

FABHALTA, a complement inhibitor, increases a patient’s susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis* (caused by any serogroup, including non-groupable strains), 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. The initiation of FABHALTA treatment is contraindicated in patients with unresolved serious infections caused by encapsulated bacteria.

Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to administration of the first dose of FABHALTA, according to the current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with FABHALTA. 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 FABHALTA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria according to ACIP recommendations, provide the patient with 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 FABHALTA. The benefits and risks of treatment with FABHALTA, as well as the benefits and risks of 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 these signs and symptoms occur. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of FABHALTA in patients who are undergoing treatment for serious infections, depending on the risks of interrupting treatment in the disease being treated.

FABHALTA is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 FABHALTA REMS

FABHALTA is available only through a restricted program under a REMS called FABHALTA REMS, because of the risk of serious infections caused by encapsulated bacteria *[see Warnings and Precautions (5.1)]*.

Notable requirements of the FABHALTA 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 according to current ACIP recommendations two weeks prior to the first dose of FABHALTA.
- 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 according to current ACIP recommendations at least two weeks prior to the first dose of FABHALTA.
- Pharmacies that dispense FABHALTA must be certified in the FABHALTA 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 infections.
- Patients must be instructed to carry the Patient Safety Card with them at all times during treatment and for 2 weeks following the last dose of FABHALTA.

Further information is available by telephone: 1-833-99FABHA (1-833-993-2242) or online at www.FABHALTA-REMS.com.

5.3 Monitoring of PNH Manifestations After FABHALTA Discontinuation

In PNH patients, after discontinuing treatment with FABHALTA, closely monitor patients for at least 2 weeks after the last dose for signs and symptoms of hemolysis. These signs include elevated lactate dehydrogenase (LDH) levels along with a sudden decrease in hemoglobin or PNH clone size, fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (such as thrombosis, stroke and myocardial infarction), dysphagia, or erectile dysfunction. If discontinuation of FABHALTA is necessary, consider alternative therapy.

If hemolysis occurs after discontinuation of FABHALTA, consider restarting treatment with FABHALTA, if appropriate, or initiating another treatment for PNH.

5.4 Hyperlipidemia

FABHALTA may increase total cholesterol, LDL-cholesterol, and serum triglycerides *[see Adverse Reactions (6.1)]*.

Of the 54 FABHALTA-treated patients who had a normal total cholesterol level at baseline in APPLY-PNH, 43% developed Grade 1 hypercholesterolemia during the randomized treatment period. One FABHALTA-treated patient in APPLY-PNH experienced increased total cholesterol that worsened to Grade 2 from Grade 1 at baseline.

Of the 34 FABHALTA-treated patients who had a normal cholesterol level at baseline in APPOINT-PNH, 24% developed Grade 1 hypercholesterolemia during the core treatment period.

Of the 60 FABHALTA-treated patients who had LDL-cholesterol ≤ 130 mg/dL at baseline in APPLY-PNH, 17% developed LDL-cholesterol > 130-160 mg/dL, 8% developed LDL-cholesterol > 160-190 mg/dL, and 7% developed LDL-cholesterol > 190 mg/dL during the randomized treatment period. Of the 36 FABHALTA-treated patients who had LDL-cholesterol ≤ 130 mg/dL at baseline in APPOINT-PNH, 11% developed LDL-cholesterol > 130-160 mg/dL and 3% developed LDL-cholesterol > 160-190 mg/dL.

Of the 52 patients with normal triglyceride levels at baseline in APPLY-PNH, 23% developed Grade 1 elevated triglycerides during the randomized treatment period. Three FABHALTA-treated patients in APPLY-PNH experienced an increase in triglycerides from Grade 1 to Grade 2.

Of the 37 FABHALTA-treated patients who had a normal triglyceride level at baseline in APPOINT-PNH, 27% developed Grade 1 elevated triglycerides in the core treatment period.

Of the 102 FABHALTA-treated patients in APPLY-PNH and APPOINT-PNH, two patients required cholesterol-lowering medications.

Monitor serum lipid parameters periodically during treatment with FABHALTA and initiate cholesterol-lowering medication, if indicated.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Infections Caused by Encapsulated Bacteria *[see Warnings and Precautions (5.1)]*.
- Hyperlipidemia *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

The data described below reflects the exposure in adults with PNH who received FABHALTA (n = 62) or anti-C5 treatment (US-approved and non-US-approved eculizumab product or US-approved and non-US-approved ravulizumab product, n = 35) in APPLY-PNH [NCT04558918] and adults who received FABHALTA (n = 40) in APPOINT-PNH [NCT04820530] at the recommended dosing regimen for 24 weeks. In APPLY-PNH, serious adverse reactions were reported in 2 (3%) patients with PNH receiving FABHALTA. Serious adverse reactions included pyelonephritis, urinary tract infection and COVID-19. In APPOINT-PNH, serious adverse reactions were reported in 2 (5%) patients with PNH receiving FABHALTA. Serious adverse reactions included COVID-19 and bacterial pneumonia. The most common adverse reactions (≥ 10%) with FABHALTA were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash.

Table 1 describes the adverse reactions that occurred in > 5% of patients treated with FABHALTA in the APPLY-PNH or APPOINT-PNH studies.

Table 1: Adverse Reactions Reported in > 5% of Patients Treated with FABHALTA in APPLY-PNH or APPOINT-PNH Studies (24-Week Treatment Period)

Adverse reactions	APPLY-PNH		APPOINT-PNH
	FABHALTA (N = 62) n (%)	Anti-C5 (Eculizumab or Ravulizumab) (N = 35) n (%)	FABHALTA (N = 40) n (%)
Headache[a]	12 (19)	1 (3)	11 (28)
Nasopharyngitis[b]	10 (16)	6 (17)	6 (15)
Diarrhea	9 (15)	2 (6)	3 (8)
Abdominal pain[a]	9 (15)	1 (3)	3 (8)
Bacterial infection[c]	7 (11)	4 (11)	2 (5)
Nausea	6 (10)	1 (3)	2 (5)
Viral infection[d]	6 (10)	11 (31)	7 (18)
Arthralgia	5 (8)	1 (3)	0
Thrombocytopenia[a]	4 (6)	0	0
Dizziness	4 (6)	0	1 (3)
Systemic hypertension[a]	4 (6)	0	0
Lipid disorder[e]	4 (6)	0	3 (8)
Rash[f]	2 (3)	0	4 (10)

[a]Includes similar terms.
[b]Nasopharyngitis contains: rhinitis allergic, upper respiratory tract infection, pharyngitis, rhinitis.
[c]Bacterial infection contains: pyelonephritis, urinary tract infection, bronchitis bacterial, bronchitis haemophilus, cholecystitis, folliculitis, cellulitis, arthritis bacterial, sepsis, klebsiella infection, staphylococcal infection, *Pseudomonas* infection, hordeolum, pneumonia bacterial.
[d]Viral infection contains: COVID-19, herpes zoster, oral herpes, nasal herpes, influenza A virus test positive, influenza.
[e]Lipid disorder contains: dyslipidemia, blood cholesterol increased, low density lipoprotein increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia.
[f]Rash contains: dermatitis allergic, acne, erythema multiforme, rash maculo-papular, rash erythematous.

Clinically relevant adverse reactions reported in less than or equal to 5% of patients includes urticaria in one patient (3%) in APPOINT-PNH.

Description of Select Adverse Reactions (graded per NCI CTCAE Version 4.03 unless noted otherwise)

Platelet Count Decreased

Of the 37 FABHALTA-treated patients who had normal platelet counts at baseline in APPLY-PNH, 43% experienced any Grade thrombocytopenia during the randomized treatment period. Three FABHALTA-treated patients in APPLY-PNH experienced decreased platelets that worsened to Grade ≥ 3 from baseline (one patient with normal platelets that worsened to Grade 4, one patient with baseline Grade 1 that worsened to Grade 4, and one patient with baseline Grade 3 that worsened to Grade 4).

Immunoglobulin A Nephropathy (IgAN)

The safety of FABHALTA was evaluated in APPLAUSE-IgAN, a randomized placebo-controlled, double-blind clinical study in adults with IgAN (eGFR ≥ 20 mL /min/1.73 m^2 at baseline).

The data below reflect FABHALTA exposure in 235 patients with IgAN (eGFR ≥ 20 mL/min/1.73 m^2 at baseline) with a median duration of 43 weeks (up to 104 weeks) in APPLAUSE-IgAN. Table 2 describes the adverse reactions that occurred in ≥ 3 % of patients treated with FABHALTA and were ≥ 2% higher in frequency than placebo. All of these adverse reactions were mild or moderate in severity.

Table 2: Adverse Reactions Reported in ≥ 3% of Adult Patients with IgAN (eGFR ≥ 20 mL /min/1.73 m^2) Treated with FABHALTA and ≥ 2% Higher in Frequency Than Placebo in APPLAUSE-IgAN

Adverse reaction	**FABHALTA (N = 235) n (%)**	**Placebo (N = 235) n (%)**
Upper respiratory tract infection	20 (9)	16 (7)
Lipid disorder[1]	15 (6)	10 (4)
Abdominal pain[1]	15 (6)	5 (2)
Nausea	8 (3)	2 (1)
Dizziness	7 (3)	2 (1)
[1] Includes similar terms.		

Complement 3 Glomerulopathy (C3G)

The safety of FABHALTA was evaluated in APPEAR-C3G, a randomized, placebo-controlled, double-blind trial in adult patients with native kidney C3G. No new adverse reactions were identified during the 6-month placebo-controlled period of APPEAR-C3G, in which 38 patients were treated with FABHALTA and 36 patients were treated with placebo. The most common adverse reactions that occurred in ≥ 10% of patients treated with FABHALTA and were ≥ 5% higher in frequency than placebo were nasopharyngitis (11% in FABHALTA, 3% placebo) and viral infections (29% in FABHALTA, 22% placebo), mainly respiratory infections. One patient (3%) on FABHALTA and none on placebo had a serious adverse reaction of pneumonia and bacteremia secondary to an encapsulated organism (*S. pneumoniae*).

7 DRUG INTERACTIONS

7.1 CYP2C8 Inducers

Concomitant use of CYP2C8 inducers (e.g., rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy of FABHALTA. Monitor the clinical response and discontinue use of the CYP2C8 inducer if loss of efficacy of FABHALTA is evident.

7.2 Strong CYP2C8 Inhibitors

Concomitant use of strong CYP2C8 inhibitors (e.g., gemfibrozil) may increase iptacopan exposure, which may result in an increased risk for adverse reactions with FABHALTA. Coadministration with a strong CYP2C8 inhibitor is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from clinical trials with FABHALTA use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH, IgAN, or C3G in pregnancy *(see Clinical Considerations)*. The use of FABHALTA in pregnant women or women planning to become pregnant may be considered following an assessment of the risks and benefits.

In animal reproduction studies, oral administration of iptacopan to pregnant rats and rabbits during organogenesis at exposures 4- to 6-times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 200 mg twice daily did not induce embryo or fetal toxicity *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of major birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombosis, infections, bleeding, miscarriages, increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

IgAN in pregnancy is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight.

C3G in pregnancy may be associated with adverse maternal outcomes, in particular preeclampsia and miscarriage, as well as adverse fetal outcomes including prematurity and low birth weight.

Data

Animal Data

In an embryo-fetal development study in rats, oral administration of iptacopan during organogenesis did not cause embryo-fetal toxicity when given up to the highest dose of 1,000 mg/kg/day, which corresponds to 4-times the MRHD based on AUC.

In an embryo-fetal development study in rabbits, oral administration of iptacopan during organogenesis did not cause embryo-fetal toxicity when given up to the highest dose of 450 mg/kg/day, which corresponds to 6-times the MRHD based on AUC.

In a pre- and postnatal development study in rats, oral administration of iptacopan during gestation, parturition, and lactation did not cause adverse effects in offspring when given up to the highest dose of 1,000 mg/kg/day, which corresponds to 4-times the MRHD based on AUC.

8.2 Lactation

Risk Summary

There are no data on the presence of iptacopan or its metabolites in either human or animal milk, the effects on the breastfed child or on milk production. Since many medicinal products are secreted into human milk, and because of the potential for serious adverse reactions in a breastfed child, breastfeeding should be discontinued during treatment and for 5 days after the final dose.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients with PNH, IgAN, or C3G have not been established.

8.5 Geriatric Use

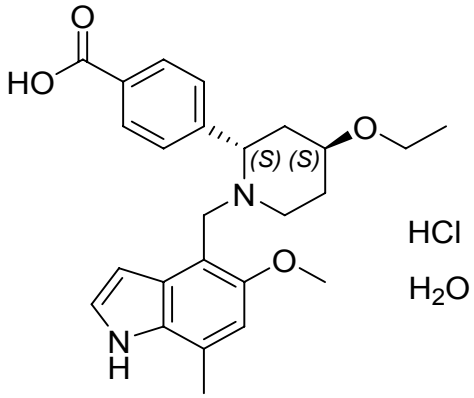
There were 29 PNH patients 65 years of age and older in APPLY-PNH and APPOINT-PNH *[see Clinical Studies (14)]*. Of the total number of FABHALTA-treated patients during the 24-week treatment period in these studies, 21 (20.6%) were 65 years of age and older, while 7 (6.9%) were 75 years of age and older. There were 8 IgAN patients 65 years of age and older in APPLAUSE-IgAN *[see Clinical Studies (14)]*. Of the total number of FABHALTA-treated patients, 3 (2.4%) were 65 years of age and older. Clinical studies of FABHALTA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients.

8.7 Hepatic Impairment

The use of FABHALTA is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

FABHALTA contains iptacopan, a complement Factor B inhibitor. The molecular weight of iptacopan hydrochloride monohydrate is approximately 477 g/mol. The chemical name is (2*S*,4*S*)-2-(4-Carboxyphenyl)-4-ethoxy-1-[(5-methoxy-7-methyl-1*H*-indol-4-yl)methyl]piperidin-1-ium chloride—water (1/1). The molecular formula is $C_{25}H_{30}N_2O_4 \cdot HCl\ H_2O$. The structure is shown below.



Iptacopan hydrochloride monohydrate is a white or almost white to pale purplish-pink powder.

FABHALTA is supplied as hard gelatin capsules for oral administration. The capsules are packaged in high-density polyethylene (HDPE) bottles with induction seals and child resistant caps. Each FABHALTA capsule contains 200 mg iptacopan (provided as 225.8 mg iptacopan hydrochloride monohydrate) and the capsule shell contains the following inactive ingredients: gelatin, red ferric oxide, titanium dioxide, yellow ferric oxide. The black printing ink contains ferrosoferric oxide, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Iptacopan binds to Factor B of the alternative complement pathway and regulates the cleavage of C3, generation of downstream effectors, and the amplification of the terminal pathway.

In PNH, intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC), while extravascular hemolysis (EVH) is facilitated by C3b opsonization. Iptacopan acts proximally in the

alternative pathway of the complement cascade to control both C3b-mediated EVH and terminal complement-mediated IVH.

In IgAN, the deposition of galactose deficient IgA1 (Gd-IgA1) containing immune complexes in the kidney locally activates the alternative complement pathway which is thought to contribute to the pathogenesis of IgAN. By binding to Factor B, iptacopan inhibits the alternative pathway.

In C3G, overactivation of the alternative complement pathway leads to C3 cleavage within the glomeruli resulting in C3 deposition and inflammation, which are thought to contribute to the pathogenesis of C3G. By binding to Factor B, iptacopan inhibits the alternative pathway.

12.2 Pharmacodynamics

Inhibition of the alternative complement pathway biomarkers, the *in vitro* alternative pathway assay and plasma Bb (fragment Bb of Factor B), started approximately 2 hours after a single iptacopan dose in healthy volunteers.

In PNH patients receiving concomitant anti-C5 treatment and FABHALTA 200 mg twice daily, the *in vitro* alternative pathway assay and plasma Bb decreased from baseline by 54.1% and 56.1%, respectively, on the first observation on Day 8. In treatment naïve PNH patients, these same biomarkers decreased from baseline by 78.4% and 58.9%, respectively, on the first observation after 4 weeks of treatment with FABHALTA 200 mg twice daily.

In PNH patients on concomitant anti-C5 treatment and FABHALTA 200 mg twice daily, the mean PNH red blood cell (RBC) clone size was 54.8% at baseline and increased to 89.2% after 13 weeks; the proportion of PNH Type II + III RBCs with C3 deposition was 12.4% at baseline and decreased to 0.2% after 13 weeks. In treatment naïve PNH patients, the mean PNH RBC clone size was 49.1% at baseline and increased to 91.1% after 12 weeks; there were negligible PNH Type II + III RBCs with C3 deposition in this population due to the predominance of IVH.

Iptacopan reduces serum LDH levels. In PNH patients previously treated with eculizumab, all patients treated with FABHALTA 200 mg twice daily achieved a reduction of LDH levels to < 1.5 times the upper limit of normal (ULN) at 13 weeks. In treatment naïve PNH patients, FABHALTA 200 mg twice daily reduced LDH by > 60% compared to baseline after 12 weeks and maintained the effect through the end of the study at 2 years.

In IgAN patients receiving 200 mg twice daily, the *in vitro* alternative pathway assay, plasma Bb, plasma soluble C5b-9 (also known as MAC), and urine soluble C5b-9 decreased from baseline by 85.2%, 17.5%, 19.5% and 96.5%, respectively, on the first observation at Month 9.

In C3G patients receiving 200 mg twice daily, the geometric mean serum C3 at baseline was 23 mg/dL and increased to 80 mg/dL at Day 14 of FABHALTA treatment. Over this same period, the placebo group geometric mean serum C3 level decreased from 25 mg/dL to 24 mg/dL. At 6 months the mean glomerular C3 deposition score (0-12) decreased by 0.8 (95% CI: -0.3, 1.8) from a baseline of 9.2 with FABHALTA and increased by 1.1 (95% CI: 0.1, 2.1) from a baseline of 9.6 with placebo. Plasma soluble C5b-9 (also known as MAC) and urine soluble C5b-9 decreased from baseline by 67% and 88%, respectively, at Day 180 of treatment with FABHALTA 200 mg twice daily compared to a 3% decrease in plasma soluble C5b-9 and a 36% decrease in urine soluble C5b-9 in the placebo group.

Cardiac Electrophysiology

In a QTc clinical study in healthy volunteers, single supra-therapeutic iptacopan doses up to 1,200 mg (which provided greater than 4-fold peak concentration of the MRHD) showed no effect on cardiac repolarization or QT interval.

12.3 Pharmacokinetics

Absorption

Following oral administration, iptacopan reached peak plasma concentrations approximately 2 hours post dose. At the recommended dosing regimen of 200 mg twice daily, steady state is achieved in approximately 5 days with minor accumulation (1.4-fold).

Effect of Food

Based on a food-effect study in healthy volunteers, a high-fat meal did not affect the exposure of iptacopan to a clinically meaningful degree.

Distribution

Iptacopan showed concentration-dependent plasma protein binding due to binding to the target Factor B in the systemic circulation. Iptacopan was 75% to 93% protein bound *in vitro* at the relevant clinical plasma concentrations. After administration of iptacopan 200 mg twice daily, the apparent volume of distribution at steady state was approximately 288 L.

Elimination

The terminal half-life ($t_{1/2}$) of iptacopan at steady state is approximately 25 hours after administration of FABHALTA 200 mg twice daily. The apparent clearance of iptacopan at steady state is 8 L/h after administration of FABHALTA 200 mg twice daily.

Metabolism

Metabolism is a predominant elimination pathway for iptacopan with approximately 50% of the dose attributed to oxidative pathways. Metabolism of iptacopan includes N-dealkylation, O-deethylation, oxidation, and dehydrogenation, mostly driven by CYP2C8 (98%) with a small contribution from CYP2D6 (2%). Iptacopan undergoes Phase 2 metabolism through glucuronidation by UGT1A1, UGT1A3, and UGT1A8. In plasma, iptacopan was the major component, accounting for 83% of the drug-related species. Two acyl glucuronides were the only metabolites detected in plasma and were minor, accounting for 8% and 5% of the drug-related species. Iptacopan metabolites are not pharmacologically active.

Excretion

In a human study, following a single 100 mg oral dose of [^{14}C]-iptacopan, mean total excretion of radioactivity (iptacopan and metabolites) was 72% in the feces and 25% in the urine, for a total mean excretion of > 96% of the dose. Specifically, 18% of the dose was excreted as parent iptacopan in the urine, and 17% of the dose was excreted as parent iptacopan in feces.

Linearity/Non-linearity

At doses between 25 mg and 200 mg twice daily, iptacopan was overall less than dose proportional. However, oral doses of 100 mg and 200 mg were approximately dose proportional.

Specific Populations

A population pharmacokinetic (PK) analysis was conducted on iptacopan data from 234 patients. Age, body weight, race, and gender did not have a clinically significant effect on iptacopan PK.

Patients with Renal Impairment

There were no clinically significant differences in the exposure of FABHALTA between patients with an eGFR in the range of 25 to <90 mL/min compared to those with normal eGFR. No data are currently available in patients on dialysis.

Patients with Hepatic Impairment

In a study in subjects with normal hepatic function and patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), or severe hepatic impairment (Child-Pugh class C), there was a negligible effect of hepatic impairment on the total (bound+unbound) exposure of iptacopan. However, unbound iptacopan AUC_{inf} increased by 48%, 58% and 271% in patients with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function.

