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に関する資料

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＜ペグセタコプラン＞

（C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎）

第 1 部（モジュール 1）
申請書等行政情報及び添付文書に関する情報

1.5　起原又は発見の経緯及び開発の経緯

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目次

1.5　起原又は発見の経緯及び開発の経緯.....3
1.5.1　申請効能での開発.....3
1.5.2　申請効能以外での開発（小児開発計画）.....3
1.5.2.1　開発の意義.....3
1.5.2.2　開発計画の概略.....4

表目次

表 1.5-1　現時点の欧州 Pediatric Investigation Plan（2024 年 9 月 24 付）の概要.....4
表 1.5-2　試験 4 の概要.....5

図目次

図 1.5-1　開発の経緯図.....3

1.5 起原又は発見の経緯及び開発の経緯

1.5.1 申請効能での開発

C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎に係る効能・効果に関する開発の経緯図を図 1.5-1 に示し、詳細はモジュール［2.5.1］項に記載した。

今般、日本人を含む C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎の患者を対象とした、ペグセタコプランの有効性及び安全性を検討する第 3 相、無作為化、プラセボ対照、二重盲検、国際多施設共同試験（APL2-C3G-310 試験）において良好な結果が得られたことから、承認事項一部変更承認申請を行うに至った。

図 1.5-1 開発の経緯図

試験項目		[redacted]
臨床試験	第 2 相試験（APL2-C3G-204 試験）	
	第 3 相試験（APL2-C3G-310 試験）	

1.5.2 申請効能以外での開発（小児開発計画）

1.5.2.1 開発の意義

C3 腎症及び一次性免疫複合体型膜性増殖性糸球体腎炎の症例の多くは、小児期後期から青年期初期～後期にかけて診断されており、診断時の最低年齢は 1.9～3 歳であった（Lu 2012、Ravindran 2018a）。また、C3 腎症は、主として 40 歳未満の患者に発症し、30～40%の患者が 18 歳未満で診断されていることが報告されている（Servais 2012、Medjeral-Thomas 2014、Bomback 2018、Chauvet 2022、Lomax-Browne 2022）。報告されている年齢データは限定的であり、確定的な結論を導くには不十分であるものの、いずれの疾患においても、概ね 6 歳未満で診断される患者は極めて少ないが、12 歳未満の患者が一定数存在すると考えられる。

12 歳未満の小児における C3 腎症及び一次性免疫複合体型膜性増殖性糸球体腎炎に対する疾患特異的治療は、現時点で承認されていない。小児患者に対する現行の治療方法は、一般に支持療法が中心であり、他の糸球体疾患の管理に用いられる治療と概ね同様である。これらには、タンパク尿、高血圧、高脂血症、浮腫、並びに糸球体疾患及び慢性腎臓病に関連するその他の症状を管理するための非特異的対症療法が含まれるが、疾患進行を抑制又は回復させることはできない（Smith 2019）。

タンパク尿を呈する小児患者には、レニン-アンジオテンシン-アルドステロン系阻害薬が処方されることが多く、タンパク尿の軽減に一定の有効性を示すとともに、腎障害に伴う高血圧の管理に寄与することが報告されている（Remuzzi 2005）。支持療法に反応しないタンパク尿を有する小児患者においては、グルココルチコイド及びミコフェノール酸モフェチルの使用を

検討することが妥当とされている（Vivarelli 2024）。しかしながら、グルココルチコイドは小児の成長及び発達に重大な影響を及ぼす可能性があり、ミコフェノール酸モフェチルも感染症リスクの増加や下痢を含む消化管障害などの有害事象が報告されている。さらに、支持療法が存在するにもかかわらず、C3 腎症及び一次性免疫複合体型膜性増殖性糸球体腎炎の予後は依然として不良であり、患者は腎不全へと持続的に進行する可能性がある（Lu 2012、Pickering 2013、Medjeral-Thomas 2014、Okpechi 2014、Regunathan-Shenk 2019、Smith 2019、Chauvet 2022）。

したがって、現時点で治療選択肢が支持療法及び経験的治療に限られている小児の C3 腎症及び一次性免疫複合体型膜性増殖性糸球体腎炎患者において、C3 調節異常に起因する持続的な腎障害から自然腎又は移植腎を保護し得る、有効性が確認された疾患修飾療法に対する高いアンメット・メディカル・ニーズが存在する。

ペグセタコプランは、補体系の根本的な調節異常を標的とすることにより、過剰な C3 分解及び腎沈着に関連する腎障害を抑制することが示されている。成人及び青年期患者を対象とした臨床試験において、グルココルチコイド及びミコフェノール酸モフェチルの併用の有無にかかわらず、ペグセタコプランは顕著な有効性と良好な安全性プロファイルを示している。これらの結果を踏まえると、12 歳未満の C3 腎症患者及び一次性免疫複合体型膜性増殖性糸球体腎炎に対する有効性も期待できる。

以上より、小児を対象としてペグセタコプランを開発する意義があると考える。

1.5.2.2 開発計画の概略

C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎における欧州 Pediatric Investigation Plan（2024 年 9 月 24 日付）の概要を表 1.5-1 に示す。2 歳以上 12 歳未満の小児を対象とした、ペグセタコプランの薬物動態、有効性及び安全性を評価するための、非盲検、単群、多施設共同試験（試験 4）には、[redacted]。[redacted]、20[redacted] 年[redacted]計画である。当該試験の概要を表 1.5-2 に示す。

表 1.5-1 現時点の欧州 Pediatric Investigation Plan（2024 年 9 月 24 付）の概要

領域	内容
非臨床試験	試験 1: 幼若ラットを用いた用量設定試験 試験 2: 幼若ラットを用いた確認的毒性試験
臨床試験	試験 3 (APL2-C3G-310 試験): 糸球体腎炎又はネフローゼ症候群を有する 12 歳以上 18 歳未満の青年期（及び成人）患者を対象としたペグセタコプランの薬物動態、有効性及び安全性を評価する多施設共同、無作為化、プラセボ対照、二重盲検試験（反応の持続性、薬物動態、長期の安全性及び有効性を評価する 26 週間の非盲検期間を含む）

領域	内容
	試験 4: 糸球体腎炎又はネフローゼ症候群を有する 2 歳以上 12 歳未満の小児を対象としたペグセタコプランの薬物動態、有効性及び安全性を評価する多施設共同、単群、非盲検、ヒストリカルコントロール試験
外挿、モデリング及びシミュレーションに関する試験	試験 5: 糸球体腎炎又はネフローゼ症候群を有する 2 歳以上 18 歳未満の小児におけるペグセタコプランの用量レジメン選択を目的とした母集団薬物動態モデルの構築 試験 6: ペグセタコプランの臨床データから構築された母集団薬物動態モデル及び曝露-反応モデルを統合し、糸球体腎炎又はネフローゼ症候群を有する小児集団における薬物動態、薬力学及び有効性に関する仮定を支持するための外挿試験

表 1.5-2　試験 4 の概要

[redacted]



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＜ペグセタコプラン＞

（C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎）

第 1 部（モジュール 1）
申請書等行政情報及び添付文書に関する情報

1.6　外国における使用状況等に関する資料

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目次

1.6　外国における使用状況等に関する資料.....3
1.6.1　外国における製造販売承認状況.....3
1.6.2　外国における添付文書等.....4
1.6.2.1　米国の添付文書.....4
1.6.2.2　欧州の添付文書.....4
1.6.2.3　企業中核データシート（CCDS）.....4

表目次

表 1.6.1-1　米国及び欧州での製造販売承認の状況.....3

1.6 外国における使用状況等に関する資料

1.6.1 外国における製造販売承認状況

本剤は、「成人の発作性夜間ヘモグロビン尿症患者の治療」の適応で 2021 年 5 月に米国で初めて承認され、2026 年 4 月現在、「発作性夜間ヘモグロビン尿症」に係る効能・効果で、米国、欧州、英国、カナダ及びオーストラリアを含む 16 の国又は地域で承認されている。本邦では 2023 年 3 月に「発作性夜間ヘモグロビン尿症」を効能・効果として製造販売承認を取得している。

今回追加する「C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎」の効能・効果に関しては、2025 年 7 月に米国で「成人及び 12 歳以上の小児 C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者の蛋白尿減少の治療」の適応で承認され、2026 年 4 月現在、米国、欧州、英国、カナダ及びオーストラリアを含む 10 の国又は地域で承認されている。