Drug Interaction Studies

Based on a clinical drug interaction study in healthy volunteers, iptacopan exposure did not change to a clinically relevant degree when coadministered with clopidogrel (a moderate CYP2C8 inhibitor) or cyclosporine (a P-gp, BCRP, and OATP 1B1/1B3 inhibitor). The exposure of digoxin (a P-gp substrate) and rosuvastatin (an OATP substrate) did not change to a clinically relevant degree when coadministered with iptacopan.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Iptacopan was not genotoxic or mutagenic in a battery of *in vitro* and *in vivo* assays.

Carcinogenicity studies conducted with oral administration of iptacopan in RasH2 transgenic mice with doses up to 1,000 mg/kg/day for 6 months and in rats with doses up to 750 mg/kg/day for 2 years did not identify any carcinogenic potential. The highest exposure to iptacopan in rats corresponds to approximately 9-times the MRHD based on AUC.

In a fertility study in male rats, iptacopan did not adversely impact fertility up to the highest tested dose of 750 mg/kg/day, which corresponds to 4-times the MRHD based on AUC. Reversible effects on the male reproductive system (testicular tubular degeneration and cellular debris in epididymis) were observed in repeat-dose toxicity studies with oral administration in dogs at doses ≥ 2-times the MRHD based on AUC, with no clear effects on sperm numbers, morphology, or motility. In a fertility and early embryonic developmental study in female rats, oral administration of iptacopan caused increased pre- and post-implantation losses when given at the highest dose of 1,000 mg/kg/day orally, which corresponds to approximately 11-times the MRHD based on AUC.

14 CLINICAL STUDIES

14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

APPLY-PNH: Anti-C5 Treatment Experienced Patients With PNH

The efficacy of FABHALTA administered orally in adults with PNH was evaluated in a multi-center, open-label, 24-week, active comparator-controlled trial (APPLY-PNH; NCT04558918).

The study enrolled adults with PNH and residual anemia (hemoglobin < 10 g/dL) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization.

Ninety-seven patients were randomized in an 8:5 ratio to switch to FABHALTA 200 mg orally twice daily (n = 62) or to continue anti-C5 treatment (US-approved and non-US-approved eculizumab product n = 23 or US-approved and non-US-approved ravulizumab product n = 12) throughout the duration of the 24-week randomized controlled period. Randomization was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months. Following completion of the 24-week randomized controlled period, all patients were eligible to enroll in a 24-week treatment extension period and receive FABHALTA monotherapy. Subsequently, patients were eligible to enter a separate long-term extension study.

Patients were required to be vaccinated against *Neisseria meningitidis* and recommended to be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. If the patient had not been previously vaccinated or if a booster was required, vaccination was administered at least 2 weeks prior to the first dose of study medication. If FABHALTA treatment was initiated earlier than 2 weeks after vaccination, antibacterial drug prophylaxis was administered.

Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 3). The mean time on prior anti-C5 treatment was 3.8 and 4.2 years for the FABHALTA and anti-C5

groups, respectively. The baseline mean PNH RBC clone size (Type II + III) was 64.6% for the FABHALTA group and 57.4% for the anti-C5 group.

Table 3: Patient Baseline Demographics and Characteristics in APPLY-PNH

Parameters	**Statistics**	**FABHALTA (n = 62)**	**Anti-C5 (Eculizumab or Ravulizumab) (n = 35)**
Age (years)	Mean (SD) min, max	51.7 (16.9) 22, 84	49.8 (16.7) 20, 82
Sex Female	 n (%)	 43 (69.4)	 24 (68.6)
Race White Asian Black or African American	 n (%) n (%) n (%)	 48 (77.4) 12 (19.4) 2 (3.2)	 26 (74.3) 7 (20.0) 2 (5.7)
Ethnicity Not Hispanic or Latino Hispanic or Latino Not reported/unknown	 n (%) n (%) n (%)	 51 (82.3) 8 (12.9) 3 (4.8)	 27 (77.1) 2 (5.7) 6 (17.1)
Hemoglobin level (g/dL)	Mean (SD)	8.9 (0.7)	8.9 (0.9)
LDH level (U/L)	Mean (SD)	269 (70)	273 (85)
Absolute reticulocyte count (ARC) (10^9/L)	Mean (SD)	193 (84)	191 (81)
At least one transfusion in 6 months prior to randomization	n (%)	35 (56.5)	21 (60.0)
History of MAVEs	n (%)	12 (19.4)	10 (28.6)
Disease duration (years)	Mean (SD)	11.9 (9.8)	13.5 (10.9)

Abbreviations: LDH, lactate dehydrogenase; MAVEs, major adverse vascular events (includes thrombosis, stroke and myocardial infarction); SD, standard deviation.

Efficacy was established based on demonstration of superiority of switching to FABHALTA compared to continuing on anti-C5 therapy in achieving hematological response after 24 weeks of treatment, without a need for transfusion, by assessing the proportion of patients demonstrating: 1) sustained increase of ≥ 2 g/dL in hemoglobin levels from baseline (hemoglobin improvement) and 2) sustained hemoglobin levels ≥ 12 g/dL. Additional efficacy endpoints included transfusion avoidance, change from baseline in hemoglobin levels and change from baseline in absolute reticulocyte counts.

The efficacy results from the APPLY-PNH trial are provided in Table 4.

Table 4: Efficacy Results for the 24-week Randomized Treatment Period for APPLY-PNH

Endpoints	**FABHALTA (N = 62)**	**Anti-C5 (Eculizumab or Ravulizumab) (N = 35)**	**Difference (95% CI) p-value**
Primary endpoints			

Patients with sustained increase of hemoglobin levels ≥ 2 g/dL[a] from baseline in the absence of transfusions Response rate (%) (95% CI)	51/62 82.3 (70.5, 90.8)	0/35 0 (0, 10.0)	 81.5[b] (71.6, 91.4) < 0.0001
Patients with sustained hemoglobin level ≥ 12 g/dL[a] in the absence of transfusions Response rate (%) (95% CI)	42/62 67.7 (54.7, 79.1)	0/35 0 (0, 10.0)	 66.6[b] (54.6, 78.6) < 0.0001
Secondary endpoints			
Patients avoiding transfusion[c,d] Transfusion avoidance rate (%) (95% CI)	59/62 95.2 (86.5, 99.0)	16/35 45.7 (28.8, 63.4)	 49.5[b] (32.5, 66.6) < 0.0001
Hemoglobin change from baseline (g/dL) (adjusted mean[e,f]) (95% CI)	3.6 (3.3, 3.9)	-0.1 (-0.5, 0.3)	3.7 (3.2, 4.1) < 0.0001
Absolute reticulocyte count change from baseline (10^9/L) (adjusted mean[e]) (95% CI)	-116 (-127, -105)	0 (-13, 14)	-116 (-132, -100) < 0.0001

Abbreviations: RR, rate ratio.
[a]Assessed between Day 126 and 168.
[b]Adjusted difference in proportion.
[c]Assessed between Day 14 and 168.
[d]Transfusion avoidance is defined as absence of administration of packed-red blood cell transfusions between Day 14 and 168.
[e]Adjusted mean assessed between Day 126 and 168.
[f]Excludes values within 30 days post-transfusion.

APPOINT-PNH: Complement Inhibitor Naïve Patients with PNH

Study APPOINT-PNH (NCT04820530) is a single arm study in adults with PNH who were not previously treated with a complement inhibitor. This study enrolled a total of 40 adults with PNH (RBC clone size ≥ 10%), hemoglobin < 10 g/dL, and LDH > 1.5 times upper limit of normal (ULN). All 40 patients received FABHALTA 200 mg orally twice daily during the 24-week open-label core treatment period. Subsequently, patients were eligible to enroll in a 24-week treatment extension period and continue to receive FABHALTA, followed by a separate long-term extension study.

The mean age of the patients was 42.1 years and 42.5% were female. The mean disease duration was 4.7 years. The baseline mean PNH RBC clone size (Type II + III) was 42.7%, mean baseline hemoglobin was 8.2 g/dL, and approximately 70% of patients required a transfusion in the 6 months prior to treatment. The baseline mean LDH level was 1,699 U/L and the mean absolute reticulocyte count was 154 X 10^9/L. About 13% of patients had a history of MAVEs. No patients discontinued from the core treatment period of the study.

In total, 77.5% (95% CI: 61.5%, 89.2%) of patients (31/40) achieved a sustained increase (between Day 126 and Day 168) in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of RBC transfusions, based on central laboratory hemoglobin values. In a sensitivity analysis, 87.5% (95% CI: 73.2%, 95.8%) of patients (35/40) achieved a sustained increase (between Day 126 and Day 168) in hemoglobin levels from baseline of

≥ 2 g/dL in the absence of RBC transfusions, including local laboratory hemoglobin values when central laboratory hemoglobin values were not available.

14.2 Immunoglobulin A Nephropathy (IgAN)

The effect of FABHALTA was evaluated in a multicenter, randomized, placebo-controlled, double-blind study (APPLAUSE-IgAN, NCT04578834) in adults with biopsy-proven IgAN, eGFR ≥ 20 mL/min/1.73 m^2, and urine protein-to-creatinine ratio (UPCR) ≥1 g/g on a stable dose of maximally-tolerated renin-angiotensin system (RAS) inhibitor therapy with or without a stable dose of an SGLT2 inhibitor. Patients with other glomerulopathies or those who had been recently treated with systemic immunosuppressants were excluded. Patients were included in either the Main Study Population (eGFR ≥ 30 mL/min/1.73 m^2) or the Severe Renal Impairment population (eGFR ≥ 20 and < 30 mL/min/1.73 m^2). Within each group, patients were randomized (1:1) to either FABHALTA 200 mg or placebo twice daily. Rescue immunosuppressive treatment could be initiated per investigator discretion during the trial.

Patients were required to be vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae* and were recommended to be vaccinated against *Haemophilus influenzae* type b. If the patient had not been previously vaccinated or if a booster was required, vaccination was administered at least 2 weeks prior to first dosing. If FABHALTA treatment was initiated earlier than 2 weeks after vaccination, antibacterial drug prophylaxis was administered.

The efficacy analysis was based on the first 250 patients with an eGFR ≥ 30 mL/min/1.73 m^2 (Main Study Population), who had completed or discontinued the study prior to the Month 9 visit. At baseline, the mean age of these patients was 39 years (range 18 to 74 years); 52% were male, 44% White, 54% Asian, and < 1% Black or African American; the mean eGFR was 64 mL/min/1.73 m^2; the geometric mean UPCR (sampled from a 24-hr urine collection) was 2.0 g/g, and 12% had a UPCR ≥ 3.5 g/g. At baseline, 99% of patients were treated with an ACEi or ARB and 13% were on an SGLT2i. Approximately 59% had a history of hypertension, 6% had a history of type 2 diabetes, and 75% had hematuria based on urine dipstick.

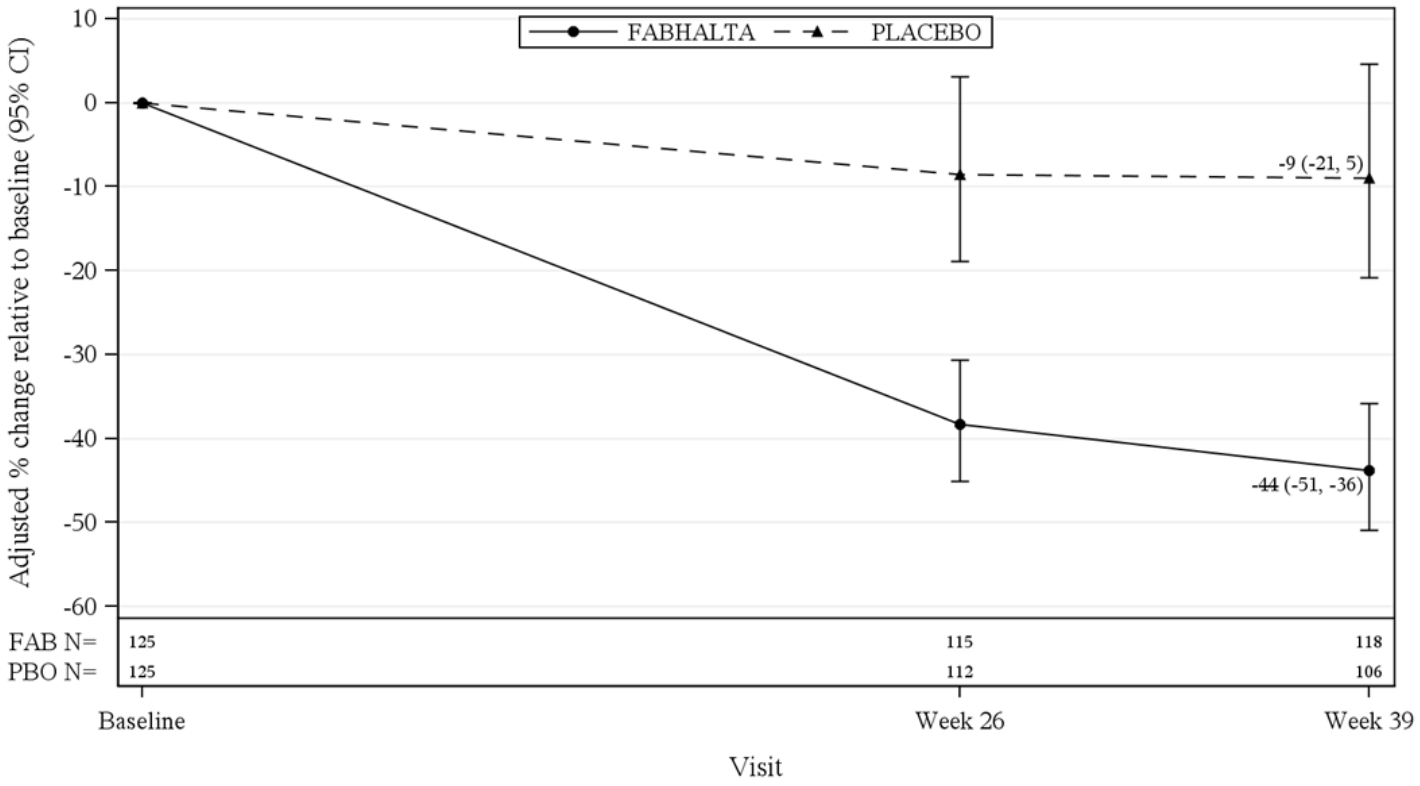
The primary endpoint was the percent reduction in UPCR (sampled from a 24-hr urine collection) at Month 9 relative to baseline (see Table 5). The mean percent change from baseline in UPCR over time is shown in Figure 1.

Table 5: Percent Reduction in UPCR at Month 9 in APPLAUSE-IgAN

	FABHALTA (N = 125)	**Placebo (N = 125)**
Geometric mean of UPCR, g/g Baseline Month 9	 1.9 (n = 125) 1.0 (n = 119)	 2.0 (n = 125) 1.7 (n = 110)
% reduction in UPCR at Month 9 relative to baseline (95% CI)[a]	44% (36%, 51%)	9% (-5%, 21%)
FABHALTA versus placebo: % reduction in UPCR at Month 9 relative to baseline (95% CI)[a]	38% (26%, 49%)	
p-value[b]	< 0.0001	

[a] Percent reduction in UPCR was obtained from the adjusted geometric mean ratios where the log transformed ratio to baseline in UPCR (sampled from 24hr urine collection) was analyzed using an MMRM; Values after taking rescue immunosuppressive treatment for IgAN were imputed to reflect disease worsening. Rescue immunosuppressive treatment for IgAN was initiated in 0 and 7 (5.6%) patients in the FABHALTA and placebo group up to Month 9, respectively.
[b] One-sided p-value statistically significant at the 0.005 level.
Abbreviations: CI, confidence interval; IgAN, immunoglobulin A nephropathy; MMRM, mixed model of repeated measures; N, number of subjects in each group; n, number of subjects with available data at the time of analysis; UPCR, urine protein-to-creatinine ratio

Figure 1: Geometric Mean Percent Change from Baseline in UPCR by Visit in APPLAUSE-IgAN



Adjusted % change relative to baseline in UPCR were obtained by analyzing the log transformed ratio to baseline in UPCR using an MMRM as described in Table 5. N represents the number of subjects with values non-missing/not imputed as per the intercurrent event handling strategy by visit and treatment group.

Abbreviations: CI, confidence interval; FAB, FABHALTA; MMRM, mixed model repeated measures; N, number of subjects in each group; PBO, placebo; UPCR, urine protein-to-creatinine ratio.

The treatment effect on UPCR at Month 9 was consistent across all subgroups including age, sex, race, baseline disease characteristics (such as baseline eGFR and proteinuria levels), and the use of SGLT2i.

14.3 Complement 3 Glomerulopathy (C3G)

The efficacy of FABHALTA in reducing proteinuria in adult patients with native kidney C3G was demonstrated in the APPEAR-C3G trial. Safety and effectiveness of FABHALTA in patients with recurrent C3G following kidney transplant have not been established.

APPEAR-C3G was a randomized, double-blind, placebo-controlled study in 74 adult patients with biopsy confirmed native kidney C3G who had a urine protein-to-creatinine ratio (UPCR) ≥ 1 g/g and eGFR ≥ 30 mL/min/1.73 m^2 (NCT04817618). Patients were randomized (1:1) to receive either FABHALTA 200 mg orally twice daily (N = 38) or placebo (N = 36) for 6 months, followed by a 6-month open-label treatment period in which all patients received FABHALTA 200 mg orally twice daily.

Patients were required to be on a maximally tolerated renin-angiotensin system (RAS) inhibitor and could be on a corticosteroid and/or mycophenolate mofetil/sodium (MMF/MPS) at baseline. All background therapies (i.e., RAS inhibitors, corticosteroids and MMF/MPS) were required to be at stable doses for 90 days prior to randomization and throughout the study. Randomization was stratified according to whether patients were receiving concomitant immunosuppressive therapy.

Patients were required to be vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae* and were recommended to be vaccinated against *Haemophilus influenzae* type b. If the patient had not been previously vaccinated or if a booster was required, vaccination was administered at least 2 weeks prior to first dosing. If

FABHALTA treatment was initiated earlier than 2 weeks after vaccination, antibacterial drug prophylaxis was administered.

At baseline, the mean age of patients was 28 years (range 18 to 60 years), 64% were male, 69% were White, 24% were Asian, and 9% were Hispanic or Latino. The mean baseline eGFR (mL/min/1.73 m^2) was 89 and 99 in the FABHALTA and placebo groups, respectively, and the geometric mean 24-hour UPCR (g/g) at baseline was 3.3 and 2.6 in the FABHALTA and placebo groups, respectively.

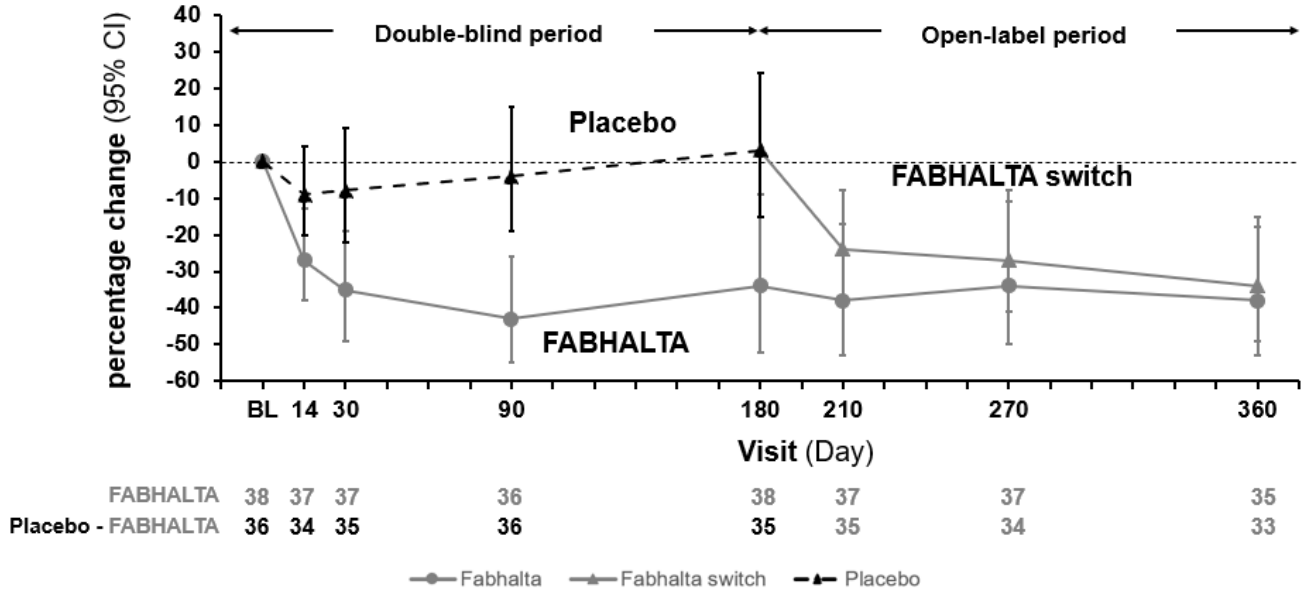
Twenty four percent of patients in the FABHALTA group and 3% in the placebo group had dense deposit disease. Baseline use of corticosteroids and/or MMF/MPS, and RAS inhibitor was balanced among the FABHALTA and placebo groups. Overall, 45% of patients were on corticosteroids and/or MMF/MPS, and 99% of patients were on a RAS inhibitor at baseline.

The primary efficacy endpoint was the log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine collection) at 6 months. At 6 months, the geometric mean UPCR ratio relative to baseline was 0.70 (95% CI: 0.57, 0.85) and 1.08 (95% CI: 0.88, 1.31) in the FABHALTA and placebo groups, respectively, resulting in a 35% reduction in 24-hour UPCR from baseline in the FABHALTA group compared to placebo (p = 0.0028).

Following the initial 6-month treatment period, all patients were treated with FABHALTA for an additional 6 months. In patients initially randomized to FABHALTA, the reduction in 24-hour UPCR seen at 6 months was maintained at Month 12. In patients who switched from placebo to FABHALTA, the magnitude of the reduction in 24-hour UPCR from Month 6 to 12 was similar to the reduction seen in patients initially randomized to FABHALTA. The geometric mean percent change from baseline in UPCR (measured as first morning void [FMV]) over time is shown in Figure 2.

Compared to patients treated with placebo, patients treated with FABHALTA had a 7-fold higher odds (p = 0.0166) of achieving a composite renal endpoint defined as a ≥ 50% reduction in 24-hour UPCR compared to baseline and stable or improved eGFR compared to baseline [≤ 15% reduction in eGFR] at 6 months. Although a greater proportion of patients in the FABHALTA arm (30%) as compared to placebo (6%) achieved a ≥ 50% reduction in 24-hour UPCR compared to baseline, there was no difference between arms in the proportion of patients with stable or improved eGFR compared to baseline at 6 months (90% in FABHALTA vs 89% in placebo).

Figure 2: Geometric Mean Percent Change from Baseline in UPCR FMV (g/g) up to Month 12 (APPEAR-C3G)



The treatment effect of FABHALTA on UPCR at Month 6 was generally consistent across subgroups including age, sex, race, baseline disease characteristics (such as baseline proteinuria and eGFR levels) and use of immunosuppressive therapies.

16 HOW SUPPLIED/STORAGE AND HANDLING

200 mg capsules: pale yellow opaque hard capsules, imprinted with "LNP200" on one half and "NVR" on the other half, packaged in a high-density polyethylene (HDPE) bottle with induction seal and child-resistant cap. Each bottle contains 60 capsules (NDC 0078-1189-20).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Serious Infections Caused by Encapsulated Bacteria

Advise patients of the risk of serious infection. Inform patients of the need to complete or update their vaccinations against encapsulated bacteria at least 2 weeks prior to receiving the first dose of FABHALTA or to receive antibacterial drug prophylaxis if FABHALTA treatment must be initiated immediately and they have not been previously vaccinated. Inform patients of the requirement to be revaccinated according to current ACIP recommendations for encapsulated bacteria while on FABHALTA therapy *[see Warnings and Precautions (5.1)]*.

Inform patients that vaccination may not prevent serious infection and to seek immediate medical attention if the following signs or symptoms occur *[see Warnings and Precautions (5.1)]*:

- fever with or without shivers or chills
- fever and a rash
- fever with chest pain and cough
- fever with breathlessness/fast breathing
- fever with high heart rate
- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- confusion
- body aches with flu-like symptoms
- clammy skin
- eyes sensitive to light

Inform patients that they will be given a Patient Safety Card for FABHALTA that they should carry with them at all times during and for 2 weeks following treatment with FABHALTA. This card describes symptoms which, if experienced, should prompt the patient to seek immediate medical evaluation.

FABHALTA REMS

FABHALTA is available only through a restricted program called FABHALTA REMS *[see Warnings and Precautions (5.2)]*.

Inform the patient of the following notable requirements:

- Patients must receive counseling about the risk of serious infections caused by encapsulated bacteria.
- Patients must receive written educational materials about this risk.
- Patients must be instructed to carry the Patient Safety Card with them at all times during and for 2 weeks following treatment with FABHALTA.

- Patients must be instructed to complete or update vaccines against encapsulated bacteria per ACIP recommendations as directed by the prescriber prior to treatment with FABHALTA.
- Patients must receive antibiotics as directed by the prescriber if they are not up to date on vaccinations against encapsulated bacteria and have to start FABHALTA right away.

Importance of Adherence to Dosing Schedule

Inform patients with PNH of the importance of taking FABHALTA as prescribed in order to minimize the risk of hemolysis.

Discontinuation

Inform patients with PNH that they may develop serious hemolysis due to PNH if FABHALTA is discontinued and that they should be monitored by their healthcare providers for at least 2 weeks following discontinuation of FABHALTA.

Inform patients who discontinue FABHALTA to keep the Patient Safety Card with them for 2 weeks after the last dose of FABHALTA. The increased risk of serious infection may continue for a few weeks after the last dose of FABHALTA.

Hyperlipidemia

Inform patients that FABHALTA may increase their cholesterol and triglycerides and that monitoring of these parameters will be needed periodically during treatment.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

For more information, visit www.FABHALTA.com or call 1-888-669-6682.

MEDICATION GUIDE
FABHALTA® (fab hal tah)
(iptacopan)
capsules, for oral use

What is the most important information I should know about FABHALTA?

FABHALTA is a medicine that affects part of your immune system. FABHALTA may lower the ability of your immune system to fight infections.

- **FABHALTA increases your chance of getting serious infections caused by encapsulated bacteria**, including *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* type b**.** These serious infections may quickly become life-threatening or fatal if not recognized and treated early.
  - You must complete or update your vaccinations against *Streptococcus pneumoniae* and *Neisseria meningitidis* at least 2 weeks before your first dose of FABHALTA.
  - If you have not completed your vaccinations and FABHALTA must be started right away, you should receive the required vaccinations as soon as possible.
  - If you have not been vaccinated and FABHALTA must be started right away, you should also receive antibiotics to take for as long as your healthcare provider tells you.
  - If you have been vaccinated against these bacteria in the past, you might need additional vaccinations before starting FABHALTA. Your healthcare provider will decide if you need additional vaccinations.
  - Vaccines do not prevent all infections caused by encapsulated bacteria. **Call your healthcare provider or get emergency medical care right away if you have any of these signs and symptoms of a serious infection:**
    - fever with or without shivers or chills
    - fever with chest pain and cough
    - fever with high heart rate
    - headache and fever
    - confusion
    - clammy skin
    - fever and a rash
    - fever with breathlessness or fast breathing
    - headache with nausea or vomiting
    - headache with stiff neck or stiff back
    - body aches with flu-like symptoms
    - eyes sensitive to light

Your healthcare provider will give you a Patient Safety Card about the risk of serious infections. Carry it with you at all times during treatment and for 2 weeks after your last dose of FABHALTA. Your risk of serious infections may continue for a few weeks after your last dose of FABHALTA. It is important to show this card to any healthcare provider who treats you. This will help them diagnose and treat you quickly.

FABHALTA is only available through a program called the FABHALTA Risk Evaluation and Mitigation Strategy (REMS). Before you can take FABHALTA, your healthcare provider must:

- enroll in the FABHALTA REMS program
- counsel you about the risk of serious infections caused by certain bacteria
- give you information about the symptoms of serious infections
- make sure that you are vaccinated against serious infections caused by encapsulated bacteria and that you receive antibiotics if you need to start FABHALTA right away and you are not up to date on your vaccinations
- give you a **Patient Safety Card** about your risk of serious infections, as discussed above

For more information about side effects, see **"What are the possible side effects of FABHALTA?"**

What is FABHALTA?

FABHALTA is a prescription medicine used to:

- treat adults with a disease called paroxysmal nocturnal hemoglobinuria (PNH).
- reduce levels of protein in the urine (proteinuria) in adults with a kidney disease called primary immunoglobulin A nephropathy (IgAN), who are at risk of their disease progressing quickly.
- treat adults with a kidney disease called complement 3 glomerulopathy (C3G), to reduce levels of protein in the urine (proteinuria).

It is not known if FABHALTA is safe and effective in children with PNH, IgAN, or C3G.

Who should not take FABHALTA?

Do not take FABHALTA if you:

- are allergic to iptacopan or any of the ingredients in FABHALTA. See the end of this Medication Guide for a complete list of ingredients in FABHALTA.

- have a serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis*, or *Haemophilus influenzae* type b when you are starting FABHALTA treatment.

Before you take FABHALTA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection or fever
- have liver problems
- are pregnant or plan to become pregnant. It is not known if FABHALTA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if FABHALTA passes into your breast milk. You should not breastfeed during treatment and for 5 days after your final dose of FABHALTA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking FABHALTA with certain other medicines may affect the way FABHALTA works and may cause side effects.

Know the medicines you take and the vaccines you receive. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take FABHALTA?

- Take FABHALTA exactly as your healthcare provider tells you. Do not change the dose or stop taking FABHALTA unless your healthcare provider tells you.
- Take 1 FABHALTA capsule 2 times each day, with or without food.
- Swallow the capsules whole. **Do not** open, break, or chew capsules.
- If you miss a dose or doses of FABHALTA, take 1 dose of FABHALTA as soon as you remember, even if it is almost time to take your next scheduled dose, and then take your next dose of FABHALTA at your regularly scheduled time.

For people with PNH:

- **If you are changing treatment from eculizumab to FABHALTA,** you should take your starting dose of FABHALTA no later than 1 week after your last dose of eculizumab.
- **If you are changing treatment from ravulizumab to FABHALTA,** you should take your starting dose of FABHALTA no later than 6 weeks after your last dose of ravulizumab.
- **If you stop taking FABHALTA,** your healthcare provider will need to monitor you closely for at least 2 weeks after stopping FABHALTA**. Stopping treatment with FABHALTA may cause a breakdown of red blood cells due to PNH**.

  Symptoms or problems that can happen due to breakdown of red blood cells include:

  - decreased hemoglobin level in your blood
  - blood in your urine
  - shortness of breath
  - trouble swallowing
  - tiredness
  - pain in the stomach (abdomen)
  - blood clots, stroke, and heart attack
  - erectile dysfunction

- It is important you take FABHALTA exactly as your healthcare provider tells you to lower the possibility of breakdown of red blood cells due to PNH.

What are the possible side effects of FABHALTA?

FABHALTA may cause serious side effects, including:

- See "**What is the most important information I should know about FABHALTA?**"
- **Increased cholesterol and triglyceride (lipid) levels in your blood.** Your healthcare provider will do blood tests to check your cholesterol and triglycerides during treatment with FABHALTA. Your healthcare provider may start you on a medicine to lower your cholesterol if needed.

The most common side effects of FABHALTA in adults include:

- headache
- nasal congestion, runny nose, cough, sneezing, and sore throat (nasopharyngitis)
- diarrhea
- pain in the stomach (abdomen)
- infections (bacterial and viral)
- nausea
- rash

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all of the possible side effects of FABHALTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FABHALTA?

- Store FABHALTA capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- The FABHALTA container contains a child resistant cap.

Keep FABHALTA and all medicines out of the reach of children.

General information about the safe and effective use of FABHALTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FABHALTA for a condition for which it was not prescribed. Do not give FABHALTA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about FABHALTA that is written for health professionals.

What are the ingredients in FABHALTA?

Active ingredient: iptacopan

Inactive ingredients: the capsule shell contains gelatin, red ferric oxide, titanium dioxide, yellow ferric oxide. The black printing ink contains ferrosoferric oxide, potassium hydroxide, propylene glycol, shellac, and strong ammonia solution.

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For more information, go to www.FABHALTA.com or call 1-888-669-6682.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 03/2025

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

Size 0 pale yellow, opaque hard capsule (21.2 to 22.2 mm) with “LNP200” on the body and “NVR” on the cap, containing white or almost white to pale purplish-pink powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paroxysmal nocturnal haemoglobinuria

FABHALTA is indicated as monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have haemolytic anaemia.

Complement 3 glomerulopathy

FABHALTA is indicated for the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended dose is 200 mg taken orally twice daily.

Healthcare professionals should advise patients about the importance of adherence to the dosing schedule. In patients with PNH, adherence is important to minimise the risk of haemolysis (see section 4.4).

If a dose or doses are missed, the patient should be advised to take one dose as soon as possible (even if it is shortly before the next scheduled dose) and then to resume the regular dosing schedule. Patients with PNH who have missed several consecutive doses should be monitored for potential signs and symptoms of haemolysis.

PNH is a disease that requires chronic treatment. Discontinuation of this medicinal product is not recommended unless clinically indicated (see section 4.4).

Patients with PNH switching from anti-C5 (eculizumab, ravulizumab) or other PNH therapies to iptacopan

To reduce the potential risk of haemolysis with abrupt treatment discontinuation:

- For patients switching from eculizumab, iptacopan should be initiated no later than 1 week after the last dose of eculizumab.
- For patients switching from ravulizumab, iptacopan should be initiated no later than 6 weeks after the last dose of ravulizumab.

Switches from complement inhibitors other than eculizumab and ravulizumab have not been studied.

Patients with C3G after kidney transplantation (recurrent C3G)

Diagnosis of recurrent C3G should be made based on histological C3 deposition in the glomeruli of the transplanted kidney. C3 deposition may be detected in a routine post-transplantation biopsy; otherwise, a biopsy should be performed when clinical signs indicate recurrent C3G. As done in study X2202 (see section 5.1), treatment with iptacopan can be started before the onset of clinical signs such as estimated glomerular filtration rate (eGFR) decrease or urine protein-to-creatinine ratio (UPCR) increase. There is limited experience with the use of iptacopan in patients with recurrent C3G after transplantation in clinical studies (see section 5.1).

Special populations

Elderly

No dose adjustment is required for patients 65 years of age and older (see section 5.2).

Renal impairment

No dose adjustment is required in patients with mild (eGFR between 60 and <90 ml/min) or moderate (eGFR between 30 and <60 ml/min) renal impairment. No data are currently available in patients with severe renal impairment or on dialysis and no dose recommendations can be given (see section 5.2).

Hepatic impairment

The use of iptacopan is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of iptacopan in children aged below 18 years have not been established. No data are available.

Method of administration

For oral use.

This medicinal product may be taken with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who are not currently vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae*, unless the risk of delaying treatment outweighs the risk of developing an infection from these encapsulated bacteria (see section 4.4).
- Patients with unresolved infection caused by encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Haemophilus influenzae* type B, at treatment initiation.

4.4 Special warnings and precautions for use

Serious infections caused by encapsulated bacteria

The use of complement inhibitors, such as iptacopan, may predispose individuals to serious, life-threatening or fatal infections caused by encapsulated bacteria. To reduce the risk of infection, all patients must be vaccinated against encapsulated bacteria, including *Neisseria meningitidis* and *Streptococcus pneumoniae*. It is recommended to vaccinate patients against *Haemophilus influenzae* type B if vaccine is available. Healthcare professionals should refer to local vaccination guideline recommendations.

Vaccines should be administered at least 2 weeks prior to administration of the first dose of iptacopan. If treatment must be initiated prior to vaccination, patients should be vaccinated as soon as possible and provided with antibacterial prophylaxis until 2 weeks after vaccine administration.

If necessary, patients may be revaccinated in accordance with local vaccination guideline recommendations.

Vaccination reduces, but does not eliminate, the risk of serious infection. Serious infection may rapidly become life-threatening or fatal if not recognised and treated early. Patients should be informed of and monitored for early signs and symptoms of serious infection. Patients should be immediately evaluated and treated if infection is suspected. The use of iptacopan during treatment of serious infection may be considered following an assessment of the risks and benefits (see section 4.8).

PNH laboratory monitoring

Patients with PNH receiving iptacopan should be monitored regularly for signs and symptoms of haemolysis, including measuring lactate dehydrogenase (LDH) levels.

Monitoring of PNH manifestations after treatment discontinuation

If treatment must be discontinued, patients with PNH should be closely monitored for signs and symptoms of haemolysis for at least 2 weeks after the last dose. These signs and symptoms include, but are not limited to, elevated LDH levels along with sudden decrease in haemoglobin or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, dysphagia, erectile dysfunction, or major adverse vascular events (MAVEs), including venous or arterial thrombosis. If treatment discontinuation is necessary, alternative therapy should be considered.

If haemolysis occurs after discontinuation of iptacopan, restarting treatment should be considered.

Co-administration with other medicinal products

Concomitant use of iptacopan with strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3 has not been studied clinically; therefore, concomitant use is not recommended due to the potential for reduced efficacy of iptacopan (see section 4.5). If an alternative concomitant medicinal product cannot be identified, patients with PNH should be monitored for potential signs and symptoms of haemolysis.

Treatment of patients with C3G

Patients with C3G treated with immunosuppressant medicinal products may show modest proteinuria reduction with iptacopan, which is likely linked to a more treatment-resistant nature of C3G in these patients.

There is no experience with the use of iptacopan in patients with C3G in native kidney who have proteinuria below 1 g/g at treatment initiation.

Educational materials

All physicians who intend to prescribe FABHALTA must ensure they have received and are familiar with the physician educational materials. Physicians must explain and discuss the benefits and risks of FABHALTA therapy with the patient and provide them with the patient information pack. The patient should be instructed to seek prompt medical care if they experience any sign or symptom of serious infection or serious haemolysis (patients with PNH) following treatment discontinuation.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on iptacopan

Strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3
Although concomitant administration of iptacopan with strong inducers of CYP2C8, UGT1A1, PgP, BCRP and OATP1B1/3, such as rifampicin, has not been studied clinically, concomitant use with iptacopan is not recommended due to the potential for reduced efficacy of iptacopan (see section 4.4).

Effects of iptacopan on other medicinal products

CYP3A4 substrates
In vitro data showed iptacopan has potential for induction of CYP3A4 and may decrease the exposure of sensitive CYP3A4 substrates. The concomitant use of iptacopan and sensitive CYP3A4 substrates has not been studied clinically. Caution should be exercised if co-administration of iptacopan with sensitive CYP3A4 substrates is required, especially for those with a narrow therapeutic index (e.g. carbamazepine, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

CYP2C8 substrates
In vitro data showed iptacopan has potential for time-dependent inhibition of CYP2C8 and may increase the exposure of sensitive CYP2C8 substrates, such as repaglinide, dasabuvir or paclitaxel. The concomitant use of iptacopan and sensitive CYP2C8 substrates has not been studied clinically. Caution should be exercised if co-administration of iptacopan with sensitive CYP2C8 substrates is required.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of iptacopan in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures between 2- and 8-fold the human exposure at the maximum recommended human dose (MRHD) (see section 5.3).

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, as well as adverse foetal outcomes, including foetal death and premature delivery.

C3G in pregnancy may be associated with adverse maternal outcomes, in particular pre-eclampsia and miscarriage, as well as adverse foetal outcomes including prematurity and low birth weight.

The use of iptacopan in pregnant women or women planning to become pregnant may only be considered following a careful assessment of the risk and benefits, if necessary.

Breast-feeding

It is unknown whether iptacopan is excreted in human milk. There are no data on the effects of iptacopan on the breast-fed newborn/infant or on milk production.

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from FABHALTA therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of iptacopan on human fertility. Available non-clinical data do not suggest an effect of iptacopan treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

FABHALTA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in adult patients with PNH were upper respiratory tract infection (18.9%), headache (18.3%) and diarrhoea (11.0%). The most commonly reported serious adverse reaction was urinary tract infection (1.2%).

The most commonly reported adverse reaction in adult patients with C3G was upper respiratory tract infection (12.9%). The most commonly reported serious adverse reaction was pneumococcal infection (1%).

Tabulated list of adverse reactions

Table 1 shows the adverse reactions observed in the clinical studies with iptacopan in patients with PNH and C3G. Adverse reactions are listed by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000) or very rare (<1/10 000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions

System Organ Class Adverse reaction	Frequency category	
	PNH	**C3G**
Infections and infestations		
Upper respiratory tract infection[1]	Very common	Very common
Urinary tract infection[2]	Common	
Bronchitis[3]	Common	
Pneumococcal infection[4]		Common
Pneumonia bacterial	Uncommon	
Blood and lymphatic system disorders		
Platelet count decreased	Common	
Nervous system disorders		
Headache[5]	Very common	
Dizziness	Common	
Gastrointestinal disorders		
Diarrhoea	Very common	
Abdominal pain[6]	Common	
Nausea	Common	
Skin and subcutaneous tissue disorders		
Urticaria	Uncommon	
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	

[1] Upper respiratory tract infection includes preferred terms influenza, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
[2] Urinary tract infection includes preferred terms urinary tract infection and cystitis escherichia.
[3] Bronchitis includes preferred terms bronchitis, bronchitis haemophilus and bronchitis bacterial.
[4] Pneumococcal infection includes preferred terms pneumonia pneumococcal and pneumococcal sepsis.
[5] Headache includes preferred terms headache and head discomfort.
[6] Abdominal pain includes preferred terms abdominal pain, abdominal pain upper, abdominal tenderness and abdominal discomfort.

Description of selected adverse reactions

Infections
In PNH clinical studies 1/164 (0.6%) patients with PNH reported serious bacterial pneumonia while receiving treatment with iptacopan; the patient had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B and recovered following treatment with antibiotics while continuing treatment with iptacopan.

In C3G completed clinical studies, 1 patient with C3G reported serious pneumococcal infection with pneumonia and sepsis while receiving treatment with iptacopan; the patient had been vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B and recovered following treatment with antibiotics. Iptacopan treatment was interrupted and restarted after recovery.

Platelet count decreased in patients with PNH
Decrease in platelet count events was reported in 12/164 (7%) patients with PNH. Of these, 5 patients had events of mild severity, 5 had moderate events and 2 had severe events. Patients with severe events had concurrent anti-platelet antibodies or idiopathic bone marrow aplasia with pre-existing thrombocytopenia. The events started within the first 2 months of iptacopan treatment in 7/12 patients, and after a longer exposure (111 to 951 days) in 5/12 patients. At the cut-off date, 7 (58%) patients had recovered or events were resolving and iptacopan treatment was continued throughout in all patients.