米国及び欧州での製造販売承認状況を表 1.6.1-1 に示す。

表 1.6.1-1 米国及び欧州での製造販売承認の状況

国又は地域	販売名	承認年月日	効能・効果
米国	EMPAVELI	2021 年 5 月 14 日	成人の発作性夜間ヘモグロビン尿症患者の治療を適応とする。
		2025 年 7 月 28 日	成人及び 12 歳以上の小児 C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者の蛋白尿減少の治療を適応とする。
欧州	ASPAVELI	2021 年 12 月 13 日	成人の溶血性貧血を伴う発作性夜間ヘモグロビン尿症に対する単剤治療を適応とする。
		2026 年 1 月 15 日	成人及び 12 歳～17 歳の C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者のレニン-アンジオテンシン系阻害薬との併用治療を適応とする。ただし、レニン-アンジオテンシン系阻害薬による治療が忍容できない、又は禁忌である場合を除く。

1.6.2 外国における添付文書等

1.6.2.1 米国の添付文書

［1.6.2.1_米国添付文書_EMPAVELI］参照。

1.6.2.2 欧州の添付文書

［1.6.2.2_欧州添付文書_ASPAVELI］参照。

1.6.2.3 企業中核データシート（CCDS）

［1.6.2.3_企業中核データシート CCDS_pegcetacoplan］参照。

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

EMPAVELI® (pegcetacoplan) injection, for subcutaneous use
Initial U.S. Approval: 2021

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA
See full prescribing information for complete boxed warning.

EMPAVELI 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 EMPAVELI, unless the risks of delaying EMPAVELI outweigh the risks 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 EMPAVELI 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)**

EMPAVELI is available only through a restricted program called EMPAVELI REMS.

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

Indication (1.2)	7/2025
Dosage and Administration (2.3)	7/2025
Warnings and Precautions (5.3)	7/2025

----------INDICATIONS AND USAGE----------
EMPAVELI is a complement inh bitor indicated:
- for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). (1.1)
- for the treatment of adult and pediatric patients aged 12 years and older with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN), to reduce proteinuria. (1.2)

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

PNH (2.2)
Recommended dosage is 1,080 mg administered subcutaneously twice weekly.

C3G or Primary IC-MPGN (2.3)
- Recommended dosage for adults is 1,080 mg administered subcutaneously twice weekly.
- Recommended dosage for pediatric patients is dependent upon patient weight. See full prescr bing information for the recommended dosage in patients with C3G or IC-MPGN. (2.2)
- EMPAVELI can be administered via a commercially available pump or with EMPAVELI Injector. (2.4)
- See Full Prescribing Information for instructions on preparation and administration. (2.2, 2.3, 2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Injection: 1,080 mg/20 mL (54 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
EMPAVELI is contraindicated:
- in patients with hypersensitivity to pegcetacoplan or any of the excipients. (4)
- for initiation in patients with unresolved serious infection caused by encapsulated bacteria. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Serious infections caused by encapsulated bacteria. (5.1)
- Infusion-Related Reactions: Monitor patients for infusion-related reactions and institute appropriate medical management as needed. (5.3)
- Interference with Laboratory Tests: Use of silica reagents in coagulation panels may result in artificially prolonged activated partial thromboplastin time (aPTT). (5.5)

---------- ADVERSE REACTIONS ----------
- The most common adverse reactions in patients with PNH (incidence ≥10%) were injection site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, pain in extremity, hypokalemia, fatigue, viral infection, cough, arthralgia, dizziness, headache, and rash. (6.1)
- The most common adverse reactions in patients with C3G or primary IC-MPGN (incidence ≥10%) were infusion site reactions, pyrexia, nasopharyngitis, influenza, cough, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apellis Pharmaceuticals, Inc. at 1-833-866-3346 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA
1 INDICATIONS AND USAGE
1.1 Paroxysmal nocturnal hemoglobinuria
1.2 C3 glomerulopathy or primary immune-complex membranoproliferative glomerulonephritis
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Vaccination and Prophylaxis
2.2 Recommended Dosage – PNH
2.3 Recommended Dosage - C3G or Primary IC-MPGN
2.4 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Infections Caused by Encapsulated Bacteria
5.2 EMPAVELI REMS
5.3 Infusion-Related Reactions
5.4 Monitoring PNH Manifestations after Discontinuation of EMPAVELI
5.5 Interference with Laboratory Tests
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.6 Immunogenicity
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Paroxysmal Nocturnal Hemoglobinuria

14.2 C3 Glomerulopathy (C3G) or Primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

EMPAVELI, 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 EMPAVELI, unless the risks of delaying therapy with EMPAVELI 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 EMPAVELI 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, EMPAVELI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the EMPAVELI REMS *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria

EMPAVELI® is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

1.2 C3 glomerulopathy or primary immune-complex membranoproliferative glomerulonephritis

EMPAVELI® is indicated for the treatment of adult and pediatric patients aged 12 years and older with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN), to reduce proteinuria.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis

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 EMPAVELI therapy *[see Warnings and Precautions (5.1)]*.

If urgent EMPAVELI 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.

Healthcare professionals who prescribe EMPAVELI must enroll in the REMS for EMPAVELI *[see Warnings and Precautions (5.2)]*.

2.2 Recommended Dosage - PNH

The recommended dose of EMPAVELI is 1,080 mg administered subcutaneously twice weekly *[see Dosage and Administration (2.4)]*.

Dosage for patients switching to EMPAVELI from C5 inhibitors

To reduce the risk of hemolysis with abrupt treatment discontinuation:

- For patients switching from eculizumab, initiate EMPAVELI while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab before continuing on monotherapy with EMPAVELI.
- For patients switching from ravulizumab, initiate EMPAVELI no more than 4 weeks after the last dose of ravulizumab.

Dose Adjustment

- For lactate dehydrogenase (LDH) levels greater than 2 × the upper limit of normal (ULN), adjust the dosing regimen to 1,080 mg every three days.
- In the event of a dose increase, monitor LDH twice weekly for at least 4 weeks.

Missed Dose

- Administer EMPAVELI as soon as possible after a missed dose. Resume the regular dosing schedule following administration of the missed dose.

2.3 Recommended Dosage - C3G or Primary IC-MPGN

For adults (18 years and older)

The recommended dose of EMPAVELI is 1,080 mg (20 mL) administered subcutaneously twice weekly *[see Dosage and Administration (2.4)]*.

For pediatric patients (12 years to less than 18 years of age)

For pediatric patients 12 years of age and older, administer EMPAVELI dose and volume based upon body weight, according to the schedule in Table 1. Administer the recommended dose of EMPAVELI subcutaneously twice weekly *[see Dosage and Administration (2.4)]* .

Table 1: Dosing recommendation in C3G or primary IC-MPGN

Patient Body Weight	First dose (infusion volume)	Second dose (infusion volume)	Maintenance dose (infusion volume)
50 kg or higher	1,080 mg (20 mL)	1,080 mg (20 mL)	1,080 mg twice weekly (20 mL)
35 kg to less than 50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
Less than 35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

Missed Dose

Administer EMPAVELI as soon as possible after a missed dose. Resume the regular dosing schedule following administration of the missed dose.

2.4 Administration

EMPAVELI is for subcutaneous administration using:

- A commercially available infusion pump with a reservoir of at least 20 mL OR
- EMPAVELI Injector, a single-use, disposable on body injector

EMPAVELI is intended for use under the guidance of a healthcare professional. Patients may self-administer or caregivers may administer EMPAVELI after proper training by a healthcare professional on how to prepare and administer EMPAVELI.

Follow the steps below and use aseptic technique to prepare and administer EMPAVELI, either by an infusion pump or EMPAVELI Injector:

- Prior to use, allow EMPAVELI to reach room temperature 20°C to 25°C (68°F to 77°F) for approximately 30 minutes. Keep the vial in the carton until ready for use to protect from light.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. EMPAVELI is a clear, colorless to slightly yellowish solution. Do not use if the liquid looks cloudy, contains particles, or is dark yellow.
- Discard any unused portion of EMPAVELI.