Blood cholesterol and blood pressure increases in patients with PNH
In patients treated with iptacopan 200 mg twice a day in PNH clinical studies, mean increases from baseline of approximately 0.7 mmol/l were seen at month 6 for total cholesterol and LDL-cholesterol. The mean values remained within the normal ranges. Increases in blood pressure, particularly diastolic blood pressure (DBP), were observed (mean increase 4.7 mmHg at month 6). The mean DBP did not exceed 80 mmHg. Total cholesterol, LDL-C and DBP increases correlated with increases in haemoglobin (improvement in anaemia) in patients with PNH (see section 5.1).

In patients treated with iptacopan 200 mg twice a day in the C3G clinical study, no clinically relevant differences were observed in total cholesterol, LDL-cholesterol or blood pressure compared to placebo.

Heart rate decrease in patients with PNH
In patients treated with iptacopan 200 mg twice a day in PNH clinical studies, a mean decrease in heart rate of approximately 5 bpm was seen at month 6 (mean of 68 bpm).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

During clinical studies, a few patients took up to 800 mg iptacopan daily and this was well tolerated. In healthy volunteers, the highest dose was 1 200 mg administered as a single dose and this was well tolerated.

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, complement inhibitors, ATC code: L04AJ08

Mechanism of action

Iptacopan is a proximal complement inhibitor that targets Factor B (FB) to selectively inhibit the alternative pathway. In PNH, inhibition of FB in the alternative pathway of the complement cascade prevents the activation of C3 convertase and the subsequent formation of C5 convertase to control both C3-mediated extravascular haemolysis (EVH) and terminal complement-mediated intravascular haemolysis (IVH).

In C3G, overactivation of the complement alternative pathway leads to deposition of C3 within the glomeruli, triggering inflammation, glomerular injury, and kidney fibrosis. Iptacopan selectively blocks the alternative pathway overactivation by inhibiting the alternative pathway related C3 convertase activity, leading to decreased cleavage of C3 and reduced C3 deposition in the kidney.

Pharmacodynamic effects

The onset of inhibition of the alternative complement pathway, measured using an *ex vivo* alternative pathway assay, Bb levels (fragment b of Factor B) and plasma levels of C5b-9, was ≤2 hours after a single iptacopan dose in healthy volunteers.

A comparable effect of iptacopan was observed in patients with PNH previously exposed to anti-C5 agents and treatment-naïve patients.

In treatment-naïve PNH patients, iptacopan 200 mg twice daily reduced LDH by >60% compared to baseline after 12 weeks and maintained the effect through to the end of the study.

In patients with C3G, the mean serum C3 level increased by 249% compared to baseline at day 14 of iptacopan treatment, reflecting inhibition of pathological C3 cleavage. The plasma soluble C5b-9 and urine soluble C5b-9 decreased from baseline by 71.8% and 92.1%, respectively, on the first observation at day 30 of treatment with iptacopan 200 mg twice daily. The effect was sustained over the observation period of 12 months. A reduction of glomerular C3 deposition at 6 months was also observed based on C3 deposit score change.

Cardiac electrophysiology

In a QTc clinical study in healthy volunteers, single supra-therapeutic iptacopan doses up to 1 200 mg (which provided greater than 4-fold exposure of the 200 mg twice daily dose), showed no effect on cardiac repolarisation or QT interval.

Clinical efficacy and safety

Paroxysmal nocturnal haemoglobinuria
The efficacy and safety of iptacopan in adult patients with PNH were evaluated in two multicentre, open-label, 24-week phase III studies: an active comparator-controlled study (APPLY-PNH) and a single-arm study (APPOINT-PNH).

APPLY-PNH: anti-C5 treatment experienced patients with PNH
APPLY-PNH enrolled adult PNH patients (RBC clone size ≥10%) with residual anaemia (haemoglobin <10 g/dl) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomisation.

Patients (N=97) were randomised in 8:5 ratio either to receive iptacopan 200 mg orally twice daily (N=62) or to continue anti-C5 treatment (eculizumab N=23; or ravulizumab N=12) throughout the duration of the 24-week randomised controlled period (RCP). Randomisation was stratified based on prior anti-C5 treatment and transfusion history within the last 6 months.

Demographics and baseline disease characteristics were generally well balanced between treatment groups. At baseline, patients had a mean (standard deviation [SD]) age of 51.7 (16.9) years (range 22-84) and 49.8 (16.7) years (range 20-82) in the iptacopan and anti-C5 groups, respectively and 69% of patients were female in both groups. The mean (SD) haemoglobin was 8.9 (0.7) g/dl and 8.9 (0.9) g/dl, in the iptacopan and anti-C5 group, respectively. Fifty-seven percent (iptacopan group) and 60% (anti-C5 group) of patients received at least one transfusion in the 6 months prior to randomisation. Amongst those, the mean (SD) number of transfusions was 3.1 (2.6) and 4.0 (4.3) in the iptacopan and anti-C5 group, respectively. The mean (SD) LDH level was 269.1 (70.1) U/l in the iptacopan group and 272.7 (84.8) U/l in the anti-C5 group. The mean (SD) absolute reticulocyte count was 193.2 (83.6) 10^9/l in the iptacopan group and 190.6 (80.9) 10^9/l in the anti-C5 group. The mean (SD) total PNH RBC clone size (Type II + III) was 64.6% (27.5%) in the iptacopan group and 57.4% (29.7%) in the anti-C5 group.

During the RCP, 1 patient in the iptacopan group discontinued treatment due to pregnancy; no patients in the anti-C5 group discontinued.

Efficacy was based on two primary endpoints to demonstrate superiority of iptacopan to anti-C5 in achieving haematological response after 24 weeks of treatment, without a need for transfusion, by assessing the proportion of patients demonstrating: 1) sustained increase of ≥2 g/dl in haemoglobin levels from baseline (haemoglobin improvement) and/or 2) sustained haemoglobin levels ≥12 g/dl.

Iptacopan demonstrated superiority to anti-C5 therapy for the two primary endpoints, as well as for several secondary endpoints including transfusion avoidance, changes from baseline in haemoglobin levels, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores, absolute reticulocyte counts (ARCs) and annualised rate of clinical breakthrough haemolysis (see Table 2).

The treatment effect of iptacopan on haemoglobin was seen as early as day 7 and sustained during the study (see Figure 1).

Table 2 Efficacy results for the 24-week randomised treatment period in APPLY-PNH

Endpoints	Iptacopan (N=62)	Anti-C5 (N=35)	Difference (95% CI) p-value
Primary endpoints			
Number of patients achieving haemoglobin improvement (sustained increase of haemoglobin levels ≥2 g/dl from baseline[a] in the absence of transfusions) Response rate[c] (%)	51/60[b] 82.3	0/35[b] 2.0	 80.2 (71.2, 87.6) <0.0001
Number of patients achieving sustained haemoglobin level ≥12 g/dl[a] in the absence of transfusions Response rate[c] (%)	42/60[b] 68.8	0/35[b] 1.8	 67.0 (56.4, 76.9) <0.0001
Secondary endpoints			
Number of patients avoiding transfusion[d,e] Transfusion avoidance rate[c] (%)	59/62[b] 94.8	14/35[b] 25.9	 68.9 (51.4, 83.9) <0.0001
Haemoglobin level change from baseline (g/dl) (adjusted mean[f])	3.60	-0.06	3.66 (3.20, 4.12) <0.0001
FACIT-Fatigue score change from baseline (adjusted mean[g])	8.59	0.31	8.29 (5.28, 11.29) <0.0001
Clinical breakthrough haemolysis[h,i], % (n/N) Annualised rate of clinical breakthrough haemolysis	3.2 (2/62) 0.07	17.1 (6/35) 0.67	 RR=0.10 (0.02, 0.61) 0.01
Absolute reticulocyte count change from baseline (10^9/l) (adjusted mean[g])	-115.8	0.3	-116.2 (-132.0, -100.3) <0.0001
LDH ratio to baseline (adjusted geometric mean[g])	0.96	0.98	Ratio = 0.99 (0.89, 1.10) 0.84
MAVEs[h] % (n/N) Annualised rate of MAVEs[h]	1.6 (1/62) 0.03	0 0	 0.03 (-0.03, 0.10) 0.32

RR: rate ratio; LDH: lactate dehydrogenase; MAVEs: major adverse vascular events

[a,d,h] Assessed between days 126 and 168[(a)], 14 and 168[(d)], 1 and 168[(h)].

[b] Based on observed data among evaluable patients. (In 2 patients with partially missing central haemoglobin data between days 126 and 168, the haematological response could not be established unequivocally. The haematological response was derived using multiple imputation. These patients did not discontinue.)

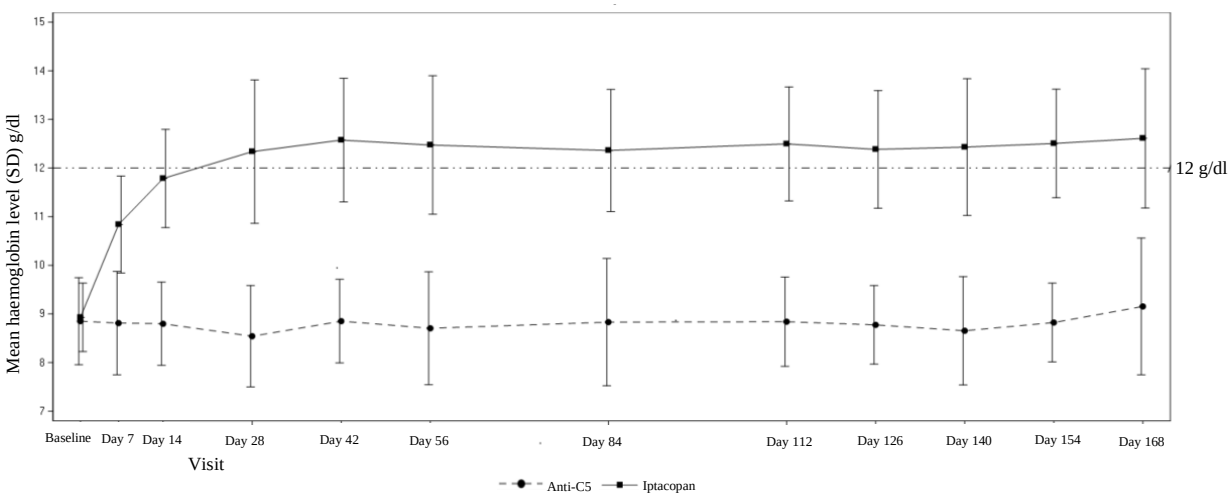
[c] Response rate reflects the model estimated proportion.

[e] Transfusion avoidance is defined as absence of administration of packed red blood cell transfusions between days 14 and 168 or meeting the criteria for transfusion between days 14 and 168.

[f,g] Adjusted mean assessed between days 126 and 168, values within 30 days after transfusion were excluded[(f)]/included[(g)] in the analysis.

[i] Clinical breakthrough haemolysis is defined as meeting clinical criteria (either decrease of haemoglobin level ≥2 g/dl compared to the last assessment or within 15 days, or signs or symptoms of gross haemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms) and laboratory criteria (LDH >1.5 x ULN and increased as compared to the last 2 assessments).

Figure 1 Mean haemoglobin level* (g/dl) during 24-week randomised treatment period in APPLY-PNH



*Note: The figure includes all haemoglobin data collected in the study, including those values within 30 days after RBC transfusion.

APPOINT-PNH: Complement inhibitor-naïve study
APPOINT-PNH was a single-arm study in 40 adult PNH patients (RBC clone size ≥10%) with haemoglobin <10 g/dl and LDH >1.5 x ULN who were not previously treated with a complement inhibitor. All 40 patients received iptacopan 200 mg orally twice daily during the 24-week open-label core treatment period.

At baseline, patients had a mean (SD) age of 42.1 (15.9) years (range 18-81) and 43% were female. The mean (SD) haemoglobin was 8.2 (1.1) g/dl. Seventy percent of patients received at least one transfusion in the 6 months prior to treatment. Amongst those the mean (SD) number of transfusions was 3.1 (2.1). The mean (SD) LDH level was 1 698.8 (683.3) U/l, and the mean (SD) absolute reticulocyte count was 154.3 (63.7) 10^9/l. The mean (SD) total PNH RBC clone size (Type II + III) was 42.7% (21.2%). No patients discontinued from the core treatment period of the study.

Efficacy was based on the primary endpoint assessing the effect of iptacopan treatment on the proportion of patients achieving haemoglobin improvement (sustained increase of ≥2 g/dl in haemoglobin levels from baseline, without a need for RBC transfusion, after 24 weeks).

See Table 3 for detailed efficacy results and see Figure 2 for the mean LDH level change during the 24-week core treatment period.

Table 3 Efficacy results for the 24-week core treatment period in APPOINT-PNH

Endpoints	**Iptacopan (N=40) 95% CI**
Primary endpoint	
Number of patients achieving haemoglobin improvement (sustained increase of haemoglobin levels ≥2 g/dl from baseline[a] in the absence of transfusions)	31/33[b]
Response rate[c] (%)	92.2 (82.5, 100.0)[d]
Secondary endpoints	
Number of patients achieving sustained haemoglobin level ≥12 g/dl[a] in the absence of transfusions	19/33[b]
Response rate[c] (%)	62.8 (47.5, 77.5)
Number of patients avoiding transfusion[e,f]	40/40[b]
Transfusion avoidance rate[c] (%)	97.6 (92.5, 100.0)
Haemoglobin level change from baseline (g/dl) (adjusted mean[g])	+4.3 (3.9, 4.7)
Clinical breakthrough haemolysis[i,j], % (n/N)	0/40
Annualised rate of clinical breakthrough haemolysis	0.0 (0.0, 0.2)
Absolute reticulocyte count change from baseline (10^9/l) (adjusted mean[h])	-82.5 (-89.3, -75.6)
LDH percent change from baseline (adjusted mean[h])	-83.6 (-84.9, -82.1)
Percentage of patients with MAVEs[j]	0.0

[a,e,j] Assessed between days 126 and 168[(a)], 14 and 168[(e)], 1 and 168[(j)].

[b] Based on observed data among evaluable patients. (In 7 patients with partially missing central haemoglobin data between days 126 and 168, the haematological response could not be established unequivocally. The haematological response was derived using multiple imputation. These patients did not discontinue.)

[c] Response rate reflects the model estimated proportion.

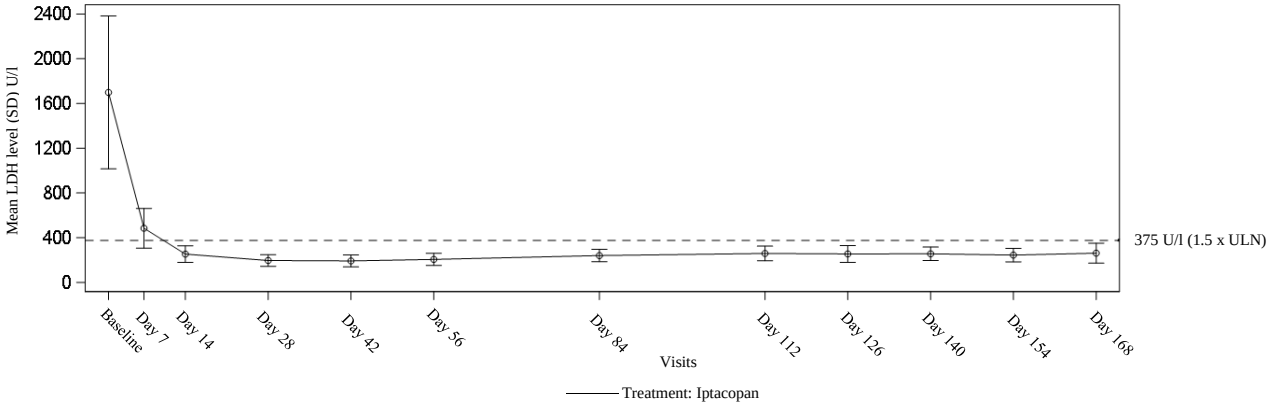
[d] The threshold for demonstration of benefit was 15%, representing the rate that would have been expected on anti-C5 treatment.

[f] Transfusion avoidance is defined as absence of administration of packed red blood cell transfusions between days 14 and 168 or meeting the criteria for transfusion between days 14 and 168.

[g,h] Adjusted mean assessed between days 126 and 168, values within 30 days after transfusion were excluded[(g)]/included[(h)] in the analysis.

[i] Clinical breakthrough haemolysis defined as meeting clinical criteria (either decrease of haemoglobin level ≥2 g/dl compared to the latest assessment or within 15 days; or signs or symptoms of gross haemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs and symptoms) and laboratory criteria (LDH >1.5 x ULN and increased as compared to the last 2 assessments).

Figure 2 Mean LDH level (U/l) during 24-week core treatment period in APPOINT-PNH



Complement 3 glomerulopathy

The efficacy and safety of iptacopan for the treatment of C3G were evaluated in a total of 101 patients with C3G in one pivotal phase III study (APPEAR-C3G, in patients with native kidney, N=74) and two supportive open-label studies (study X2202 in patients with native kidney (N=16) and patients with recurrent C3G (N=11), and a roll-over extension study).

APPEAR-C3G

APPEAR-C3G, a multicentre, randomised, double-blind, placebo-controlled study, enrolled 74 adult patients with biopsy-confirmed C3G, UPCR ≥1 g/g, and eGFR ≥30 ml/min/1.73 m^2.

Patients were randomised (1:1) to receive either iptacopan 200 mg orally twice daily (N=38) or placebo (N=36) for 6 months, followed by a 6-month open-label treatment period in which patients received iptacopan 200 mg orally twice daily. All 74 patients completed the double-blind period and 73 patients completed the open-label treatment period with iptacopan.

Patients were on a stable maximally tolerated dose of a renin-angiotensin system (RAS) inhibitor. Randomisation was stratified according to whether or not patients were receiving concomitant immunosuppressive therapy (i.e. corticosteroid and/or mycophenolate mofetil/sodium [MMF/MPS]). All of these therapies (i.e. RAS inhibitors, corticosteroids and MMF/MPS) were required to be at stable doses 90 days prior to randomisation and throughout the study.

At baseline, patients had a mean (standard deviation [SD]) age of 26.1 (10.4) years (range 18-52) and 29.8 (10.8) years (range 18-60) in the iptacopan and placebo groups, respectively. At the time of C3G diagnosis, 40% (iptacopan) and 17% (placebo) of patients were <18 years old. Females were 29% (iptacopan) and 44% (placebo). The geometric mean UPCR was 3.33 g/g and 2.58 g/g in the iptacopan and placebo groups, respectively. The mean modelled historical eGFR slope prior to randomisation was -10.75 vs. -7.64 ml/min/1.73m^2 per year in iptacopan and placebo arms, respectively. The mean (SD) eGFR was 89.3 (35.2) ml/min/1.73 m^2 and 99.2 (26.9) ml/min/1.73 m^2 in the iptacopan and placebo groups, respectively. Subtypes were C3 glomerulonephritis (C3GN) in 68% (iptacopan) and 89% (placebo) of patients, and dense deposit disease (DDD) in 23.7% (iptacopan) and 2.8% (placebo). A stable dose of immunosuppressive therapy with corticosteroid and/or MMF/MPS was used by 42% (iptacopan) and 47% (placebo) of patients.

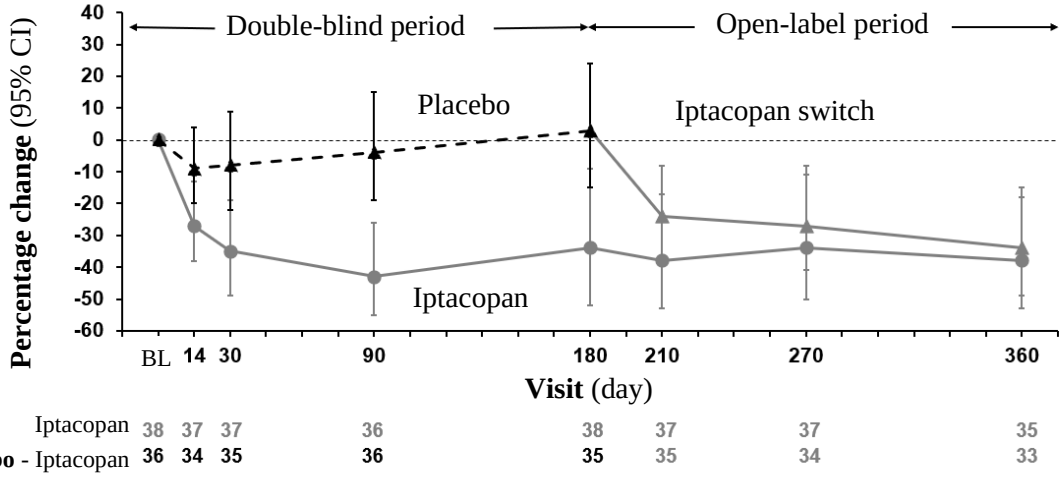
The primary efficacy endpoint was percent reduction in 24-hour UPCR compared to baseline after 6 months of treatment.

Iptacopan was superior to placebo, with a statistically significant 35.1% reduction (95% CI: 13.8%, 51.1%, 1-sided p=0.0014) in 24-hour UPCR from baseline compared to placebo after 6 months of treatment (-30.2% and +7.6% for iptacopan and placebo, respectively). The effect of iptacopan on 24-hour UPCR was sustained up to 12 months (-40.0% from baseline). Patients who switched from placebo to iptacopan in the 6-month open-label treatment period experienced a 31.0% reduction in 24-

hour UPCR from month 6 to month 12. First morning void (FMV) UPCR trajectory is described in Figure 3.

In a post-hoc analysis, iptacopan reduced the percentage of patients with nephrotic range proteinuria (defined as UPCR ≥3 g/g) from 55.3% at baseline to 31.6% and 36.8% at months 6 and 12, respectively. The percentage of patients with nephrotic range proteinuria randomised to placebo increased from 30.6% at baseline to 41.7% at month 6. After switching to iptacopan treatment, it decreased to 27.8% at month 12.

Figure 3 Geometric mean percent change from baseline in FMV UPCR up to 12 months (APPEAR-C3G)



Iptacopan treatment for 6 months resulted in a numerical improvement of 2.2 ml/min/1.73 m^2 (95% CI: -2.7, 7.1, 1-sided p=0.3241) in eGFR from baseline compared to placebo (1.3 and -0.9 ml/min/1.73 m^2 for iptacopan and placebo, respectively). The eGFR remained stable during the 12 months duration of the study in the iptacopan treatment arm (+0.4 ml/min/1.73 m^2 from baseline).

Iptacopan treatment for 6 months resulted in a mean difference in glomerular C3 deposition of -1.9 (95% CI: -3.3, -0.5; nominal 1-sided p=0.0053) from baseline compared to placebo. Change from baseline on iptacopan was -0.78 (95% CI: -1.81, 0.25) compared to an increase of 1.09 (95% CI: 0.11, 2.08) with placebo.

X2202 and roll-over extension study
The efficacy of iptacopan in adults with C3G was supported by an open-label phase II study X2202 in patients with C3G in native kidney (N=16) and patients with recurrent C3G post-kidney transplantation (N=11) for 3 months.

Diagnosis of recurrent C3G required histological assessment of glomerular C3 staining intensity on a recent biopsy of the transplanted kidney. The baseline mean age was 35 years (range 18-70), the geometric mean UPCR was 0.32 g/g, the mean (SD) eGFR was 52.2 (17.29) ml/min/1.73m^2, and the median C3 deposit score was 3 on a scale of 0-12 at baseline. All patients were on MMF/MPS and/or corticosteroids in addition to calcineurin inhibitors.

In patients with native kidney, iptacopan resulted in a statistically significant 45% (-162.6 g/mol) reduction in 24-hour UPCR (p=0.0003) at 3 months. In patients with recurrent C3G, iptacopan significantly reduced the histological C3 deposit score by 2.50 (p=0.0313) at 3 months.

Most (n=26) patients from the study transitioned to a roll-over extension study to receive iptacopan 200 mg twice daily for up to 39 months. Mean UPCR and eGFR remained stable throughout the study in the 16 patients with C3G in native kidney. Among the 10 subjects with recurrent C3G after transplantation, 2 patients dropped out due to deterioration of renal function. In the other

8 participants, eGFR and UPCR remained essentially constant until the end of the observation period (up to 48 months).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with FABHALTA in one or more subsets of the paediatric population in PNH and C3G (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, iptacopan reached peak plasma concentrations approximately 2 hours post dose. At the recommended dosing regimen of 200 mg twice daily, steady state is achieved in approximately 5 days with minor accumulation (1.4-fold). In healthy volunteers, steady-state $C_{max,ss}$ (geo-mean (%CV)) was 4 020 ng/ml (23.8%) and $AUC_{tau,ss}$ was 25 400 ng*hr/ml (15.2%). Inter- and intra-subject variability in iptacopan pharmacokinetics is low to moderate.

Results from a food-effect study with a high-fat high-calorie meal in healthy volunteers indicated that C_{max} and area under the curve (AUC) of iptacopan were not affected by food. Therefore, iptacopan may be taken with or without food.

Distribution

Iptacopan showed concentration-dependent plasma protein binding due to binding to the target FB in the systemic circulation. Iptacopan was 75 to 93% protein bound *in vitro* at the relevant clinical plasma concentrations. After administration of iptacopan 200 mg twice daily, the geo-mean apparent volume of distribution at steady state was approximately 265 litres.

Biotransformation

Metabolism is a predominant elimination pathway for iptacopan, with approximately 50% of the dose attributed to oxidative pathways. Metabolism of iptacopan includes N-dealkylation, O-deethylation, oxidation and dehydrogenation, mostly driven by CYP2C8 with a small contribution from CYP2D6. Direct glucuronidation (by UGT1A1, UGT1A3 and UGT1A8) is a minor pathway. In plasma, iptacopan was the major component, accounting for 83% of the $AUC_{0\text{-}48\ h}$. Two acyl glucuronides were the only metabolites detected in plasma and were minor, accounting for 8% and 5% of the $AUC_{0\text{-}48\ h}$. Iptacopan metabolites are not considered pharmacologically active.

Elimination

In a study in healthy volunteers, following a single 100 mg oral dose of [^{14}C]-iptacopan, mean total excretion of radioactivity (iptacopan and metabolites) was 71.5% in the faeces and 24.8% in the urine. Specifically, 17.9% of the dose was excreted as parent iptacopan in the urine and 16.8% in faeces. The apparent clearance (CL/F) after administration of iptacopan 200 mg twice daily at steady state is 7 960 ml/h. The half-life ($t_{½}$) of iptacopan at steady state is approximately 25 hours after administration of iptacopan 200 mg twice daily.

Linearity/non-linearity

At doses between 25 and 100 mg twice daily, the pharmacokinetics of iptacopan were overall less than dose proportional. However, oral doses of 100 mg and 200 mg were approximately dose proportional. Non-linearity was primarily attributed to the saturable binding of iptacopan to its target FB in plasma.

Drug interactions

A dedicated interaction study in which iptacopan was co-administered with other medicinal products was conducted in healthy volunteers and did not demonstrate any clinically relevant interactions.

Iptacopan as a substrate
CYP2C8 inhibitors
When iptacopan is co-administered with clopidogrel (a moderate CYP2C8 inhibitor), the iptacopan C_{max} and the AUC increased by 5% and 36%, respectively.

OATP1B1/OATP1B3 inhibitors
When iptacopan is co-administered with ciclosporin (a strong OATP 1B1/1B3 inhibitor, and a PgP and BCRP inhibitor), the iptacopan C_{max} and AUC increased by 41% and 50%, respectively.

Iptacopan as an inhibitor
PgP substrates
In the presence of iptacopan, the C_{max} of digoxin (a PgP substrate) increased by 8% while its AUC was unchanged.

OATP substrates
In the presence of iptacopan, the C_{max} and AUC of rosuvastatin (an OATP substrate) remained unchanged.

Special populations

A population pharmacokinetic (PK) analysis was conducted on data from 234 patients. Age (18 to 84 years), body weight, eGFR, race and gender did not significantly influence iptacopan PK. Studies that included Asian subjects showed that the PK of iptacopan were similar to Caucasian (white) subjects.

Renal impairment
The effect of renal impairment on the clearance of iptacopan was assessed using a population PK analysis. There were no clinically relevant differences in the clearance of iptacopan between patients with normal renal function and patients with mild (eGFR between 60 and 90 ml/min) or moderate (eGFR between 30 and 60 ml/min) renal impairment and no dose adjustment is required (see section 4.2). Patients with severe renal impairment or on dialysis have not been studied.

Hepatic impairment
Based on a study in subjects with mild (Child-Pugh A, n=8), moderate (Child-Pugh B, n=8) or severe (Child-Pugh C, n=6) hepatic impairment, a negligible effect on the total systemic exposure of iptacopan was observed compared to subjects with normal hepatic function. Unbound iptacopan C_{max} increased 1.4-, 1.7- and 2.1-fold, and unbound iptacopan AUC_{inf} increased by 1.5-, 1.6- and 3.7-fold in subjects with mild, moderate and severe hepatic impairment, respectively (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Reproductive toxicity

In oral dose animal fertility studies, iptacopan did not impact fertility in male rats up to the highest dose tested (750 mg/kg/day), which corresponds to 6-fold the MRHD based on AUC. Reversible effects on the male reproductive system (testicular tubular degeneration and hypospermatogenesis) were observed in repeated dose toxicity studies after oral administration in rats and dogs at doses >3-

fold the MRHD based on AUC, with no apparent effects on sperm numbers, morphology or motility, or fertility.

In the female fertility and early embryonic developmental study in rats, iptacopan-related findings were limited to increased pre-and post-implantation losses and, consequently, decreased numbers of live embryos only at the highest dose of 1 000 mg/kg/day orally, which corresponds to ~5-fold the MRHD based on total AUC. The dose of 300 mg/kg/day is the no-observed-adverse-effect level (NOAEL) which corresponds to ~2-fold the MRHD based on AUC.

Animal reproduction studies in rats and rabbits demonstrated that oral administration of iptacopan during organogenesis did not induce adverse embryo or foetal toxicity up to the highest doses, which correspond to 5-fold (for rats) and 8-fold (for rabbits) the MRHD of 200 mg twice daily based on AUC.

In the pre- and postnatal development study in rats, with iptacopan administered orally to females during gestation, parturition and lactation (from gestational day 6 to lactation day 21), there were no adverse effects on pregnant dams or offspring up to the highest dose tested of 1 000 mg/kg/day (estimated 5-fold the MRHD based on AUC).

Repeated dose toxicity

In the chronic toxicity study, one male dog at the highest dose level (margin to clinical exposure near 20-fold), was sacrificed 103 days after completed iptacopan administration due to irreversible non-regenerative severe anaemia associated with bone marrow fibrosis. During the treatment phase, haematology findings indicating inflammation and dyserythropoiesis were observed. No mechanism for the observed findings has been identified and a relation to treatment cannot be excluded.

Mutagenicity and carcinogenicity

Iptacopan was not genotoxic or mutagenic in a battery of *in vitro* and *in vivo* assays.

Carcinogenicity studies conducted with iptacopan in mice and rats via oral administration did not identify any carcinogenic potential. The highest doses of iptacopan studied in mice (1 000 mg/kg/day) and rats (750 mg/kg/day) were approximately 4- and 12-fold the MRHD based on AUC, respectively.

Phototoxicity

In vitro and *in vivo* phototoxicity tests were equivocal. In the *in vivo* phototoxicity study, with iptacopan at doses between 100 and 1 000 mg/kg (equivalent to 38-fold the human total C_{max} at the MRHD), some mice showed a non-dose-response pattern of transient minimal erythema, scabs and dryness and slight increase in average ear weight subsequent to irradiation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell

Gelatin
Red iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink

Black iron oxide (E172)
Concentrated ammonia solution (E527)
Potassium hydroxide (E525)
Propylene glycol (E1520)
Shellac (E904)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

FABHALTA is supplied in PVC/PE/PVDC blisters with aluminium foil backing.

Packs containing 28 or 56 hard capsules.
Multipacks containing 168 (3 packs of 56) hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 May 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Pharmaceutical Manufacturing LLC
Verovškova Ulica 57
1000 Ljubljana
Slovenia

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Novartis Farmacéutica S.A.
Gran Via De Les Corts Catalanes 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of FABHALTA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The educational programme is aimed at providing healthcare professionals (HCPs) and patients/caregivers with educational information on the following safety areas of interest:

- Infections caused by encapsulated bacteria
- Serious haemolysis following discontinuation of iptacopan in patients with PNH

The MAH shall ensure that in each Member State where FABHALTA is marketed, all HCPs and patients/caregivers who are expected to prescribe or use FABHALTA have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals

- **The Guide for healthcare professionals shall contain the following key messages:**
  - FABHALTA may increase the risk of serious infections with encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae.*
  - Ensure patients are vaccinated against *N. meningitidis* and *S. pneumoniae* before starting treatment, and/or receive antibiotic prophylaxis until 2 weeks after vaccination.
  - Recommend vaccination against *H. influenzae* to patients where vaccines are available.
  - Ensure that FABHALTA is only dispensed after a written confirmation that the patient has received vaccination against *N. meningitidis* and *S. pneumoniae*, in accordance with current national vaccination guidelines, and/or is receiving prophylactic antibiotic.
  - Ensure prescribers or pharmacists receive annual reminders of mandatory revaccinations in accordance with current national vaccination guidelines (including *N. meningitidis*, *S. pneumoniae*, and, if appropriate, *H. influenzae*)
  - Monitor patients for signs and symptoms of sepsis, meningitis or pneumonia, such as: fever with or without shivers or chills, headache and a fever, fever and a rash, fever with chest pain and cough, fever with breathlessness/fast breathing, fever with high heart rate, headache with nausea or vomiting, headache with a stiff neck or stiff back, confusion, body aches with flu-like symptoms, clammy skin, eyes sensitive to light. If bacterial infection is suspected, treat with antibiotics immediately.
  - In patients with PNH, discontinuation of FABHALTA may increase the risk of serious haemolysis, therefore advice on adherence to the dosing schedule is important, as is close monitoring for signs of haemolysis following treatment discontinuation. If discontinuation of FABHALTA is necessary, alternative therapy should be considered. If haemolysis occurs after discontinuation of FABHALTA, restarting FABHALTA treatment should be considered. Possible signs and

symptoms you need to look out for are: elevated lactate dehydrogenase (LDH) levels along with sudden decrease in haemoglobin or PNH clone size, fatigue, haemoglobinuria, abdominal pain, dyspnoea, dysphagia, erectile dysfunction or major adverse vascular events including thrombosis.
- Details about the PASS for patients with PNH and how to enter patients, if applicable.

The patient information pack:
- Package leaflet
- Patient/caregiver guide
- Patient safety card

- **The Patient/caregiver guide shall contain the following key messages:**
  - Treatment with FABHALTA may increase the risk of serious infections.
  - Doctors will inform you about which vaccinations are required prior to treatment and/or the need to receive antibiotic prophylaxis.
  - Signs and symptoms of serious infection are: fever with or without shivers or chills, headache and a fever, fever and a rash, fever with chest pain and cough, fever with breathlessness/fast breathing, fever with high heart rate, headache with nausea or vomiting, headache with a stiff neck or stiff back, confusion, body aches with flu-like symptoms, clammy skin, eyes sensitive to light.
  - Contact your doctor in case you experience any of the signs and symptoms above and seek immediate medical care at the nearest medical centre.
  - If you have PNH, discontinuation of FABHALTA may increase the risk of serious breakdown of red blood cells (haemolysis). It is important that you adhere to the scheduled treatment regimen. Possible signs and symptoms you need to look out for are: fatigue, blood in the urine, abdominal pain, shortness of breath, difficulty swallowing, erectile dysfunction or major adverse vascular events including thrombosis.
  - Tell your doctor before discontinuing FABHALTA.
  - If you miss a dose, take it as soon as you can, even if it is close to the next dose.
  - You will receive a patient safety card and will need to carry it with you and tell any treating healthcare professional that you are being treated with FABHALTA.
  - If you have any adverse reactions, including infections or serious haemolysis, it is important that you report them immediately.
  - You will be informed of the details to enroll in the PASS if you have PNH.

- **Patient Safety Card:**
  - Statement that the patient is receiving FABHALTA.
  - Signs and symptoms of serious infection caused by encapsulated bacteria and warning to seek immediate treatment with antibiotics if bacterial infection is suspected.
  - Contact details where a healthcare professional can receive further information.

- **System for Controlled Access:**
  - The MAH shall ensure that in each Member State where FABHALTA is marketed, a system aimed to control access beyond the level of routine risk minimisation measures is in place. The following requirement needs to be fulfilled before the product is dispensed:
  - Submission of written confirmation of the patient's vaccination against *N. meningitidis* and *S. pneumoniae* infections and/or receipt of prophylactic antibiotic according to national guidelines.

- **Annual reminder of mandatory revaccinations:**
  - The MAH shall send to prescribers or pharmacists who prescribe/dispense FABHALTA an annual reminder in order that the prescriber/pharmacist checks if a revaccination (booster vaccination) against *N. meningitidis* and *S. pneumoniae*

infections is required for their patients on treatment with FABHALTA, in accordance with current national vaccination guidelines.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF PACK CONTAINING 28 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/001 28 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF PACK CONTAINING 28 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

14 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

'QR code to be included'
www.fabhalta.eu
Scan me

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/001 28 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF PACK CONTAINING 56 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

56 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

'QR code to be included'
www.fabhalta.eu
Scan me

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
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Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/002 56 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Multipack: 168 (3 x 56) capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/003 168 (3 x 56) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg hard capsules
iptacopan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains iptacopan hydrochloride monohydrate equivalent to 200 mg iptacopan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

56 capsules
Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

'QR code to be included'
www.fabhalta.eu
Scan me

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1802/003 168 (3 x 56) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

FABHALTA 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

FABHALTA 200 mg capsules
iptacopan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

FABHALTA 200 mg hard capsules
iptacopan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What FABHALTA is and what it is used for

FABHALTA contains the active substance iptacopan, which belongs to a group of medicines called complement inhibitors.

FABHALTA is used:
- on its own in adults to treat paroxysmal nocturnal haemoglobinuria (PNH), a disease in which the immune system (the body's natural defence system) attacks and damages red blood cells. FABHALTA is used in adults who have anaemia (low levels of red blood cells) due to the breakdown of their red blood cells.
- in adults to treat patients with a disease called complement 3 glomerulopathy (C3G)
  - together with a renin-angiotensin-system inhibitor (RAS inhibitor), or
  - alone if an RAS inhibitor does not work well or cannot be used.

The active substance in FABHALTA, iptacopan, targets a protein called Factor B, which is involved in a part of the body's immune system called the "complement system".

In patients with PNH, the complement system is overactive, causing the destruction and breakdown of the red blood cells, which can lead to anaemia, tiredness, difficulty in functioning, pain, pain in the stomach (abdomen), dark urine, shortness of breath, difficulty swallowing, impotence and blood clots. By attaching to and blocking the Factor B protein, iptacopan can stop the complement system from attacking the red blood cells. This medicine has been shown to increase the number of red blood cells and thus may improve symptoms of anaemia.

In patients with C3G, the complement system is overactive, leading to deposition of C3 within the glomeruli (a part of the kidneys) causing inflammation and fibrosis (tissue scarring and thickening). As a result, patients with C3G often have high levels of protein in their urine (proteinuria) and progressive decline in kidney function over time. By attaching to the Factor B protein, iptacopan can

reduce the deposition of C3 in the kidney. This medicine has been shown to reduce levels of protein in the urine and the decline in kidney function.

2. What you need to know before you take FABHALTA

Do not take FABHALTA
- if you are allergic to iptacopan or any of the other ingredients of this medicine (listed in section 6).
- if you have not been vaccinated against *Neisseria meningitidis* and *Streptococcus pneumoniae*, unless your doctor decides that urgent treatment with FABHALTA is needed.
- if you have an infection caused by a type of bacteria called encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Haemophilus influenzae* type B, before starting FABHALTA treatment.

Warnings and precautions
Serious infection caused by encapsulated bacteria
FABHALTA may increase your risk of infection caused by encapsulated bacteria, including *Neisseria meningitidis* (bacteria that cause meningococcal disease, including serious infection of the linings of the brain and of the blood) and *Streptococcus pneumoniae* (bacteria causing pneumococcal disease, including infection of the lungs, ears and blood).

Talk to your doctor before you start FABHALTA to be sure that you receive vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae*. You may also receive vaccination against *Haemophilus influenzae* type B if this is available in your country. Even if you have had these vaccinations in the past, you might still need to be revaccinated before starting FABHALTA.

These vaccinations should be given at least 2 weeks before starting FABHALTA. If this is not possible, you will be vaccinated as soon as possible after you start FABHALTA and your doctor will prescribe antibiotics for you to use until 2 weeks after you have been vaccinated to reduce the risk of infection.

You should be aware that vaccination reduces the risk of serious infections but may not prevent all serious infections. You should be closely monitored by your doctor for symptoms of infection.

Tell your doctor immediately if you get any of the following symptoms of serious infection during treatment with FABHALTA:
- fever with or without shivers or chills
- headache and a fever
- fever and a rash
- fever with chest pain and cough
- fever with breathlessness/fast breathing
- fever with high heart rate
- headache with feeling sick (nausea) or vomiting
- headache with stiff neck or stiff back
- confusion
- body aches with flu-like symptoms
- clammy skin
- eyes sensitive to light

Children and adolescents
Do not give FABHALTA to children or adolescents below 18 years of age. No data are available on the safety and effectiveness of FABHALTA in this age group.

Other medicines and FABHALTA
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription. In particular:

Tell your doctor or pharmacist if you are using certain medicines because they may stop FABHALTA from working properly:
- certain medicines used to treat bacterial infections – such as rifampicin

Tell your doctor or pharmacist if you are using any of the following medicines because FABHALTA may stop these medicines from working properly:
- certain medicines used to treat epilepsy – such as carbamazepine
- certain medicines used to prevent organ rejection after an organ transplant – such as ciclosporin, sirolimus, tacrolimus
- certain medicines used to treat migraines – such as ergotamine
- certain medicines used to treat chronic pain – such as fentanyl
- certain medicines used to control involuntary movements or sounds – such as pimozide
- certain medicines used to treat an abnormal heart rhythm – such as quinidine
- certain medicines used to treat type 2 diabetes – such as repaglinide
- certain medicines used to treat hepatitis C infection – such as dasabuvir
- certain medicines used to treat cancer – such as paclitaxel

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. You should also tell your doctor if you become pregnant during treatment with FABHALTA. Your doctor will discuss with you the potential risks of taking FABHALTA during pregnancy or breast-feeding.

Your doctor will decide whether you should take FABHALTA while you are pregnant only after a careful risk-benefit assessment.

It is unkown whether iptacopan, the active substance in FABHALTA, passes into human milk and may affect the breast-fed newborn/infant.