Preparation with Infusion Pump
- Refer to the EMPAVELI Instructions for Use and the infusion pump manufacturer's instructions for full preparation and administration information.
- Use a needleless transfer device (such as a vial adapter) or a transfer needle to fill the syringe.
- Rotate infusion sites (i.e., abdomen, thighs, hips, upper arms) from one infusion to the next. Do not infuse where the skin is tender, bruised, red, or hard. Avoid infusing into tattoos, scars, or stretch marks.
- If multi-infusion sets are needed, ensure the infusion sites are at least 3 inches apart.
- The typical infusion time is approximately 30 minutes (if using two infusion sites) or approximately 60 minutes (if using one infusion site).

Preparation with EMPAVELI Injector
- Refer to the EMPAVELI Injector Instructions for Use, which comes with the device.
- Use a needleless transfer device (such as a vial adapter).
- EMPAVELI Injector is for abdominal subcutaneous use only. Rotate the site of each subcutaneous administration. Do not inject where the skin is tender, bruised, red, or hard. Avoid injecting into tattoos, scars, or stretch marks.
- Injection time is approximately 30 to 60 minutes.

3 DOSAGE FORMS AND STRENGTHS

Injection: 1,080 mg/20 mL (54 mg/mL) clear, colorless to slightly yellowish solution in a single-dose vial.

4 CONTRAINDICATIONS

EMPAVELI is contraindicated:
- in patients with hypersensitivity to pegcetacoplan or to any of the excipients *[see Warnings and Precautions (5.3)]*.
- for initiation in patients with unresolved serious infection caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections Caused by Encapsulated Bacteria

EMPAVELI, 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 initation of EMPAVELI treatment is contraindicated in patients with unresolved serious infection caused by encapsulated bacteria.

Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to administration of the first dose of EMPAVELI, according to the most current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with EMPAVELI. 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 EMPAVELI 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 EMPAVELI. The benefits and risks of treatment with EMPAVELI, 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 EMPAVELI in patients who are undergoing treatment for serious infections.

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

5.2 EMPAVELI REMS

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

Notable requirements of the EMPAVELI 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 the patients with the REMS educational materials.
- Prescribers must assess patient vaccination status for encapsulated bacteria and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of EMPAVELI.
- Prescribers must provide a prescription for antibacterial drug prophylaxis if treatment must be started urgently, and the patient is not up to date with vaccinations against encapsulated bacteria according to current ACIP recommendations at least two weeks prior to the first dose of EMPAVELI.
- Pharmacies that dispense EMPAVELI must be certified in the EMPAVELI 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 signs and symptoms of serious infections.
- Patients must be instructed to carry the Patient Safety Card with them at all times during and for 2 months following treatment discontinuation with EMPAVELI.

Further information is available at www.empavelirems.com or 1-888-343-7073

5.3 Infusion-Related Reactions

Systemic hypersensitivity reactions (e.g., facial swelling, rash, urticaria, pyrexia) have occurred in patients treated with EMPAVELI, which may resolve after treatment with antihistamines. Cases of anaphylaxis leading to treatment discontinuation have been reported. If a severe hypersensitivity reaction (including anaphylaxis) occurs, discontinue EMPAVELI infusion immediately, institute appropriate treatment, per standard of care, and monitor until signs and symptoms are resolved.

5.4 Monitoring PNH Manifestations after Discontinuation of EMPAVELI

After discontinuing treatment with EMPAVELI, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH levels along with sudden decrease in PNH clone size or hemoglobin, or reappearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues EMPAVELI for at least 8 weeks to detect hemolysis and other reactions. If hemolysis, including elevated LDH, occurs after discontinuation of EMPAVELI, consider restarting treatment with EMPAVELI.

5.5 Interference with Laboratory Tests

There may be interference between silica reagents in coagulation panels and EMPAVELI that results in artificially prolonged activated partial thromboplastin time (aPTT); therefore, avoid the use of silica reagents in coagulation panels.

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)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*

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

Study in Complement-Inhibitor Experienced Adult Patients with PNH (Study APL2-302)

The data described below reflect the exposure in 80 adult patients with PNH who received EMPAVELI (n=41) or eculizumab (n=39) at the recommended dosing regimens for 16 weeks. Serious adverse reactions were reported in 7 (17%) patients with PNH receiving EMPAVELI. The most common serious adverse reaction in patients treated with EMPAVELI was infections (5%). The most common adverse reactions (≥10%) with EMPAVELI were injection-site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection, and fatigue.

Table 2 describes the adverse reactions that occurred in ≥5% of patients treated with EMPAVELI in Study APL2-302.

Table 2: Adverse Reactions Reported in ≥5% of Patients Treated with EMPAVELI in Study APL2-302

Adverse Reaction	EMPAVELI (N=41) n (%)	Eculizumab (N=39) n (%)
General disorders and administration site conditions		
Injection-site reaction*[a]	16 (39)	2 (5)
Fatigue*	5 (12)	9 (23)
Chest pain*	3 (7)	1 (3)
Infections and infestations		
Infections*	12 (29)	10 (26)
Respiratory tract infection*	6 (15)	5 (13)

Adverse Reaction	EMPAVELI (N=41) n (%)	Eculizumab (N=39) n (%)
Viral Infection*	5 (12)	3 (8)
Gastrointestinal disorders		
Diarrhea	9 (22)	1 (3)
Abdominal pain*	8 (20)	4 (10)
Musculoskeletal disorders		
Back pain*	3 (7)	4 (10)
Nervous system disorders		
Headache	3 (7)	9 (23)
Vascular disorders		
Systemic hypertension*	3 (7)	1 (3)

* Grouped terms

[a] Term includes injection-site erythema, injection-site reaction, injection-site swelling, injection-site induration, injection-site bruising, injection-site pain, injection-site pruritus, vaccination site reaction, administration site swelling, injection-site hemorrhage, injection -site edema, injection-site warmth, administration site pain, application site pain, injection-site mass, injection-site rash, vaccination site pain

Clinically relevant adverse reactions in less than 5% of patients include:

- Intestinal ischemia
- Biliary sepsis
- Hypersensitivity pneumonitis

After the randomized control period, 77 patients continued the study, and all were treated with EMPAVELI monotherapy at the recommended dosing regimen for up to 48 weeks. Serious adverse reactions were reported in 18 patients (23%). Additional adverse reactions reported in >5% of patients treated with EMPAVELI during the open-label part of the study compared to the randomized controlled part in Table 1 were cough (12%), arthralgia (8%), oropharyngeal pain (8%), pyrexia (8%), pain in extremity (7%), thrombocytopenia (7%), abdominal distension (5%), acute kidney injury (5%), anxiety (5%), and myalgia (5%). One patient (1%) died due to COVID-19 infection.

Description of Select Adverse Reactions

Injection-Site Reactions

Injection/infusion-site reactions (e.g., erythema, swelling, induration, pruritus, and pain) have been reported during Study APL2-302. These reactions were mild or moderate in severity.

Diarrhea

Seventeen cases of diarrhea have been reported during the 48 weeks. Fifteen of the cases were mild and two were moderate.

Study in Complement-Inhibitor Naïve Adult Patients with PNH (Study APL2-308)

The data described below reflect the exposure in adult patients with PNH who received EMPAVELI (n=46) or the control arm (supportive care excluding complement inhibitors) (n=18) in Study APL2-308 *[see Clinical Studies (14.1)]*. One patient (2%) who received EMPAVELI died due to septic shock. Serious adverse reactions were reported in 6 (13%) patients with PNH receiving EMPAVELI. The most common adverse reaction (≥10%) in patients treated with EMPAVELI were injection site reactions, infections, viral infection, pain in extremity, hypokalemia, arthralgia, dizziness, abdominal pain, rash, and headache.

Table 3 describes the adverse reactions that occurred in ≥5% of patients treated with EMPAVELI in Study APL2-308.