Your doctor will decide whether you should stop breast-feeding or stop FABHALTA treatment, taking into account the benefit of breast-feeding for your baby and the benefit of treatment for yourself.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

3. How to take FABHALTA

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Do not exceed the prescribed dose.

The recommended dose is 200 mg (one capsule) to be taken by mouth twice daily (once in the morning and once in the evening). Swallow the FABHALTA capsule with a glass of water.

Taking FABHALTA at the same time each day will help you to remember when to take your medicine.

It is important that you take FABHALTA according to your doctor’s instructions. For patients with PNH, this is important to reduce the risk of breakdown of red blood cells due to PNH.

FABHALTA with food
FABHALTA can be taken with or without food.

Switching from other PNH medicines to FABHALTA
If you are switching from any other PNH medicine, ask your doctor when to start taking FABHALTA.

How long to take FABHALTA
PNH is a lifelong condition and it is expected that you will need to use FABHALTA for a long time. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you have questions about how long you will need to take FABHALTA, talk to your doctor.

If you take more FABHALTA than you should
If you have accidently taken too many capsules or if someone else accidentally takes your medicine, talk to your doctor immediately.

If you forget to take FABHALTA
If you miss a dose or doses, take one dose of FABHALTA as soon as you remember (even if it is shortly before the next scheduled dose), then take the next dose at the usual time. If you have PNH and you miss several doses in a row, contact your doctor who may decide to monitor you for any signs of the breakdown of red blood cells (see section "If you stop taking FABHALTA" below).

If you stop taking FABHALTA
Stopping your treatment with FABHALTA can make your condition worse. Do not stop taking FABHALTA without talking to your doctor first.

If you have PNH and your doctor decides to stop your treatment with this medicine, you will be monitored closely for at least 2 weeks after stopping treatment for any signs of the breakdown of red blood cells. Your doctor may prescribe a different PNH medicine or restart your FABHALTA treatment.

Symptoms or problems that can happen due to breakdown of red blood cells include:
- low levels of haemoglobin in your blood, as seen in blood tests
- tiredness
- blood in the urine
- pain in the stomach (abdomen)
- shortness of breath
- trouble swallowing
- erectile dysfunction (impotence)
- blood clots (thrombosis)

If you experience any of these after stopping treatment, contact your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

<u>Serious side effects</u>

The most serious side effect is serious infection. If you experience any of the symptoms of serious infection listed under "Serious infection caused by encapsulated bacteria" in section 2 of this leaflet, you should immediately inform your doctor.

Side effects for PNH

Very common (may affect more than 1 in 10 people)
- infections of the nose and throat (upper respiratory tract infection)
- headache
- diarrhoea

Common (may affect up to 1 in 10 people)
- persistent cough or irritation of the airways (bronchitis)
- low levels of platelets (which help the blood clot) in the blood (thrombocytopenia), which may cause you to bleed or bruise more easily
- dizziness
- pain in the stomach (abdomen)
- feeling sick (nausea)
- joint pain (arthralgia)
- urinary tract infection

Uncommon (may affect up to 1 in 100 people)
- lung infection, which can cause chest pain, cough and fever
- itchy rash (urticaria)

Side effects for C3G

Very common (may affect more than 1 in 10 people)
- infections of the nose and throat (upper respiratory tract infection)

Common (may affect up to 1 in 10 people)
- pneumococcal infection including lung infection (pneumonia) and blood infection (sepsis)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store FABHALTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What FABHALTA contains
- The active substance is iptacopan.
- The other ingredients are:
  - Capsule shell: gelatin, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172)

- Printing ink: black iron oxide (E172), concentrated ammonia solution (E527), potassium hydroxide (E525), propylene glycol (E1520), Shellac (E904)

What FABHALTA looks like and contents of the pack
Pale yellow, opaque hard capsules, with “LNP200” on the body and “NVR” on the cap, containing white or almost white to pale purplish-pink powder. The capsule size is approximately 21 to 22 mm.

FABHALTA is supplied in PVC/PE/PVDC blisters with aluminium foil backing.

FABHALTA is available in
- packs containing 28 or 56 hard capsules and in
- multipacks comprising 3 cartons, each containing 56 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Novartis Europharm Limited
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Manufacturer
Novartis Pharmaceutical Manufacturing LLC
Verovškova Ulica 57
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Slovenia

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Germany

Novartis Farmacéutica S.A.
Gran Via De Les Corts Catalanes 764
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Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Sverige
Novartis Sverige AB
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

同種同効品一覧

C3 腎症を適応とする本邦既承認の医薬品は無く，本剤に関する同種同効品はない。

最新の添付文書を参照すること

2024年8月改訂（第2版）からの変更

日本標準商品分類番号
873999

貯法：室温保存

有効期間：36ヵ月

補体B因子阻害剤
イプタコパン塩酸塩水和物カプセル

承認番号	30600AMX00147000
販売開始	2024年8月

ファビハルタ®カプセル200mg

FABHALTA® capsules

劇薬、処方箋医薬品
（注意－医師等の処方箋により使用すること）

NOVARTIS

1. 警告

1.1 本剤は補体経路を阻害するため、髄膜炎菌、肺炎球菌、インフルエンザ菌等の莢膜形成細菌による重篤な感染症を発症することがあり、特に髄膜炎菌感染症は急激に重症化し、死亡に至るおそれもあるため、以下の点に十分注意すること。［5.21、9.1.1、9.1.2、11.1.1、11.1.2参照］

1.1.1 本剤の投与に際しては、髄膜炎菌等による感染症の初期徴候（発熱、頭痛、項部硬直等）に注意して観察を十分に行い、髄膜炎菌等の重篤な感染症が疑われた場合には、直ちに診察し、抗菌剤の投与等の適切な処置を行うこと。

1.1.2 髄膜炎菌、肺炎球菌及びインフルエンザ菌b型に対するワクチンの接種歴を確認し、未接種の場合又は追加接種が必要な場合は、原則、本剤投与前にワクチンを接種すること。必要に応じて、本剤投与中のワクチンの追加接種を考慮すること。

1.1.3 髄膜炎菌感染症は致命的な経過をたどることがあるので、緊急時に十分に措置できる医療施設及び医師のもとで、あるいは髄膜炎菌感染症の診断及び治療が可能な医療施設との連携下で本剤を投与すること。

1.1.4 髄膜炎菌等の莢膜形成細菌による感染症のリスクについて患者に説明し、当該感染症の初期徴候を確実に理解させ、感染症に関連する症状が発現した場合には、主治医に連絡するよう患者に注意を与えること。

1.2 発作性夜間ヘモグロビン尿症又はC3腎症に十分な知識を持つ医師のもとで、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与開始に先立ち、本剤は疾病を完治させる薬剤ではないことを含め、本剤の有効性及び危険性を患者又はその家族に十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

2.1 髄膜炎菌感染症に罹患している患者［症状を悪化させるおそれがある。］［11.1.1参照］

2.2 肺炎球菌、インフルエンザ菌等の莢膜形成細菌による重篤な感染症に罹患している患者［症状を悪化させるおそれがある。］［11.1.2参照］

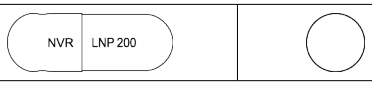
2.3 本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	ファビハルタカプセル200mg
有効成分	1カプセル中イプタコパン塩酸塩水和物225.80mg（イプタコパンとして200mg）
添加剤	カプセル本体にゼラチン、三二酸化鉄、酸化チタン含有

3.2 製剤の性状

販売名		ファビハルタカプセル200mg
性状	外観	微黄色不透明の硬カプセル
	内容物	白色～薄い帯紫赤白色の粉末
外形		
識別コード		NVR LNP200
大きさ（約）		長径：21.7mm　短径：7.6mm　質量：0.32g

4. 効能又は効果

○発作性夜間ヘモグロビン尿症
○C3腎症

5. 効能又は効果に関連する注意

〈効能共通〉

5.21 本剤は、補体B因子に結合して補体第二経路を阻害するため、髄膜炎菌、肺炎球菌、インフルエンザ菌等の莢膜形成細菌による感染症を発症しやすくなる可能性があることから、本剤の有効性及び安全性を十分に理解した上で、本剤投与の是非を慎重に検討し、適切な対象患者に使用すること。また、本剤投与に際しては、髄膜炎菌、肺炎球菌及びインフルエンザ菌b型に対するワクチンの接種歴を確認し、未接種の場合又は追加接種が必要な場合は、原則、本剤投与開始の少なくとも2週間前までにそれらのワクチンを接種すること。必要に応じて、本剤投与中のワクチンの追加接種を考慮すること。［1.1、9.1.1、9.1.2、11.1.1、11.1.2、17.1.1、17.1.2参照］

〈発作性夜間ヘモグロビン尿症〉

5.12 補体（C5）阻害剤による適切な治療を行っても、十分な効果が得られない場合に投与すること。［17.1.1参照］

〈C3腎症〉

5.3 「臨床成績」の項の内容を熟知し、臨床試験に組み入れられた患者の背景（尿蛋白、腎機能等）を十分に理解した上で、適応患者を選択すること。［17.1.2 参照］

6. 用法及び用量

通常、成人にはイプタコパンとして1回200mgを1日2回経口投与する。

7. 用法及び用量に関連する注意

〈発作性夜間ヘモグロビン尿症〉

7.1 補体（C5）阻害剤から本剤に切り替える際は、補体（C5）阻害剤の中止に伴う溶血のリスクを低減するため、前治療薬との投与間隔を考慮すること。［17.1.1参照］

・エクリズマブ（遺伝子組換え）から切り替える場合、エクリズマブ（遺伝子組換え）の最終投与1週間後を目安に本剤の投与を開始すること。

・ラブリズマブ（遺伝子組換え）から切り替える場合、ラブリズマブ（遺伝子組換え）の最終投与6週間後を目安に本剤の投与を開始すること。

8. 重要な基本的注意

〈発作性夜間ヘモグロビン尿症〉

8.1 本剤を中止した場合に溶血が認められるおそれがある。本剤の投与を中止した患者では、本剤の最終投与から最低2週間は、溶血に付随する臨床症状及びその徴候［LDH値の上昇を伴うヘモグロビン（Hb）値の急激な減少、疲労、ヘモグロビン尿、腹痛、呼吸困難、主要血管事象（血栓症）、嚥下障害又は勃起不全等］の変化を注意深く観察し、必要に応じて適切な処置を行うこと。

8.2 本剤投与により、総コレステロール、LDLコレステロール及びトリグリセリドの上昇等の脂質異常症があらわれることがあるので、本剤投与開始後は定期的に血液検査を実施すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 髄膜炎菌感染症の既往のある患者

髄膜炎菌感染症に罹患しやすくなるおそれがある。[1.1、5.21、11.1.1参照]

9.1.2 感染症の患者又は感染症が疑われる患者

特に莢膜形成細菌（髄膜炎菌、肺炎球菌、インフルエンザ菌等）による感染症が悪化するおそれがある。[1.1、5.21、11.1.1、11.1.2参照]

9.2 腎機能障害患者

9.2.1 重度（eGFRが30mL/min/1.73m²未満）の腎機能障害のある患者

患者の状態を慎重に観察し、副作用発現に十分注意すること。本剤の血中濃度が上昇し、本剤の副作用が増強されるおそれがある。[16.6.1参照]

9.3 肝機能障害患者

患者の状態を慎重に観察し、副作用発現に十分注意すること。非結合型の血中イプタコパン濃度が上昇し、本剤の副作用が増強されるおそれがある。[16.6.2参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。雌ラットを用いた受胎能及び着床までの初期胚発生試験において、臨床用量の5.4倍の曝露（AUC）で、着床前及び着床後胚死亡率の高値、並びに生存胎児数の低値が認められている。

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤の母乳中への移行は不明である。

9.7 小児等

小児等を対象とした臨床試験は実施していない。

10. 相互作用

本剤は主にCYP2C8で代謝され、有機アニオントランスポーター（OATP）1B1及びOATP1B3の基質である。また、本剤は、CYP2C8阻害作用及びCYP3A4誘導作用を有する。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP2C8を阻害する薬剤 クロピドグレル等 [16.7.1参照]	本剤の副作用が増強されるおそれがあるため、患者の状態を慎重に観察し、副作用発現に十分注意すること。	これらの薬剤のCYP2C8阻害作用により、本剤の血中濃度が上昇する可能性がある。
OATP1B1及びOATP1B3を阻害する薬剤 シクロスポリン等 [16.7.2参照]	本剤の副作用が増強されるおそれがあるため、患者の状態を慎重に観察し、副作用発現に十分注意すること。	これらの薬剤のOATP1B1及びOATP1B3阻害作用により、本剤の血中濃度が上昇する可能性がある。
CYP3A4の基質となる薬剤 ミダゾラム等 [16.7.4参照]	これらの薬剤の有効性が減弱するおそれがある。	本剤のCYP3A4誘導作用により、これらの薬剤の血中濃度が低下する可能性がある。
CYP2C8の基質となる薬剤 レパグリニド等 [16.7.4参照]	これらの薬剤の副作用が増強されるおそれがあるため、患者の状態を慎重に観察し、副作用発現に十分注意すること。	本剤のCYP2C8阻害作用により、これらの薬剤の血中濃度が上昇する可能性がある。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 髄膜炎菌感染症（頻度不明）

髄膜炎又は敗血症を発症し、急速に生命を脅かす、あるいは死亡に至るおそれがある。本剤の投与に際しては、当該感染症の初期徴候（発熱、頭痛、項部硬直、羞明、精神状態の変化、痙攣、悪心・嘔吐、紫斑、点状出血等）等の観察を十分に行うこと。髄膜炎菌感染症が疑われた場合には、直ちに診察し、抗菌剤の投与等の適切な処置を行うこと。[1.1、2.1、5.21、9.1.1、9.1.2参照]

11.1.2 重篤な感染症（0.6%）

肺炎球菌、インフルエンザ菌等の莢膜形成細菌による重篤な感染症があらわれることがあり、肺炎球菌感染症では敗血症に至った症例が報告されている。[1.1、2.2、5.21、9.1.2参照]

11.2 その他の副作用

	~~5%以上~~	5%未満	頻度不明
血液およびリンパ系障害	~~血小板数減少~~	―血小板数減少	―
胃腸障害	―	下痢、腹痛、悪心	―
感染症および寄生虫症	―	上気道感染、尿路感染、気管支炎	細菌性肺炎
筋骨格系および結合組織障害	―	関節痛	―
神経系障害	~~頭痛~~	頭痛、浮動性めまい	―
皮膚および皮下組織障害	―	―	蕁麻疹

14. 適用上の注意

14.1 薬剤交付時の注意

PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

16. 薬物動態

16.1 血中濃度

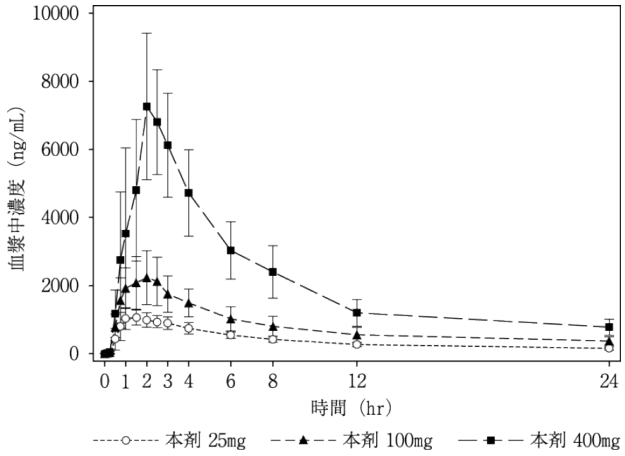
16.1.1 単回投与

日本人健康成人（24例）に本剤25、100及び400mg[注1)]を単回経口投与したとき、投与1.5～2.25時間後（中央値）にCmaxに到達し、曝露量は用量比を下回った。T1/2は13.2～24.7時間であった[1)]。

本剤25、100及び400mgを単回経口投与したときの血漿中薬物動態パラメータ

薬物動態パラメータ	25mg n=8	100mg n=8	400mg n=8
Cmax (ng/mL)	1160 ± 254	2460 ± 735	7990 ± 1360
AUClast (ng・h/mL)	12400 ± 3240	28300 ± 8930	78300 ± 23600
Tmax (h) ※	1.50 (1.00～3.00)	1.75 (1.00～2.50)	2.25 (1.00～3.00)
T1/2 (h)	13.2 ± 2.15	15.1 ± 3.64	24.7 ± 15.6

平均値±標準偏差　※中央値（最小値～最大値）



日本人健康成人に本剤25、100及び400mgを単回経口投与したときの血漿中未変化体濃度推移（平均値±標準偏差）

16.1.2 反復投与

健康成人（6例）に本剤200mgを1日2回反復経口投与したとき、投与約2時間後（中央値）にCmaxに到達した。トラフ濃度の推移から投与約5日目で定常状態に達し、投与14日目の累積率は約1.4であった。本剤200mgを1日2回反復経口投与したときの、定常状態におけるイプタコパンのT1/2は、25時間であった。本剤25mg～200mg[注1)]1日2回反復経口投与したとき、25～100mgの用量間では曝露量の増加は用量比を下回ったが、100mg及び200mg間では概ね用量に比例して曝露量が増加した[2)]（外国人データ）。

16.2 吸収

16.2.1 食事の影響

健康成人（12例）に本剤100mg[注1)]を空腹時及び高脂肪食摂取後に単回経口投与したとき、イプタコパンの曝露量は食事による影響を受けなかった[2)]（外国人データ）。

16.3 分布

16.3.1 血漿蛋白結合率

イプタコパンは全身循環血中でB因子に結合することにより濃度依存的な血漿蛋白結合を示した。イプタコパンの1000～10000ng/mLの血漿中濃度において、血漿蛋白結合率は75%～93%であった[3]（*in vitro*）。

16.3.2 体組織への分布

健康成人（6例）に本剤200mgを1日2回反復経口投与したとき、定常状態における見かけの分布容積は288Lであった[2]（外国人データ）。

16.4 代謝

イプタコパンの主な消失経路は代謝であった。イプタコパンの代謝にはN-脱アルキル化、O-脱エチル化、酸化等があり、主にCYP2C8（酸化的代謝における寄与率98%）により代謝される[4]。健康成人に^{14}C標識した本剤100mg[注1)]を単回経口投与したときの血漿中の主な成分は未変化体であるイプタコパンであり、血漿中総放射能のAUC0-48hの83.0%であった[5]（外国人データ）。

16.5 排泄

健康成人に^{14}C標識した本剤100mg[注1)]を単回経口投与したときの、総放射能（イプタコパン及び代謝物）の平均総排泄率は、投与量のそれぞれ便中71.5%及び尿中24.8%であり、投与量の96%以上が排泄された。未変化体として投与量の17.9%が尿中に、16.8%が便中に排泄された[5]（外国人データ）。

16.6 特定の背景を有する患者

16.6.1 腎機能障害者

母集団薬物動態解析を用いて、発作性夜間ヘモグロビン尿症患者及びC3腎症患者における腎機能障害がイプタコパンの曝露量に及ぼす影響を評価した。その結果、発作性夜間ヘモグロビン尿症患者では、腎機能が正常な患者（98例）、軽度（eGFR 60以上、90mL/min/1.73m^{2}未満）（45例）、中等度（eGFR 30以上、60mL/min/1.73m^{2}未満）（17例）及び重度（eGFR 30mL/min/1.73m^{2}未満）（1例）の腎機能障害患者におけるイプタコパンのAUCtauの平均値は、それぞれ32100、37500、43800及び47000ng・h/mL、Cmaxの平均値はそれぞれ3940、4480、5170及び5610ng/mLと推定された。C3腎症患者では、腎機能が正常な患者（46例）、軽度（eGFR 60以上、90mL/min/1.73m^{2}未満）（26例）、中等度（eGFR 30以上、60mL/min/1.73m^{2}未満）（20例）及び重度（eGFR 30mL/min/1.73m^{2}未満）（8例）の腎機能障害患者におけるイプタコパンのAUCtauの平均値は、それぞれ31560、31900、40610及び48950ng・h/mL、Cmaxの平均値はそれぞれ3910、3680、4790及び5170ng/mLと推定された。なお、透析患者については評価を行っていない。［9.2.1参照］

16.6.2 肝機能障害者

軽度（Child-Pugh分類A）、中等度（Child-Pugh分類B）又は重度（Child-Pugh分類C）の肝機能障害患者に本剤200mgを単回経口投与し、肝機能障害がイプタコパンの曝露量に及ぼす影響を評価した。血漿中のイプタコパンについて、軽度の肝機能障害患者（8例）ではCmaxが約1.04倍に増加したが、中等度（8例）又は重度（6例）の肝機能障害患者では変化は認められなかった。軽度及び重度の肝機能障害患者ではいずれもAUCinfが1.03倍に増加したが、中等度の肝機能障害患者では変化は認められなかった。その一方、血漿中の非結合型のイプタコパンについて、軽度、中等度及び重度の肝機能障害患者でCmaxはそれぞれ1.38倍、1.67倍及び2.11倍に増加した。また、AUCinfはそれぞれ1.48倍、1.58倍及び3.71倍に増加した[6]（外国人データ）。［9.3参照］

16.7 薬物相互作用

16.7.1 クロピドグレル

健康成人（18例）にクロピドグレル（CYP2C8阻害剤）を投与初日に300mg、2日目から75mgを1日1回4日間反復経口投与し、2日目に本剤100mg[注1)]を単回投与したとき、本剤の単独投与時に対するクロピドグレル併用時のイプタコパンのCmax及びAUCinfの幾何平均値の比はそれぞれ1.05及び1.36であった[7]（外国人データ）。［10.2参照］

16.7.2 シクロスポリン

健康成人（20例）にシクロスポリン（OATP1B1/1B3阻害剤）175mgを1日2回4日間反復経口投与し、1日目に本剤100mg[注1)]を単回投与したとき、本剤の単独投与時に対するシクロスポリン併用時のイプタコパンのCmax及びAUCinfの幾何平均値の比はそれぞれ1.41及び1.50であった[7]（外国人データ）。［10.2参照］

16.7.3 ジゴキシン、ロスバスタチン

健康成人（17例）に本剤200mgを1日2回15日間反復経口投与し、投与6日目にジゴキシン（P-gpの基質）0.25mg及びロスバスタチン（OATP1B1/1B3の基質）10mgを単回投与したとき、ジゴキシンの単独投与時に対する本剤併用時のCmax及びAUCinfの幾何平均値の比はそれぞれ1.08及び1.02であった。ロスバスタチンの単独投与時に対する本剤併用時のCmax及びAUCinfの幾何平均値の比はそれぞれ1.00及び1.01であった[7]（外国人データ）。

16.7.4 *In vitro*試験

*In vitro*試験においてイプタコパンはCYP2C8の阻害作用及びCYP3A4の誘導作用を示した[8]。［10.2参照］

注1）本剤の承認された用法及び用量は、「通常、成人にはイプタコパンとして1回200mgを1日2回経口投与する」である。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈発作性夜間ヘモグロビン尿症〉

17.1.1 国際共同第Ⅲ相試験（APPLY-PNH試験）

補体C5阻害剤（エクリズマブ又はラブリズマブ）による治療を行ってもヘモグロビン（Hb）値が10g/dL未満である発作性夜間ヘモグロビン尿症患者97例（日本人9例を含む）を対象として、多施設共同ランダム化非盲検実薬対照並行群間比較試験を実施した。なお、治験薬初回投与2週間前までの髄膜炎菌ワクチン接種を必須とし、肺炎球菌及びインフルエンザ菌に対するワクチンも、実施国又は地域で使用可能であれば接種することとした。また、接種から2週間以内に本剤の投与を開始する必要がある場合は、抗菌剤を予防投与することとした。試験は24週間の主要評価期（本剤又は補体C5阻害剤を投与）、及び24週間の継続投与期（本剤を投与）で構成された。本剤は、1回200mgを1日2回経口投与した。

主要評価項目である「無輸血でDay126～168にHb値のベースラインから2g/dL以上の増加」及び「無輸血でDay126～168にHb値12g/dL以上」と定義する奏効の有無について、奏効患者数及び調整群間差は以下のとおりであり、いずれにおいても補体C5阻害剤に対する本剤の優越性が検証された。

	本剤群 （62例、うち日本人6例）	補体C5阻害剤群 （35例、うち日本人3例）
無輸血でHb値2g/dL以上の増加		
奏効患者数[a)]	51/60例	0/35例
調整群間差 （本剤群－補体C5阻害剤群） ［95%信頼区間］ p値[b) c)]	80.2% ［71.2, 87.6］ <0.0001	
無輸血でHb値12g/dL以上		
奏効患者数[a)]	42/60例	0/35例
調整群間差 （本剤群－補体C5阻害剤群） ［95%信頼区間］ p値[b) c)]	67.0% ［56.4, 76.9］ <0.0001	

a）観察データに基づく評価可能症例のうちの奏効患者数

b）投与群を独立変数とし、前治療の補体C5阻害剤の種類、無作為化前6ヵ月の輸血歴の有無、性、年齢（45歳以上／未満）、ベースラインのヘモグロビン値（9g/dL以上／未満）を共変量とするFirth補正を用いた共通の切片を持つロジスティック回帰モデルにより算出。調整群間差はモデルから算出した各被験者の予測奏効確率に対する群ごとの平均値の差であり、95%信頼区間はbootstrap法を用いた。

c）有意水準は片側0.0125

継続投与期終了時の本剤投与による副作用発現割合は、21.9%（21/96例）であった。主な副作用は頭痛5.2%（5/96例）、血小板数減少及び悪心4.2%（4/96例）、下痢及び関節痛3.1%（3/96例）であった[9]。［5.1、5.2、7.1参照］

〈C3腎症〉

17.1.2 国際共同第Ⅲ相試験（APPEAR-C3G試験）

最大推奨用量又は最高忍容用量のレニン-アンジオテンシン系阻害薬を含む支持療法を受けているにもかかわらず尿蛋白クレアチニン比（UPCR）が1g/g以上で推算GFR（eGFR）が30mL/min/1.73m^{2}以上のC3腎症患者74例（日本人4例を含む）を対象として、多施設共同ランダム化二重盲検プラセボ対照並行群間比較試験を実施した。なお、治験薬初回投与2週間前までの髄膜炎菌ワクチン及び肺炎球菌ワクチン接種を必須とし、インフルエンザ菌に対するワクチンも、実施国又は地域で使用可能であれば接種することとした。また、接種から2週間以内に本剤の投与を開始する必要がある場合は、抗菌剤を予防投与することとした。試験は6ヵ月間の二重盲検投与期（本剤又はプラ

セボを投与)、及び6ヵ月間の非盲検投与期（本剤を投与）で構成された。二重盲検投与期では、本剤1回200mg又はプラセボを、非盲検投与期では本剤1回200mgを1日2回経口投与した。二重盲検投与期の主要評価項目である投与6ヵ月時の24時間蓄尿によるUPCRのベースラインに対する比について、本剤のプラセボに対する優越性が検証された。

	本剤群 （38例、うち日本人2例）[a]	プラセボ群 （36例、うち日本人2例）[a]
ベースラインのUPCR（g/g）の平均値±標準偏差（例数）	3.85±2.29（38）	2.93±1.71（36）
投与6ヵ月時のUPCR（g/g）の平均値±標準偏差（例数）	3.03±2.61（37）	3.14±1.56（36）
投与6ヵ月時のUPCRのベースラインに対する比の最小二乗幾何平均値[95%信頼区間][b]	0.698 [0.572, 0.852]	1.076 [0.881, 1.313]
投与6ヵ月時のUPCRのベースラインに対する比の本剤vsプラセボ		
最小二乗幾何平均の比[95%信頼区間][b]	0.649［0.489, 0.862］	
減少率[95%信頼区間]%[b]	35.1[13.8, 51.1]	
p値[b][c]	0.0014	

a）解析に含めた被験者数（ベースライン又は共変量に欠測値がない被験者数）

b）抗蛋白尿療法の開始又は増量後及び腎代替療法の開始後のデータは欠測とみなし、本剤群はJump to reference（J2R）法、プラセボ群はMissing at random（MAR）を仮定した上で、多重代入法により欠測値を補完した。目的変数を各評価時点のUPCRのベースラインに対する比の対数変換値、説明変数を投与群、評価時点、投与群と評価時点の交互作用、無作為化時のステロイド又はミコフェノール酸の使用有無及びベースラインUPCRの対数変換値とし、被験者内の時点間の相関に無構造の共分散行列を用いたmixed model with repeated measures（MMRM）により算出した。

c）有意水準は片側0.025

本試験終了時の本剤投与による副作用発現割合は、13.5%（10/74例）であり、2例以上に発現した副作用はなかった[10]。［5.1、5.3参照］

18. 薬効薬理

18.1 作用機序

〈効能共通〉

イプタコパンは補体B因子に結合してその活性を阻害することで、C3転換酵素の活性を阻害して補体第二経路の活性化を阻害し、下流のC5転換酵素形成を含むカスケード反応を阻止する。

〈発作性夜間ヘモグロビン尿症〉

発作性夜間ヘモグロビン尿症患者において、イプタコパンは膜侵襲複合体形成を阻害して血管内溶血を抑制するとともに、C3フラグメントのオプソニン化を阻害して血管外溶血を抑制する。

〈C3腎症〉

C3腎症では、補体第二経路が過剰に活性化して分解されたC3が糸球体に沈着し炎症が生じることにより、腎機能が低下して、最終的に腎不全に至る。C3腎症患者において、イプタコパンは補体B因子に結合することにより補体第二経路の過剰な活性化を阻害する[11]。

18.2 補体B因子への結合作用

イプタコパンは競合結合アッセイでレポーター分子の補体B因子触媒ドメインへの結合を阻害した（IC50値：9.6nM）[10,12]（*in vitro*）。

18.3 補体第二経路活性化の阻害作用

18.3.1 イプタコパンはマウス血清でC3フラグメント沈着を阻害し、ヒト血清で膜侵襲複合体の形成を阻害した[10,12]（*in vitro*）。

18.3.2 イプタコパンは発作性夜間ヘモグロビン尿症患者由来赤血球の溶血及び赤血球表面へのC3フラグメント沈着を阻害した[11]（*in vitro*）。

18.3.3 イプタコパンは、関節炎を自然発症するマウス血清を移入することにより作製した関節炎モデルマウス[11]、及びラット尿細管上皮タンパク質Fx1Aに対する抗体を含有したヒツジ血清を投与して作製した受動的ヘイマン腎炎モデルラットに対し、疾患の進行又は発症を抑制した[12,13]（*in vivo*）。

19. 有効成分に関する理化学的知見

一般的名称

イプタコパン塩酸塩水和物（Iptacopan Hydrochloride Hydrate）

化学名

4-{(2*S*,4*S*)-4-Ethoxy-1-[(5-methoxy-7-methyl-1*H*-indol-4-yl)methyl]piperidin-2-yl}benzoic acid monohydrochloride monohydrate

分子式

$C_{25}H_{30}N_2O_4 \cdot HCl \cdot H_2O$

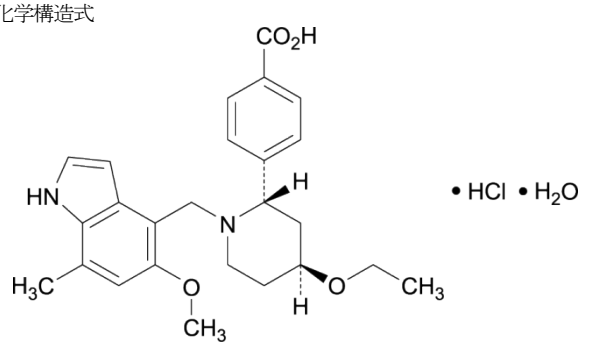
分子量

476.99

性状

白色～薄い帯紫赤白色の粉末である。

化学構造式



21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

21.2 日本人での投与経験が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

21.3 本剤の投与が、発作性夜間ヘモグロビン尿症の診断、治療に精通し、本剤のリスク等についても十分に管理できる医師・医療機関のもとで、髄膜炎菌感染症の診断、治療に精通した医師との連携を取った上でのみ行われるよう、製造販売にあたって必要な措置を講じること。

22. 包装

14カプセル［14カプセル（PTP）×1］

23. 主要文献

1）社内資料：日本人健康被験者を対象とした単回投与試験（X1102試験）（2024年6月24日承認、CTD2.7.2-2.2.1） ［20240082］

2）社内資料：外国人健康被験者を対象とした単回又は反復投与試験及び食事の影響試験（X2101試験）（2024年6月24日承認、CTD2.7.2-2.2.2） ［20240083］

3）社内資料：血球移行性及び血漿蛋白結合（2024年6月24日承認、CTD2.7.2-2.1.1） ［20240084］

4）社内資料：代謝（2024年6月24日承認、CTD2.7.2-2.1.2） ［20240085］

5）社内資料：マスバランス試験（A2101試験）（2024年6月24日承認、CTD2.7.2-2.2.3） ［20240086］

6）社内資料：肝機能障害患者を対象とした薬物動態試験（A2105試験）（2024年6月24日承認、CTD2.7.2-2.4.1） ［20240089］

7）社内資料：薬物間相互作用試験（A2104試験）（2024年6月24日承認、CTD2.7.2-2.5.1） ［20240090］

8）社内資料：*In vitro*試験（2024年6月24日承認、CTD2.7.2-3.4.1） ［20240095］

9）社内資料：国際共同第III相試験（C12302/APPLY-PNH試験）（2024年6月24日承認、CTD2.7.6-4.1.1） ［20240096］

10) 社内資料：国際共同第III相試験(B12301/APPEAR-C3G試験)(20XX年X月X日承認、CTD2.7.6-4.1.1) [20250018]
11) Schubart A, et al.: PNAS. 2019;116(16):7926-7931 [20240093]
12) 社内資料：*In vitro*活性の検討（2024年6月24日承認、CTD2.6.2-2.1) [20240092]
13) 社内資料：*In vivo*ラット受動的ヘイマン腎炎モデルの検討（2024年6月24日承認、CTD2.6.2-2.3.2.2) [20240094]

24. 文献請求先及び問い合わせ先

ノバルティスファーマ株式会社 ノバルティスダイレクト
〒105-6333 東京都港区虎ノ門1-23-1

25. 保険給付上の注意

本剤は新医薬品であるため、厚生労働省告示第97号（平成20年3月19日付）に基づき、2025年8月末日までは、投薬期間は1回14日分を限度とされています。

26. 製造販売業者等

26.1 製造販売（輸入）

ノバルティス ファーマ株式会社
東京都港区虎ノ門１－２３－１

目　　次

略号一覧

略号	省略していない表現 (英)	省略していない表現 (日)
b.i.d.	bis in die/twice a day	1 日 2 回
C3	complement component 3	補体成分 3
eGFR	estimated glomerular filtration rate	推算糸球体濾過量
MMRM	mixed model with repeated measures	反復測定混合効果モデル
UPCR	urinary protein to creatinine ratio	尿蛋白／クレアチニン比

1　効能又は効果欄

1.1　効能又は効果

○発作性夜間ヘモグロビン尿症

○C3 腎症

（下線：変更箇所）

1.2　効能又は効果の設定根拠

C3 腎症患者を対象とした日本参加の国際共同第 III 相試験（B12301 試験），外国第 II 相試験（X2202 試験），及び両試験の投与期を完了した被験者が移行できる継続試験（B12001B 試験）において，成人 C3 腎症に対する LNP023 の臨床的に意味のある有効性が示され，忍容性及び安全性は良好であったことから，効能又は効果を「C3 腎症」と設定した。

有効性

B12301 試験は，腎移植を受けたことがない C3 腎症患者 74 名を対象とした，ランダム化，二重盲検，プラセボ対照，並行群間比較試験である。主要評価項目である Month 6 の UPCR（24 時間蓄尿）のベースラインに対する比の調整幾何平均値は，LNP023 群でプラセボ群と比べて 35.1%減少し（片側 p 値 = 0.0014，MMRM），LNP023 群のプラセボ群に対する優越性が検証された。副次評価項目である Month 6 の eGFR のベースラインからの変化量の調整平均値の群間差（LNP023 群 − プラセボ群）は 2.156 mL/min/1.73m^2 で統計学的に有意な差ではなかったものの，LNP023 群ではプラセボ群と比べて eGFR の数値的な改善がみられた（2.5-4.3.4.1 項）。また，試験登録前 2 年間の血清クレアチニン値を収集して eGFR を算出し（ヒストリカルデータ），LNP023 投与前後の eGFR slope を評価した。その結果，LNP023 投与前には eGFR の継続的な低下がみられたが，LNP023 投与後にはその低下が抑制され，eGFR を安定化することが示された［eGFR slope の投与前後の変化は LNP023 群の投与 6 ヵ月後で 10.73 mL/min/1.73m^2/year］。

B12301 試験の日本人被験者数は各群 2 名と少ないものの，日本人被験者でも LNP023 投与後に UPCR の減少傾向がみられ，eGFR のベースラインからの変化量の推移に LNP023 投与後の明らかな悪化傾向はみられず，全体集団と同様の結果が示唆された。

X2202 試験は，C3 腎症患者を対象とした単群試験である。腎移植を受けたことがない C3 腎症被験者（コホート A）では，主要評価項目である Month 3 の UPCR（24 時間蓄尿）のベースラインに対する比の調整幾何平均値は 45%減少した（両側 p 値 = 0.0003，MMRM）。腎移植後に C3 腎症の再発を認めた被験者（コホート B）では，主要評価項目である Month 3 の C3 沈着スコアのベースラインとの差の中央値の Hodges-Lehmann 推定値は−2.50 で，ベースラインからの減少がみられた（p = 0.0313）。

B12001B 試験は，親試験の投与期を完了した C3 腎症患者を組み入れた継続試験である。X2202 試験から移行した全被験者が Month 33（B12001B 試験の Month 30 に相当）を終了した時点で，

X2202 試験から移行した被験者を対象に実施した中間解析の結果から，LNP023 を Month 33 まで投与した場合の長期的な効果の持続が確認された。

以上より，C3 腎症患者に対する LNP023 の臨床的に意味のある有効性が示された。

安全性

B12301 試験の 6 ヵ月間の二重盲検投与期のデータから，LNP023 の安全性及び忍容性にプラセボとの明らかな違いは特定されなかった。死亡又は投与中止に至った有害事象は報告されなかった。主要なリスクである莢膜形成細菌による感染症が報告されたものの，適切な処置によりいずれも回復した。髄膜炎菌による感染症の報告はなかった。また，併合データ（B12301 試験，X2202 試験，及び B12001B 試験）から，LNP023 の投与期間の延長に伴う新たな安全性の問題は認められなかった。

以上より，C3 腎症患者に LNP023 を投与したときの安全性プロファイルは，LNP023 の既承認の発作性夜間ヘモグロビン尿症患者に対する安全性プロファイルと同様であり，C3 腎症で新たに認められた安全性の問題はなかった。また，日本人に特有の安全性の問題は認められなかった。

2　効能又は効果に関連する注意欄

2.1　効能又は効果に関連する注意

〈効能共通〉

5.1. 本剤は、補体 B 因子に結合して補体第二経路を阻害するため、髄膜炎菌、肺炎球菌、インフルエンザ菌等の莢膜形成細菌による感染症を発症しやすくなる可能性があることから、本剤の有効性及び安全性を十分に理解した上で、本剤投与の是非を慎重に検討し、適切な対象患者に使用すること。また、本剤投与に際しては、髄膜炎菌、肺炎球菌及びインフルエンザ菌 b 型に対するワクチンの接種歴を確認し、未接種の場合又は追加接種が必要な場合は、原則、本剤投与開始の少なくとも 2 週間前までにそれらのワクチンを接種すること。必要に応じて、本剤投与中のワクチンの追加接種を考慮すること。［1.1、9.1.1、9.1.2、11.1.1-11.1.3、17.1.1、17.1.2 参照］

〈発作性夜間ヘモグロビン尿症〉

5.2. 補体（C5）阻害剤による適切な治療を行っても、十分な効果が得られない場合に投与すること。［17.1.1 参照］

〈C3 腎症〉

5.3. 「臨床成績」の項の内容を熟知し、臨床試験に組み入れられた患者の背景（尿蛋白、腎機能等）を十分に理解した上で、適応患者を選択すること。［17.1.2 参照］

（下線：変更箇所）

2.2　効能又は効果に関連する注意の設定根拠

効能追加に伴い，効能共通の注意と効能ごとの注意を記載するため，〈効能共通〉，〈発作性夜間ヘモグロビン尿症〉，〈C3 腎症〉の項を作成した。〈効能共通〉及び〈発作性夜間ヘモグロビン尿症〉の記載は順番を入れ替えたが，内容は初回承認時から変更はない。

〈C3 腎症〉の項については，臨床試験に組み入れられた患者及びその試験成績を理解した上で，本剤の適応となる患者を適切に選択する必要があるため，使用上の注意として注意喚起することとした。

3　用法及び用量欄

3.1　用法及び用量

通常，成人にはイプタコパンとして 1 回 200㎎を 1 日 2 回経口投与する。（初回承認時より変更無し）

3.2　用法及び用量の設定根拠

C3 腎症患者に対する LNP023 の添付文書の用法及び用量は，200 mg b.i.d.で実施した検証試験である B12301 試験で，LNP023 の臨床的及び統計学的に意味のある有効性が認められたこと，忍容性は良好で安全性に大きな問題はみられなかったこと（1.2 項），バイオマーカーの結果から C3 腎症に関連する血清中 C3 値及び補体系バイオマーカーに対する LNP023 の効果が裏付けられたこと（2.7.3-3.2.5 項）を踏まえて設定した。

4　用法及び用量に関連する注意欄

4.1　用法及び用量に関連する注意

〈発作性夜間ヘモグロビン尿症〉

7.1. 補体（C5）阻害剤から本剤に切り替える際は，補体（C5）阻害剤の中止に伴う溶血のリスクを低減するため，前治療薬との投与間隔を考慮すること。［17.1.1 参照］

- エクリズマブ（遺伝子組換え）から切り替える場合，エクリズマブ（遺伝子組換え）の最終投与 1 週間後を目安に本剤の投与を開始すること。
- ラブリズマブ（遺伝子組換え）から切り替える場合，ラブリズマブ（遺伝子組換え）の最終投与 6 週間後を目安に本剤の投与を開始すること。

（下線：変更箇所）

4.2　用法及び用量に関連する注意の設定根拠

本項に設定している注意喚起は，発作性夜間ヘモグロビン尿症患者のみに該当するため，現行添付文書に基づき設定し，適応症特有の注意喚起として区別した。

目　　次

1 使用上の注意（案）及びその設定根拠

今回の適応追加の承認申請に際し，使用上の注意（案）は，2024 年 8 月改訂時の添付文書及び C3 腎症患者を対象とした臨床試験（日本参加の国際共同第 III 相試験（B12301 試験），外国第 II 相試験（X2202 試験），及び両試験の投与期を完了した被験者が移行できる継続試験（B12001B 試験））の結果を基に総合的に勘案し，作成した。