Table 3: Adverse Reactions Reported in ≥5% of Patients Treated with EMPAVELI in Study APL2-308

Adverse Reaction	EMPAVELI (N=46) n (%) Exposure Adjusted Rate (per 100 pt yrs)	Control Arm[a] (N=18) n (%) Exposure Adjusted Rate (per 100 pt yrs)
General disorders and administration site conditions		
Injection-site reaction*[b]	12 (26) 42	0 0
Pyrexia	4(9) 14	0 0
Peripheral edema*	3 (7) 11	0 0
Infections and Infestations		
Infections*	9 (20) 32	4 (22) 74
Viral infection*	6 (13) 21	2 (11) 37
Musculoskeletal and connective tissue disorders		
Pain in extremity	6 (13) 21	0 0
Arthralgia	5 (11) 18	0 0
Musculoskeletal pain	3 (7) 11	0 0
Metabolism and nutrition disorders		
Hypokalemia	6 (13) 21	2 (11) 37
Nervous system disorders		
Dizziness	5 (11) 18	0 0
Headache	5 (11) 18	0 0
Somnolence	3 (7) 11	0 0
Gastrointestinal disorders		
Abdominal pain*	5 (11) 18	1 (6) 18
Skin and subcutaneous tissue disorders		
Rash*	5(11) 18	0 0
Ecchymosis	3 (7) 11	0 0
Erythema	3 (7) 11	0 0

Adverse Reaction	EMPAVELI (N=46) n (%) Exposure Adjusted Rate (per 100 pt yrs)	Control Arm[a] (N=18) n (%) Exposure Adjusted Rate (per 100 pt yrs)
Blood and lymphatic system disorders		
Thrombocytopenia	3 (7) 11	1 (6) 18
Respiratory, thoracic and mediastinal disorders		
Cough*	4 (9) 14	0 0
Epistaxis	3 (7) 11	0 0
Investigations		
Blood creatinine increased	3 (7) 11	0 0

[a]Control Arm = supportive care (excluding complement inhibitors)
EMPAVELI (N=46) group includes patients who received EMPAVELI at any point during the study, including patients randomized to EMPAVELI (N=35) and patients randomized to the control arm and crossed over to EMPAVELI treatment (N=11).
*Grouped terms
[b] Term includes injection-site bruising, injection-site hemorrhage, injection-site swelling, application site reaction, infusion-site pruritus, injection-site erythema, injection-site rash, puncture site reaction.

C3 Glomerulopathy or Primary IC-MPGN

Study in Adult and Pediatric Patients 12 Years of age and older with C3G or primary IC-MPGN (Study APL2-C3G-310)

The data described below reflects the exposure in adult (n=35) and pediatric patients 12 years of age and older (n=28) with native kidney C3G (n=46), native kidney primary IC-MPGN (n=12), or recurrent C3G following kidney transplant (n=5) who received EMPAVELI at the recommended dosing regimens during the 26-week placebo-controlled period of APL2-C3G-310. Serious adverse reactions due to viral infections resulting in hospitalizations occurred in 2 (3%) patients with C3G or primary IC-MPGN receiving EMPAVELI and 1 (2%) patient on placebo. One patient (2%) on EMPAVELI with native kidney C3G died because of respiratory failure due to COVID-19 pneumonia; there were no deaths in the placebo arm.

Table 4 describes the adverse reactions that were reported in ≥5% of patients (adults and pediatric patients 12 years of age and older) treated with EMPAVELI and at a greater incidence than placebo in APL2-C3G-310. Adverse reactions in pediatric patients were similar to those seen in adults.

The placebo-controlled period of APL2-C3G-310 was followed by a 26-week open-label period. During the open-label period, one patient with native kidney C3G had a serious adverse event of pneumonia secondary to *Streptococcus pneumoniae*, and one patient with recurrent C3G following kidney transplant developed herpes zoster meningoencephalitis while on concomitant immunosuppression, leading to treatment discontinuation.

Table 4: Adverse Reactions Reported in ≥5% of Patients (adult and pediatric) Treated with EMPAVELI and Greater than Placebo in Study APL2-C3G-310

Adverse Reaction	EMPAVELI (N=63) n (%)	Placebo (N=61) n (%)
General disorders and administration site conditions		
Infusion-site reactions*	16 (25)	14 (23)
Pyrexia	12 (19)	6 (10)
Fatigue	4 (6)	1 (2)
Infections and infestations		
Nasopharyngitis	11 (18)	7 (12)
Influenza	7 (11)	3 (5)
Gastrointestinal disorders		
Nausea	6 (10)	4 (7)
Respiratory, thoracic and mediastinal disorders		
Cough	6 (10)	1 (2)

* Term includes the following reactions at the infusion site: erythema, pruritus, swelling, bruising, induration, pain, hemorrhage, discomfort, oedema, rash, and hypoaesthesia.

Study in Adult recurrent C3G or primary IC-MPGN following kidney transplant (Study APL2-C3G-204)

In a study in 13 adults with recurrent C3G or primary IC-MPGN after kidney transplant (NCT#04572854), one patient with primary IC-MPGN experienced a serious adverse event of *Pneumocystis jirovecii* pneumonia while on EMPAVELI and concurrent immunosuppressive medications.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of EMPAVELI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to EMPAVELI exposure.

- Anaphylaxis and urticaria *[see Warnings and Precautions (5.3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on EMPAVELI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH in pregnancy *(see Clinical Considerations)*. The use of EMPAVELI may be considered following an assessment of the risks and benefits.

Treatment of pregnant cynomolgus monkeys with pegcetacoplan at a subcutaneous dose of 28 mg/kg/day (2.9 times human exposure based on AUC) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths compared to controls *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defect, 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 fetal/neonatal risk

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

Data

Animal Data

Animal reproduction studies with pegcetacoplan were conducted in cynomolgus monkeys. Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times human exposure based on AUC) from the gestation period through parturition resulted in a statistically significant increase in abortions and stillbirths compared to controls. No increase in abortions or stillbirths occurred at a dose of 7 mg/kg/day (1.3 times human exposure based on AUC). No maternal toxicity or teratogenic effects were observed in offspring delivered at term. No developmental effects were observed in infants up to 6 months postpartum. Systemic exposure to pegcetacoplan of less than 1% of maternal levels was detected in fetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester.

8.2 Lactation

Risk Summary

It is not known whether pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. There are no data on the effects of pegcetacoplan on milk production. Pegcetacoplan is present in milk of lactating monkeys *(see Animal Data)*. Since many medicinal products are secreted into human milk, and because of the potential for serious adverse reaction in a breastfeeding child, breastfeeding should be discontinued during treatment and for 40 days after the last dose.

Data

Animal Data

Pegcetacoplan was detectable in milk of lactating monkeys at less than 1% concentration of serum levels but was not detectable in the serum of nursing infants.

8.3 Females and Males of Reproductive Potential

Contraception

Females

EMPAVELI may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Pregnancy testing is recommended for females of reproductive potential prior to treatment with EMPAVELI. Advise female patients of reproductive potential to use effective contraception during treatment with EMPAVELI and for 40 days after the last dose.

8.4 Pediatric Use

The safety and effectiveness of EMPAVELI for the treatment of C3G or primary IC-MPGN have been established in pediatric patients aged 12 years and older. Use of EMPAVELI for this indication is supported by evidence from an adequate and well controlled trial that enrolled 55 pediatric patients aged 12 years and older *[see Adverse Reactions (6.1), and Clinical Studies (14.2)]*. The safety and effectiveness of EMPAVELI in pediatric patients less than 12 years of age with C3G or IC-MPGN have not been established.

Safety and effectiveness of EMPAVELI in pediatric patients with PNH have not been established.

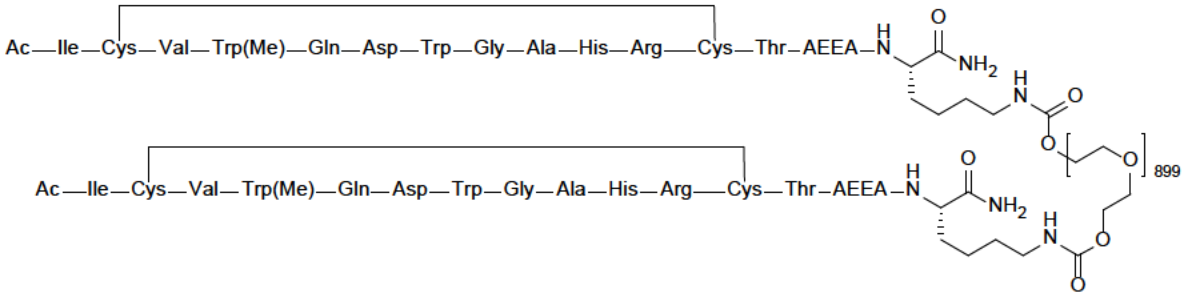
8.5 Geriatric Use

Clinical studies of EMPAVELI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between geriatric and younger patients.