C3 腎症患者に本剤を投与したときの安全性プロファイルは，本剤の既承認の発作性夜間ヘモグロビン尿症患者に対する安全性プロファイルと同様であり，C3 腎症で新たに認められた安全性の問題はなかった。

今回の適応追加の承認申請において，「1.警告」，「8.重要な基本的注意」,「9.1 合併症・既往歴等のある患者」及び「11.副作用」以外の変更は不要と判断した。以下に，今回改訂する注意喚起について，設定根拠とともに記載した。

2 「1.警告」欄

2.1 「1.警告」

1.1 本剤は補体経路を阻害するため、髄膜炎菌、肺炎球菌、インフルエンザ菌等の莢膜形成細菌による重篤な感染症を発症することがあり、特に髄膜炎菌感染症は急激に重症化し、死亡に至るおそれもあるため、以下の点に十分注意すること。［~~5.2~~1、9.1.1、9.1.2、11.1.1、11.1.2 参照］

1.1.1 本剤の投与に際しては、髄膜炎菌等による感染症の初期徴候（発熱、頭痛、項部硬直等）に注意して観察を十分に行い、髄膜炎菌等の重篤な感染症が疑われた場合には、直ちに診察し、抗菌剤の投与等の適切な処置を行うこと。

1.1.2 髄膜炎菌、肺炎球菌及びインフルエンザ菌 b 型に対するワクチンの接種歴を確認し、未接種の場合又は追加接種が必要な場合は、原則、本剤投与前にワクチンを接種すること。必要に応じて、本剤投与中のワクチンの追加接種を考慮すること。

1.1.3 髄膜炎菌感染症は致命的な経過をたどることがあるので、緊急時に十分に措置できる医療施設及び医師のもとで、あるいは髄膜炎菌感染症の診断及び治療が可能な医療施設との連携下で本剤を投与すること。

1.1.4 髄膜炎菌等の莢膜形成細菌による感染症のリスクについて患者に説明し、当該感染症の初期徴候を確実に理解させ、感染症に関連する症状が発現した場合には、主治医に連絡するよう患者に注意を与えること。

1.2 発作性夜間ヘモグロビン尿症<u>又は C3 腎症</u>に十分な知識を持つ医師のもとで、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与開始に先立ち、本剤は疾病を完治させる薬剤ではないことを含め、本剤の有効性及び危険性を患者又はその家族に十分説明し、同意を得てから投与すること。

2.2 「1.警告」の設定根拠

1.1 本適応追加に伴い，「5.効能又は効果に関連する注意」を変更したため，適切な参照先となるよう変更した。

1.2 当該注意喚起は，C3 腎症患者においても必要であることから追記した。

上記以外の項目については，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

3 「8.重要な基本的注意」欄

3.1 「8.重要な基本的注意」

〈発作性夜間ヘモグロビン尿症〉

8.1 本剤を中止した場合に溶血が認められるおそれがある。本剤の投与を中止した患者では、本剤の最終投与から最低 2 週間は、溶血に付随する臨床症状及びその徴候［LDH 値の上昇を伴うヘモグロビン（Hb）値の急激な減少、疲労、ヘモグロビン尿、腹痛、呼吸困難、主要血管事象（血栓症）、嚥下障害又は勃起不全等］の変化を注意深く観察し、必要に応じて適切な処置を行うこと。

8.2 本剤投与により、総コレステロール、LDL コレステロール及びトリグリセリドの上昇等の脂質異常症があらわれることがあるので、本剤投与開始後は定期的に血液検査を実施すること。

3.2 「8.重要な基本的注意」の設定根拠

本項に設定している注意喚起は，いずれも発作性夜間ヘモグロビン尿症患者のみに該当すること及び変更を要する追加情報は得られていないことから，現行添付文書に基づき設定し，適応症特有の注意喚起として区別した。

4 「9.特定の背景を有する患者に関する注意」欄

4.1 「9.1 合併症・既往歴等のある患者」

9.1.1 髄膜炎菌感染症の既往のある患者

髄膜炎菌感染症に罹患しやすくなるおそれがある。［1.1、5.~~2~~1、11.1.1 参照］

9.1.2 感染症の患者又は感染症が疑われる患者

特に莢膜形成細菌（髄膜炎菌、肺炎球菌、インフルエンザ菌等）による感染症が悪化するおそれがある。［1.1、5.~~2~~1、11.1.1、11.1.2 参照］

4.2 「9.1 合併症・既往歴等の患者のある患者」の設定根拠

9.1.1，9.1.2 本適応追加に伴い，「5.効能又は効果に関連する注意」の項を変更したため，適切な参照先となるよう変更した。

上記以外については，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

5 「11.副作用」欄

5.1 「11.副作用」

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 髄膜炎菌感染症（頻度不明）

髄膜炎又は敗血症を発症し、急速に生命を脅かす、あるいは死亡に至るおそれがある。本剤の投与に際しては、当該感染症の初期徴候（発熱、頭痛、項部硬直、羞明、精神状態の変化、痙攣、悪心・嘔吐、紫斑、点状出血等）等の観察を十分に行うこと。髄膜炎菌感染症が疑われた場合には、直ちに診察し、抗菌剤の投与等の適切な処置を行うこと。［1.1、2.1、5.~~2~~1、9.1.1、9.1.2 参照］

11.1.2 重篤な感染症（0.6%）

肺炎球菌、インフルエンザ菌等の莢膜形成細菌による重篤な感染症があらわれることがあり、肺炎球菌感染症では敗血症に至った症例が報告されている。［1.1、2.2、5.~~2~~1、9.1.2参照］

11.2 その他の副作用

	~~5%以上~~	5%未満	頻度不明
血液およびリンパ系障害	~~血小板数減少~~	―血小板数減少	―
胃腸障害	―	下痢、腹痛、悪心	―
感染症および寄生虫症	―	上気道感染、 尿路感染、気管支炎	細菌性肺炎
筋骨格系および結合組織障害	―	関節痛	―
神経系障害	~~頭痛~~	頭痛、浮動性めまい	―
皮膚および皮下組織障害	―	―	蕁麻疹

5.2 「11.副作用」の設定根拠

副作用の発現頻度は，発作性夜間ヘモグロビン尿症の国際共同第 III 相試験（C12302 試験）の副作用集計に B12301 試験（成人の試験終了時）を加えた副作用の併合解析から算出し，その結果に基づき変更した。

5.2.1 「11.1 重大な副作用」の設定根拠

11.1.1 本適応追加に伴い，「5.効能又は効果に関連する注意」の項を変更したため，適切な参照先となるよう変更した。

11.1.2 B12301 試験（成人の試験終了時）及び B12001B 試験において肺炎球菌性肺炎が 2 例に発現し，いずれも治験担当医師により治験薬との関連ありと判断された。本 2 症例はいずれも敗血症を併発した。また，本剤の企業中核データシート（CCDS）において，肺炎球菌感染症が副作用として新たに記載された。臨床試験で報告された症例の重篤性及び CCDS の記載状況を踏まえ，肺炎球菌感染症に関する注意喚起を追記した。なお，本適応追加に伴い，「5.効能又は効果に関連する注意」の項を変更したため，適切な参照先となるよう変更した。

上記以外については，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

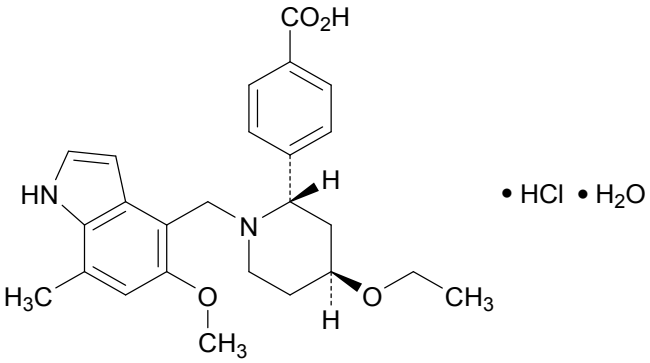
5.2.2 「11.2 その他の副作用」の設定根拠

副作用の発現頻度以外については，変更を要する追加情報は得られていないことから，現行添付文書に基づき設定した。

1.9 一般的名称に係る文書

既承認医薬品に係る資料を参照

〈現行〉

化学名・別名	【日本名】イプタコパン塩酸塩水和物 【英名】Iptacopan Hydrochloride Hydrate 【化学名】 日本名：4-{(2*S*,4*S*)-4-エトキシ-1-[(5-メトキシ-7-メチル-1*H*-インドール-4-イル)メチル]ピペリジン-2-イル}安息香酸　一塩酸塩一水和物 英名：4-{(2*S*,4*S*)-4-Ethoxy-1-[(5-methoxy-7-methyl-1*H*-indol-4-yl)methyl]piperidin-2-yl}benzoic acid monohydrochloride monohydrate
構造式	
効能・効果	発作性夜間ヘモグロビン尿症
用法・用量	通常，成人にはイプタコパンとして 1 回 200㎎を 1 日 2 回経口投与する。
劇薬等の指定	原体及び製剤はいずれも劇薬に該当する。
市販名及び有効成分・分量	原体：イプタコパン塩酸塩水和物 製剤：ファビハルタカプセル 200mg［1 カプセル中イプタコパン塩酸塩水和物 225.80mg（イプタコパンとして 200mg）を含有］
毒性	単回投与毒性試験

動物種	投与経路	概略の致死量 (mg/kg)
イヌ	経口	> 1000
サル	経口	> 600

LNP023 の急性毒性については，イヌを用いた 2 週間反復投与毒性試験における用量漸増投与試験相及びサルを用いた用量漸増投与試験の成績から評価した。

反復投与毒性試験

動物種	投与期間 (週間)	投与経路	投与量 (mg/kg/日)	無毒性量 (mg/kg/日)	主な所見
ラット	4	経口	0, 100, 300, 1000	300	≥ 100 mg/kg：総ビリルビン・直接ビリルビン↑，甲状腺重量(雌)↑ ≥ 300 mg/kg：蛋白尿(雄) 1000 mg/kg：蛋白尿(雌), TSH(雌)↑，甲状腺：濾胞細胞肥大(雌)，ハーダー腺：炎症性細胞浸潤を伴う変性／再生性変化 回復性：4 週間の休薬により回復又は回復傾向が認められた。

	ラット	13	経口	0, 50, 150, 500	雄：150 雌：500	≥ 50 mg/kg：T3・T4↑，前立腺重量↑ 500 mg/kg：流涎，甲状腺重量(雄)↑，甲状腺：濾胞細胞肥大，精巣：精細管変性，精子検査（背景値との比較）：総精子数，精子運動率，精子速度，及び異常精子数の変動 回復性：前立腺重量の変化を除いて，いずれの変化においても 8 週間の休薬により回復又は回復傾向が認められた。
	ラット	26	経口	0, 50, 150, 750	750	≥ 50 mg/kg：体重増加量(雄)↓／(雌)↑，甲状腺／上皮小体重量↑，精巣重量↑ ≥ 150 mg/kg：クレアチニン(雄)↓，甲状腺：濾胞細胞肥大 750 mg/kg：流涎，摂餌量(雌)↑，ALP・総ビリルビン↑，クレアチニン(雌)↓，T3・T4↑，TSH(雌)↑，甲状腺：大型化(雄) 回復性：27 週間の休薬による回復性が認められた。
	イヌ	4	経口	0, 15, 50, 300	50	15 mg/kg：ビリルビン(雄)↑ ≥ 15 mg/kg：心拍数↑，T4↑，甲状腺重量↓，甲状腺：濾胞細胞肥大 ≥ 50 mg/kg：ビリルビン(雌)↑ 300 mg/kg：体重(雌)↓，ビリルビン(雄)↑，甲状腺：小型化(雌)，精巣・精巣上体重量↓，心臓：心筋細胞の変性／壊死，精巣：生殖細胞剥離，精巣上体：精子減少・精巣上体管内細胞残屑，肝臓：胆管過形成・クッパー細胞色素沈着(雌) 回復性：4 週間の休薬により回復又は回復傾向が認められた。

	イヌ	13	経口	0, 5, 30, 150	雄：5 雌：30	≥ 5 mg/kg：総テストステロン・アンドロステンジオン↑，甲状腺重量(雌)↑ ≥ 30 mg/kg：甲状腺重量(雄)↑，腸間膜リンパ節：リンパ系細胞枯渇，精巣：精細管変性，精巣上体：精巣上体管腔細胞残屑，甲状腺：濾胞細胞肥大(雌) 150 mg/kg：体重増加量・摂餌量↓，心拍数↑，血小板数(雌)↑，前立腺・精巣・精巣上体重量↑，脾臓(雌)・下顎リンパ節(雄)：リンパ系細胞枯渇，甲状腺：濾胞細胞肥大(雄)，肝臓：胆管過形成・単細胞壊死，肝細胞・クッパー細胞：色素沈着(雌雄)，骨髄(雄)：顆粒球比率・顆粒球／赤芽球（M / E）比↑，赤芽球比率↓ 同群の雌雄各 1 例で以下に示す炎症を示唆する変化が認められた：好中球数・白血球数・赤血球系パラメータ・血小板数(雄)↓，好中球数(雌)↓・単球数・フィブリノゲン(雌)↑，グロブリン・総蛋白(雌雄)↑，アルブミン／グロブリン比(雌雄)↓ 回復性：8 週間の休薬により回復又は回復傾向が認められた。
	イヌ	39	経口	0, 5, 30, 150	雄：5 雌：30	150 mg/kg：回復性試験 Day 103 に一般状態不良のため雄 1 例を安楽死処分（骨髄線維症を伴う重度の非再生性貧血が原因であり，投薬関連である可能性が考えられた）。 ≥ 5 mg/kg：TDAR：一次応答（IgM 及び IgG 抗体価）↓，甲状腺重量(雄)↑，甲状腺：濾胞細胞肥大(雄) ≥ 30 mg/kg：嘔吐，T3(雄)↑，補体 AP 活性完全阻害，TDAR：二次応答(雌)↓，前立腺重量↑，精巣：精細管変性，精巣上体：精巣上体管管腔細胞残屑 150 mg/kg：心拍数↑，PR・QT 間隔↓，TSH(雄)↑，甲状腺重量(雌)↑，精巣重量↓，肝臓：クッパー細胞の色素沈着（ヘモジデリン），甲状腺：濾胞細胞肥大(雌) 回復性：27 週間の休薬により回復性が認められた。

副　作　用	国際共同第 III 相試験（APPLY-PNH 試験，CLNP023C12302 試験）において，継続投与期終了時の本剤投与による副作用発現率は，21.9%（21/96 例）であった。主な副作用は頭痛 5.2%（5/96 例），血小板数減少及び悪心 4.2%（4/96 例），下痢及び関節痛 3.1%（3/96 例）であった。
会　社	ノバルティスファーマ株式会社　製剤：輸入

〈追加・変更〉（下線部）

化学名・別名	
構　造　式	
効能・効果	発作性夜間ヘモグロビン尿症 C3 腎症
用法・用量	
劇薬等の指定	
市販名及び有効成分・分量	
毒　性	
副　作　用	国際共同第 III 相試験（APPLY-PNH 試験，CLNP023C12302 試験）において，継続投与期終了時の本剤投与による副作用発現率は，21.9%（21/96 例）であった。主な副作用は頭痛 5.2%（5/96 例），血小板数減少及び悪心 4.2%（4/96 例），下痢及び関節痛 3.1%（3/96 例）であった。 国際共同第Ⅲ相試験（APPEAR-C3G 試験，CLNP023B12301 試験）において，二重盲検投与期終了時の本剤投与による副作用発現割合は、15.8%（6/38 例）であった。本剤群で 2 例以上に発現した副作用はなかった。
会　社	

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1 第 3 部

該当資料なし

2 第 4 部

該当資料なし

3 第 5 部

添付資料番号	Report No. /Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.2 全臨床試験一覧表							
5.2	―	全臨床試験一覧表	―	―	国内	評価	―
5.3 臨床試験報告書							
5.3.1 生物薬剤学試験報告書							
5.3.1.1 バイオアベイラビリティ（BA）試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.1.2 比較 BA 試験及び生物学的同等性（BE）試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.1.3 In Vitro-In Vivo の関連を検討した試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.1.4 生物学的及び理化学的分析法検討報告書							
5.3.1.4-1	DMPK-R1900470-01	Quantitative determination of LNP023 in human K_2EDTA plasma by LC-MS/MS Amendment no.1	20[redacted] 年[redacted] 月[redacted] 日	中国	海外	参考	―
5.3.1.4-2	BMD R2150018	Quantitative determination of circulating Bb fragment of factor B and soluble C5b-9 in human K2-EDTA plasma assays	20[redacted] 年[redacted] 月[redacted] 日	フランス	海外	参考	―
5.3.1.4-3	BMD R2150018-01	Quantitative determination of circulating Bb fragment of factor B and soluble C5b-9 in human K2-EDTA plasma assays Amendment 01	20[redacted] 年[redacted] 月[redacted] 日	フランス	海外	参考	―
5.3.1.4-4	BMD R1750148a	Quantitative determination of SC5b-9 in human urine	20[redacted] 年[redacted] 月[redacted] 日	ノバルティス	海外	参考	―
5.3.1.4-5	BMD R1650118a	Extension of stability for the soluble C5b-9 assay in human EDTA plasma	20[redacted] 年[redacted] 月[redacted] 日	フランス	海外	参考	―
5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書							
―	―	該当資料なし	―	―	―	―	―

添付資料番号	Report No. /Study No.	表　題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.3　臨床薬物動態（PK）試験報告書							
―	―	該当資料なし	―	―	―	―	―
5.3.4　臨床薬力学（PD）試験報告書							
―	―	該当資料なし	―	―	―	―	―

添付資料番号	表題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.5 有効性及び安全性試験報告書						
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5.3.5.1-1	LNP023B12301 総括報告書	2021 年 7 月 28 日～20[redacted] 年[redacted] 月[redacted] 日（データカットオフ日）本報告時点で継続中	日本，ドイツ，フランス，インド，米国，中国，イスラエル，イタリア，スペイン，イギリス，アルゼンチン，ブラジル，カナダ，チェコ，ギリシャ，オランダ，スイス，及びトルコ	国際共同	評価	あり
	LNP023B12301 M12 総括報告書	2021 年 7 月 28 日～20[redacted] 年[redacted] 月[redacted] 日（データカットオフ日）本報告時点で継続中	日本，ドイツ，フランス，インド，米国，中国，イスラエル，イタリア，スペイン，イギリス，アルゼンチン，ブラジル，カナダ，チェコ，ギリシャ，オランダ，スイス，トルコ	国際共同	評価	あり
5.3.5.2 非対照試験報告書						

添付資料番号	表題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.5.2-1	LNP023X2202 総括報告書	2019 年 2 月 20 日～2021 年 4 月 23 日	フランス，ドイツ，イタリア，スペイン，イギリス，米国	海外	評価	あり
	LNP023X2202 Note to file	－	－	－	－	－
5.3.5.2-2	LNP023B12001B IA2 総括報告書	2019 年 10 月 3 日～20[redacted] 年[redacted] 月[redacted] 日（データカットオフ日）本報告時点で継続中	イギリス，フランス，イタリア，スペイン，米国，ドイツ	国際共同	評価	あり
	LNP023B12001B IA4 総括報告書	2019 年 10 月 3 日～20[redacted] 年[redacted] 月[redacted] 日（データカットオフ日）本報告時点で継続中	イギリス，フランス，イタリア，スペイン，米国，ドイツ	国際共同	評価	あり
	LNP023B12001B IA5 総括報告書	2019 年 10 月 3 日～20[redacted] 年[redacted] 月[redacted] 日（データカットオフ日）本報告時点で継続中	フランス，ドイツ，イタリア，スペイン，英国，米国	外国	評価	あり
5.3.5.3 複数の試験成績を併せて解析した報告書						
5.3.5.3-1	SCE Appendix 1	－	－	－	－	あり
5.3.5.3-2	SCS Appendix 1	－	－	－	－	あり
5.3.5.3-3	SCS Appendix 2	－	－	－	－	－
5.3.5.3-4	SCS Appendix 4	－	－	－	－	－

添付資料番号	表題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.5.3-5	J-SCE Appendix 1	—	—	—	—	あり
5.3.5.3-6	J-SCS Appendix 1	—	—	—	—	あり
5.3.5.3-7	SCE Appendix 1 - US	—	—	—	—	あり
5.3.5.3-8	SCE Appendix 2 - US	—	—	—	—	あり
5.3.5.3-9	SCS Appendix 1 - US	—	—	—	—	あり
5.3.5.3-10	SCS Appendix 2- US	—	—	—	—	—
5.3.5.3-11	SCS Appendix 4- US	—	—	—	—	—
5.3.5.3-12	J-SCE Appendix 2	—	—	—	—	あり
5.3.5.3-13	J-SCS Appendix 2	—	—	—	—	あり
5.3.5.4　その他の臨床試験報告書						
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5.3.6　市販後の使用経験に関する報告書						
5.3.6-1	PERIODIC SAFETY UPDATE REPORT (PSUR)	Period covered: 2023 年 12 月 5 日～ 2024 年 6 月 4 日	—	—	—	—
5.3.6-2	PERIODIC SAFETY UPDATE REPORT (PSUR)	Period covered: 2024 年 6 月 5 日～ 2024 年 12 月 4 日	—	—	—	—
5.3.7　患者データ一覧表及び症例記録						
—	該当資料なし	—	—	—	—	—

添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
5.4 参考文献 （評価／参考の別：参考資料）		
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添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
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