11 DESCRIPTION

EMPAVELI contains pegcetacoplan, a complement inhibitor. Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kiloDalton (kDa) PEG molecule. The peptide portions of pegcetacoplan contain 1-methyl-L-tryptophan (Trp(Me)) in position 4 and amino(ethoxyethoxy)acetic acid (AEEA) in position 14.

The molecular weight of pegcetacoplan is approximately 43.5 kDa. The molecular formula is $C_{1970}H_{3848}N_{50}O_{947}S_4$. The structure of pegcetacoplan is shown below.



EMPAVELI injection is a sterile, clear, colorless to slightly yellowish aqueous solution for subcutaneous use and is supplied in a 20-mL single-dose vial. Each 1 mL of solution contains 54 mg of pegcetacoplan, 41 mg of sorbitol, 0.384 mg of glacial acetic acid, 0.490 mg of sodium acetate trihydrate, and Water for Injection USP. EMPAVELI may also contain sodium hydroxide and/or additional glacial acetic acid for adjustment to a target pH of 5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation.

In PNH, extravascular hemolysis (EVH) is facilitated by C3b opsonization while intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan acts proximally in the complement cascade controlling both C3b-mediated EVH and terminal complement-mediated IVH.

In C3G and primary IC-MPGN, complement dysregulation and overactivation causes deposition of C3 fragments in glomeruli, which contributes to the pathogenesis of C3G and is thought to contribute to the pathogenesis of IC-MPGN. Pegcetacoplan binds C3 and its activation fragment C3b, therefore inhibiting C3 activation, decreasing C3 glomerular fragment deposition, and decreasing C5 convertase activity and subsequent assembly of C5b-9.

12.2 Pharmacodynamics

In patients with PNH administered multiple doses of pegcetacoplan, the mean C3 concentration increased from 94 mg/dL at baseline to 380 mg/dL at Week 16 and sustained through Week 48 (Study APL2-302). In study APL2-308, the mean C3 concentration increased from 95 mg/dL at baseline to 356 mg/dL at Week 26 *[see Clinical Studies (14.1)]*.

The percentage of PNH Type II + III RBCs increased from 66.2% at baseline to 93.9% at Week 16 and sustained through Week 48 (Study APL2-302). In Study APL2-308, the mean percentage of PNH Type II + III RBCs increased from 42.4% at baseline to 90% at Week 26.

The mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 17.8% at baseline to 0.2% at Week 16 and sustained through Week 48 (Study APL2-302). In Study APL2-308, the mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 2.85% at baseline to 0.09% at Week 26.

In patients with C3G or primary IC-MPGN administered pegcetacoplan SC infusion twice weekly, mean (SD) serum C3 levels increased from 62 (48) mg/dL at baseline to 371 (120) mg/dL at Week 26 compared to no change with placebo. Mean (SD) plasma soluble C5b-9 levels decreased from 903 (698) ng/mL at baseline to 290 (249) ng/mL at Week 26 with EMPAVELI compared to no change with placebo. Of patients with evaluable kidney biopsies (n=69), 74% of patients on pegcetacoplan had a decrease in C3 complement staining by at least 2 orders of magnitude from baseline to Week 26 compared to 12% on placebo.

Cardiac Electrophysiology
At the recommended dose of EMPAVELI, no large mean increases in QTc interval (i.e., greater than 20 msec) were observed.

12.3 Pharmacokinetics

In patients with PNH, the serum pegcetacoplan concentrations achieved steady-state approximately 4 to 6 weeks following the first dose. The exposure of pegcetacoplan increased proportionally over a dose range from 45 to 1,440 mg (0.04 to 1.33 times the approved recommended dose). The mean (CV%) trough serum concentration observed at Week 16 was 706 (15.1%) mcg/mL and sustained through Week 48 (Study APL2-302). In Study APL2-308, mean (CV%) trough serum concentration was 744 (25.5%) mcg/mL at Week 26.

In patients with C3G or primary IC-MPGN, serum pegcetacoplan concentrations reached steady state approximately 4 to 8 weeks following twice weekly SC infusion. The mean (CV%) trough serum concentrations ranged between 716 (31%) and 766 (23%) mcg/mL from Week 4 to Week 26.

Absorption
The median T_{max} of pegcetacoplan is between 108 and 144 hours (4.5 to 6 days) after a single dose.

Distribution
The mean (CV%) volume of distribution of pegcetacoplan is approximately 3.98 L (32%) in patients with PNH.

The estimated mean (CV%) volume of distribution of pegcetacoplan is approximately 4.79 L (38%) and 4.58 L (29%) in patients with C3G or primary IC-MPGN, respectively.

Elimination

The estimated mean (CV%) of clearance (CL) is 0.36 L/day (30%) and median effective half-life of elimination ($t_{1/2}$) is 8.6 days in patients with PNH.

The estimated mean (CV%) of clearance (CL) is 0.32 L/day (54%) and median $t_{1/2}$ is 10.2 days in patients with C3G. The estimated mean (CV%) of clearance (CL) is 0.3 L/day (51%) and median $t_{1/2}$ is 10.8 days in patients with primary IC-MPGN.

Metabolism

Pegcetacoplan is expected to be metabolized into small peptides and amino acids by catabolic pathways.

Specific Populations

There were no clinically significant differences on the pharmacokinetics of pegcetacoplan based on age (19 to 81 years old), sex, race (Asian vs. non-Asian), renal impairment, and hepatic function as evaluated by total bilirubin (0.06-8.8 mg/dL), albumin (1.8-5.5 g/dL), aspartate aminotransferase (6-302 IU/L), or alanine aminotransferase (4-209 IU/L).

In patients with C3G or primary IC-MPGN, there were no clinically significant differences in pharmacokinetics of pegcetacoplan based on age (12 to 74 years old), diagnosis (C3G vs primary IC-MPGN), and urine protein-to-creatinine ratio (UPCR) (133-13300 mg/g).

12.6 Immunogenicity

PNH

There is insufficient information to characterize the anti-drug antibody response to EMPAVELI and the effects of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of pegcetacoplan products in PNH patients.

C3G or primary IC-MPGN

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the study described below with the incidence of anti-drug antibodies in other studies.

During the 26-week placebo-controlled period in Study APL2-C3G-310, 14 of 62 participants (23%) with C3G or primary IC-MPGN randomized to pegcetacoplan developed anti–pegcetacoplan peptide antibodies. Two of 62 participants (3%) developed anti–pegcetacoplan peptide neutralizing antibodies. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of pegcetacoplan over the treatment duration of 26 weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of pegcetacoplan have not been conducted.

Pegcetacoplan was not mutagenic when tested in an *in vitro* bacterial reverse mutation (Ames) and was not genotoxic in an *in vitro* assay in human TK6 cells or in an *in vivo* micronucleus assay in mice.

Effects of pegcetacoplan on fertility have not been studied in animals. There were no microscopic abnormalities in male or female reproductive organs in toxicity studies in rabbits and monkeys.

13.2 Animal Toxicology and/or Pharmacology

In toxicology studies in rabbits and cynomolgus monkeys, epithelial vacuolation and infiltrates of vacuolated macrophages were observed in multiple tissues, including the renal tubules, following daily subcutaneous doses of pegcetacoplan up to 7 times the human dose. These findings are attributable to uptake of the PEG moieties of pegcetacoplan. Renal degeneration was observed microscopically in rabbits at exposures (C_{max} and AUC) less than those for the human dose, and in monkeys at exposures approximately 2.7-fold those for the human dose. The clinical significance of these findings is uncertain.

14 CLINICAL STUDIES

14.1 Paroxysmal Nocturnal Hemoglobinuria

The efficacy and safety of EMPAVELI in patients with PNH were assessed in two open-label, randomized-controlled Phase 3 studies: Study APL2-302 (NCT03500549) and Study APL2-308 (NCT04085601). All patients who completed the studies were eligible to enroll in a separate long-term extension study.

In both studies, patients were vaccinated against *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B (Hib), either within 2 years prior to Day 1 or within 2 weeks after starting treatment with EMPAVELI. Patients vaccinated after initiation of treatment with EMPAVELI received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. In addition, prophylactic antibiotic therapy was administered at the discretion of the investigator in accordance with local treatment guidelines for patients with PNH receiving treatment with a complement inhibitor.

A dose of 1,080 mg twice weekly was used for patients randomized to the EMPAVELI group of each study. If required, the dose of EMPAVELI could be adjusted to 1,080 mg every 3 days. EMPAVELI was administered as a subcutaneous infusion; the infusion time was approximately 20 to 40 minutes.

Study in Complement-Inhibitor Experienced Adult Patients with PNH (Study APL2-302)

The study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with Hb levels less than 10.5 g/dL.

Eligible patients entered a 4-week run-in period during which they received EMPAVELI 1,080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomized in a 1:1 ratio to receive either 1,080 mg of EMPAVELI twice weekly or their current dose of eculizumab through the duration of the 16-week randomized controlled period (RCP).

Randomization was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28 (<4; ≥4) and platelet count at screening (<100,000/mm^3; ≥100,000/mm^3). Following completion of the RCP, all patients entered a 32-week open-label period (OLP) and received monotherapy with EMPAVELI. Patients initially randomized to eculizumab entered a second 4-week run-in period during which they received EMPAVELI in addition to eculizumab before continuing on to receive EMPAVELI monotherapy. All patients who completed the 48-week period were eligible to enroll in a separate long-term extension study.

A total of 80 patients were randomized to receive treatment, 41 to EMPAVELI and 39 to eculizumab. Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 5). The median times from PNH diagnosis to Day -28 were 6 and 9.7 years, respectively, for EMPAVELI and eculizumab. The baseline mean total PNH RBC clone sizes (Type III) were 47% for EMPAVELI and 50% for eculizumab. Twenty-nine percent and 23% of patients had a history of major adverse vascular events, and 37% and 26% had a history of thrombosis for patients receiving EMPAVELI or eculizumab, respectively. Within 28 days prior to the first dose of EMPAVELI or eculizumab, respectively, 34% and 31% of patients used anti-thrombotic agents (anti-platelet and/or anticoagulants). During Study APL2-302, 37% and 36% of patients on EMPAVELI and eculizumab, respectively, used antithrombotic agents. A total of 38 patients in the group treated with EMPAVELI and 39 patients in the eculizumab group completed the 16-week RCP and continued into the 32-week OLP. Because of adverse reactions of hemolysis, 3 patients were discontinued from the EMPAVELI group during the RCP. Two out of 41 patients in the EMPAVELI group needed the dose adjustment to 1,080 mg every 3 days.

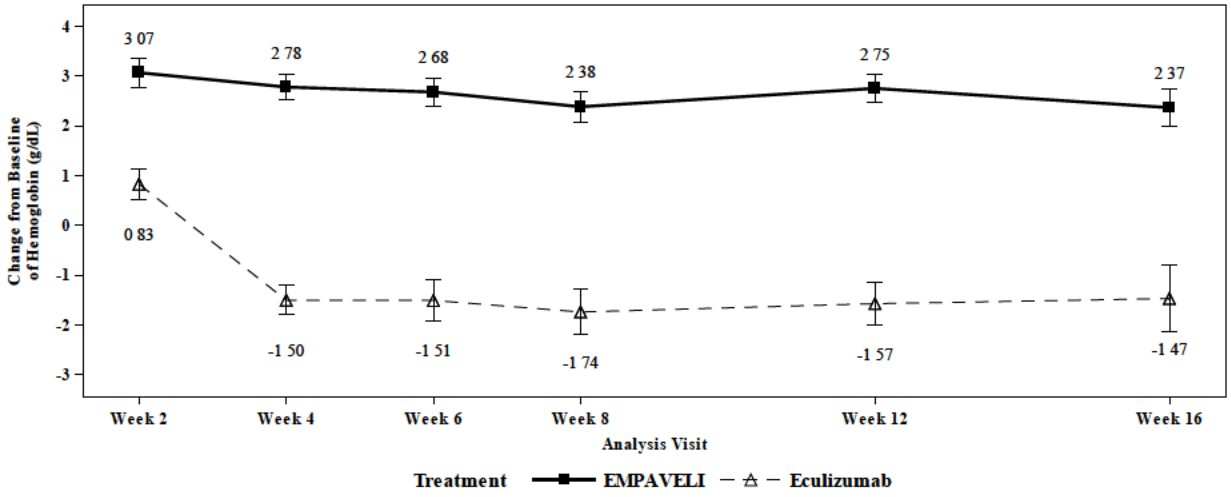
Table 5: Patient Baseline Demographics and Characteristics in Study APL2-302

Parameter	Statistics	EMPAVELI (N=41)	Eculizumab (N=39)
Age (years)	Mean (SD)	50.2 (16.3)	47.3 (15.8)
Sex			
Female	n (%)	27 (65.9)	22 (56.4)
Race			
Asian	n (%)	5 (12.2)	7 (17.9)
Black or African American	n (%)	2 (4.9)	0
White	n (%)	24 (58.5)	25 (64.1)
Other	n (%)	0	1 (2.6)
Not reported	n (%)	10 (24.4)	6 (15.4)
Ethnicity			
Hispanic or Latino	n (%)	2 (4.9)	1 (2.6)
Not Hispanic or Latino	n (%)	29 (70.7)	32 (82.1)
Not reported	n (%)	10 (24.4)	6 (15.4)
Hemoglobin level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
Absolute reticulocyte count (10^9 cells/L)	Mean (SD)	218 (75)	216 (69.1)
LDH level (U/L)	Mean (SD)	257.5 (97.7)	308.6 (284.8)
Number of transfusions in last 12 months prior to Day -28	Mean (SD)	6.1 (7.3)	6.9 (7.7)
<4	n (%)	20 (48.8)	16 (41)
≥4	n (%)	21 (51.2)	23 (59)

The efficacy of EMPAVELI was based on change from baseline to Week 16 (during RCP) in hemoglobin level. Baseline was defined as the average of measurements recorded prior to taking the first dose of EMPAVELI. Supportive efficacy data included transfusion avoidance, defined as the proportion of patients who did not require a transfusion during the RCP, and change from baseline to Week 16 in absolute reticulocyte count (ARC).

EMPAVELI was superior to eculizumab for the change from baseline in hemoglobin level at Week 16 (p<0.0001). The adjusted mean change from baseline in hemoglobin level was 2.37 g/dL in the group treated with EMPAVELI versus -1.47 g/dL in the eculizumab group (Figure 1), demonstrating an adjusted mean increase of 3.84 g/dL with EMPAVELI compared to eculizumab at Week 16 (95% CI, 2.33-5.34).

Figure 1: Adjusted Mean (± SE) Change from Baseline to Week 16 in Hemoglobin (g/dL) in Study APL2-302*



*Treatment effect estimates from a mixed model are shown. The mixed model contained the categorical effects of treatment, visit, treatment by visit interaction, and stratification factors (transfusion history and platelet count at screening), and the continuous covariate of baseline value.

Non-inferiority was demonstrated in the endpoints of transfusion avoidance and change from baseline in ARC at Week 16.

The adjusted means, treatment differences, and confidence intervals (CIs) for additional efficacy results are shown in Table 6.

Table 6: Additional Efficacy Results at Week 16 in Study APL2-302

	EMPAVELI (N=41)	Eculizumab (N=39)	Difference (95% CI)
Transfusion avoidance, n (%)	35 (85%)	6 (15%)	63%* (48%, 77%)
Change from baseline in ARC (10^9 cells/L), LS† mean (SE)‡	-136 (6.5)	28 (11.9)	-164 (-189.9, -137.3)

*Difference in percentages and 95% CI were based on the stratified Miettinen–Nurminen method.
†LS = Least square
‡SE = Standard error

Efficacy was generally similar across subgroups based on sex, race, and age.

All 77 patients who completed the RCP entered the 32- week OLP, during which all patients received EMPAVELI, resulting in a total exposure of up to 48 weeks. Between Week 16 and Week 48, 10 patients discontinued the study, all due to adverse reactions, and thirteen patients had a dose adjustment to 1,080 mg every three days. The efficacy results at Week 48 were generally consistent with those at Week 16.

Study in Complement-Inhibitor Naïve Adult Patients with PNH (Study APL2-308)

Study APL2-308 enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrollment and with Hb levels less than the lower limit of normal (LLN). Eligible patients were randomized in a 2:1 ratio to receive EMPAVELI or supportive care [excluding complement inhibitors (e.g., transfusions, corticosteroids, supplements such as iron, folate, and vitamin B_{12}), hereafter referred to as the control arm] through the duration of the 26-week treatment period. Randomization was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to

Day -28 (<4; ≥4). At any point during the study, a patient assigned to the control arm treatment group who had Hb levels ≥2 g/dL below baseline or presented with a PNH associated thromboembolic event was offered cross-over to EMPAVELI for the remainder of the study.

A total of 53 patients were randomized, 35 to EMPAVELI and 18 to the control arm. Demographics and baseline disease characteristics were generally well balanced between treatment groups (see Table 7). The mean times from PNH diagnosis to Day 1 were 5.7 and 5.5 years, respectively, for EMPAVELI and the control arm. The baseline mean total PNH RBC clone sizes (Type III) were 31% for EMPAVELI and 28% for the control arm. In the EMPAVELI group, 2.9% of patients had a history of major adverse vascular events. Two patients (5.7%) in the EMPAVELI group and 3 patients (16.7%) in the control arm group had a history of at least 1 type of thrombosis. Within 28 days prior to the first dose of EMPAVELI or the control arm, respectively, 17.1% and 27.8% of patients used anti-thrombotic agents (anti-platelet and/or anticoagulants). During Study APL2-308, 8.6% and 0% of patients on EMPAVELI and the control arm, respectively, used antithrombotic agents. Eleven of 18 patients randomized to the control transitioned to cross-over therapy with EMPAVELI due to a decreased Hb level ≥2 g/dL below baseline. Three patients treated with EMPAVELI required dose adjustment to 1,080 mg every 3 days. Three patients (5.7%; two patients in the EMPAVELI group and one patient in the control arm group) discontinued the study, none due to an adverse reaction.

Table 7: Patient Baseline Demographics and Characteristics in Study APL2-308

Parameter	**Statistics**	**EMPAVELI (N=35)**	**Control Arm[a] (N=18)**
Age (years)	Mean (SD)	42.2 (12.7)	49.1 (15.6)
Sex Female	n (%)	16 (45.7)	8 (44.4)
Race American Indian or Alaska Native	n (%)	9 (25.7)	2 (11.1)
Asian	n (%)	23 (65.7)	16 (88.9)
Black or African American	n (%)	2 (5.7)	0
Other	n (%)	1 (2.9)	0
Ethnicity Hispanic or Latino	n (%)	12 (34.3)	2 (11.1)
Not Hispanic or Latino	n (%)	23 (65.7)	16 (88.9)
Hemoglobin level (g/dL)	Mean (SD)	9.4 (1.4)	8.7 (0.8)
Absolute reticulocyte count (10^9 cells/L)	Mean (SD)	230.2 (81)	180.3 (109.1)
LDH level (U/L)	Mean (SD)	2151 (909.4)	1945.9 (1003.7)
Number of transfusions in last 12 months prior to Day -28	Mean (SD)	3.9 (4.4)	5.1 (5)
<4	n (%)	21 (60)	8 (44.4)
≥4	n (%)	14 (40)	10 (55.6)

[a]Control Arm = supportive care (excluding complement inhibitors)

The efficacy of EMPAVELI was based on the percentage of patients achieving hemoglobin stabilization, defined as avoidance of a >1 g/dL decrease in hemoglobin levels from baseline in the absence of transfusion, and the change from baseline in LDH level. Supportive efficacy data included change from baseline in absolute reticulocyte count (ARC), change from baseline in hemoglobin, and transfusion avoidance, defined as the proportion of patients who did not require a transfusion through Week 26. Baseline was defined as the average of measurements recorded prior to taking the first dose of EMPAVELI or prior to randomization to the control arm treatment group.

Efficacy results are shown in Table 8 below.

Table 8: Efficacy Results During the 26-Week Study in Study APL2-308

	EMPAVELI (N=35)	**Control Arm[a] (N=18)**	**Difference (95% CI) p-value**
Hemoglobin Stabilization[§] (n, %)	30 (85.7%)	0 (0%)	73% (57%, 89%) p<0.0001*
Change from Baseline in LDH[b] (LS[†] Mean CFB, SE[‡])	-1870 (101)	-400 (313)	-1470 (-2113.4, -827.3) p<0.0001
Change from baseline in ARC[b] (LS[†] Mean CFB, SE[‡])	-123 (9.2)	-19 (25.2)	-103 (-158.9, -48.7) p = 0.0002
Change from baseline in Hb[b] (LS[†] Mean CFB, SE[‡])	2.9 (0.38)	0.3 (0.76)	2.7 (0.99, 4.35) p = 0.0019
Transfusion Avoidance[§] (n, %)	32 (91%)	1 (6%)	72% (56%, 89%) p<0.0001*

[a]Control Arm = supportive care (excluding complement inhibitors)
[b]The post baseline missing values (including the values after cross-over from the control arm) are imputed using a multiple imputation method.
Data collected after cross-over from the control arm is excluded in analyses.
[§]Patients who crossed over from the control arm group to the EMPAVELI group, withdrew from the study, or were lost to follow up are considered as failing to achieve the criteria.
*p-value is obtained by stratified Cochran-Mantel-Haenszel test.
[†]LS = Least square
[‡]SE = Standard error

14.2 C3 Glomerulopathy (C3G) or Primary Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

The efficacy of EMPAVELI in reducing proteinuria in adult and pediatric patients aged 12 years and older with native kidney C3G, native kidney IC-MPGN, or recurrent C3G following kidney transplant was demonstrated in Study APL2-C3G-310. Safety and effectiveness of EMPVAELI in patients with recurrent IC-MPGN following kidney transplant have not been established.

APL2-C3G-310 is a randomized, double-blind, placebo-controlled study that included 124 adult and pediatric patients aged 12 years and older and weighing at least 30 kg with biopsy-proven, native kidney or post-transplant recurrent C3G, or native kidney primary IC-MPGN, eGFR ≥30 mL/min/1.73 m^2, proteinuria ≥1 g/day, and urine protein-to-creatinine ratio (UPCR) ≥1 g/g (NTC 05067127). For at least 12 weeks before randomization and throughout the 26-week placebo-controlled period, patients were required to be on stable and optimized doses of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and/or sodium-glucose cotransporter-2 (SGLT2) inhibitors. Immunosuppressant medication doses (e.g., steroids no higher than 20 mg daily, mycophenolate mofetil, tacrolimus) had to be stable for at least 12 weeks before randomization and throughout the 26-week placebo-controlled period.

Patients were randomized (1:1) to EMPAVELI or placebo, administered twice weekly as a subcutaneous (SC) infusion for 26 weeks. Randomization was stratified by post-transplant recurrence and by kidney biopsy obtained within 28 weeks of screening. Adults and pediatric patients weighing 50 kg or more received EMPAVELI 1,080 mg (20 mL) twice weekly. Pediatric patients weighing 35 kg to less than 50 kg received 648 mg (12 mL) for the first infusion and 810 mg (15 mL) for each infusion thereafter. Pediatric patients weighing 30 kg to less than 35 kg received EMPAVELI 540 mg (10 mL) for the first 2 infusions and 648 mg (12 mL) twice weekly thereafter.

Patients were vaccinated against *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* type B (Hib) at least 14 days prior to randomization, unless documented evidence existed that participants received the recommended vaccinations or were non-responders to vaccination.

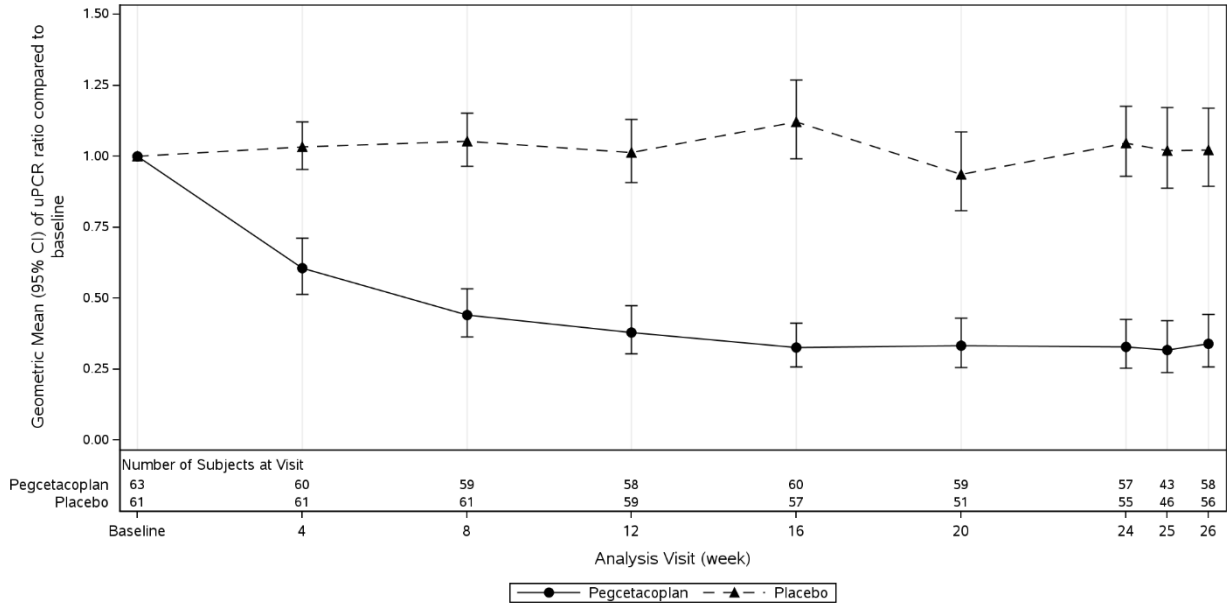
At baseline, the mean age was 26 years (range 12 to 74 years); 57% were female, 73% White, 15% Asian, 1% Black or African American, and 11% others. The study population included 55 pediatric patients 12 years to less than 18 years of age; mean age 14.7 years (28 randomized to EMPAVELI and 27 to placebo). Disease type was reasonably balanced between the treatment groups. Overall, 88 patients (71%) had native kidney C3G, 27 patients (22%) had native kidney primary IC-MPGN, and 8 patients (6%) had post-kidney transplant recurrent C3G. At baseline, mean UPCR from triplicate first morning urine (FMU) collections was 3.1 g/g and 2.5 g/g in the pegcetacoplan and placebo groups, respectively; mean eGFR (mL/min/1.73 m^2) was 79 and 87 in the pegcetacoplan and placebo groups, respectively; and mean baseline serum albumin was approximately 3.4 g/dL in both treatment groups.

Approximately 91% of patients were treated with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), 72% with immunosuppressants (e.g., mycophenolate mofetil, tacrolimus), 40% with systemic corticosteroids, and 11% with sodium-glucose co-transporter 2 (SGLT2) inhibitors. Use of each of these medications was balanced between the treatment groups.

The primary efficacy endpoint was the log-transformed ratio of UPCR (sampled from first morning urine collections) at Week 26 compared to baseline. At Week 26, the geometric mean UPCR ratio relative to baseline was 0.33 (95% CI: 0.25, 0.43) and 1.03 (95% CI: 0.91, 1.16) in the EMPAVELI and placebo groups, respectively, resulting in a 68% reduction in UPCR from baseline in the EMPAVELI group compared to placebo ($p<0.0001$). The treatment effect was consistent across all subgroups including disease type, age, transplant status (C3G), sex, race, baseline disease characteristics (eGFR and UPCR), and immunosuppressant use.

Figure 2 shows the geometric mean UPCR ratio compared to baseline over time.

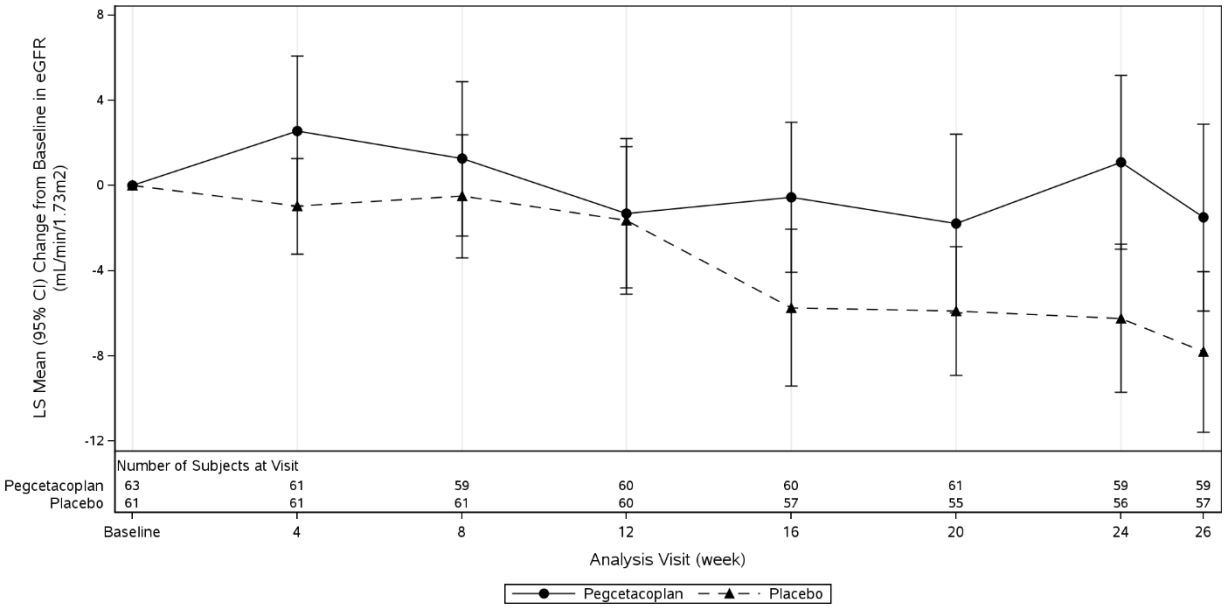
Figure 2: Geometric Mean of UPCR Ratio Compared to Baseline Over 26 Weeks of Treatment - Study APL2-C3G-310



Abbreviations: FMU = first-morning spot urine;
UPCR = urine protein-to-creatinine ratio.

During the 26-week placebo-controlled period, 49% of patients in the EMPAVELI group achieved a composite renal endpoint defined as a ≥50% reduction in UPCR and stable eGFR (≤15% reduction from baseline) compared with 3% of patients in the placebo group (odds ratio [95% CI] of 27 [6, 124], p<0.0001). Sixty percent of patients in the EMPAVELI group achieved a 50% or greater reduction in UPCR from baseline to Week 26 compared with 5% in the placebo arm, and 68% of patients in the EMPAVELI group had a stable eGFR (≤15% reduction from baseline to Week 26) compared with 59% in the placebo group. Over the first 6 months of treatment, EMPAVELI reduced the loss of kidney function compared to placebo (Figure 3). The efficacy of EMPAVELI in pediatric patients 12 years of age and older was similar to adults.

Figure 3: **LS Mean of eGFR Compared to Baseline Over 26 Weeks of Treatment - Study APL2-C3G-310**



Abbreviations: LS = least square
LS Mean (95% CI) of difference between EMPAVELI and placebo at Week 26 is 6.31 (0.50, 12.12) mL/min/1.73m^2.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
EMPAVELI injection is a clear, colorless to slightly yellowish aqueous solution for subcutaneous infusion supplied as 1,080 mg/20 mL (54 mg/mL) solution in 20-mL single-dose vials.

EMPAVELI is available in 20-mL single-dose vials individually packaged in cartons that are supplied in 8-count convenience cartons. NDC 73606-010-01.

Storage and Handling
Store vials of EMPAVELI refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not use beyond the expiration date stamped on the carton.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Dosing
For weight-based dosing, instruct caregivers and patients on the proper techniques for preparing, storing, measuring, and administering EMPAVELI via EMPAVELI Injector or commercially available infusion pump.

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 EMPAVELI or receive antibacterial drug prophylaxis if EMPAVELI treatment must be initiated immediately and they have not been previously vaccinated. Inform the patient that they are required to be revaccinated according to current ACIP recommendations for encapsulated bacteria while on EMPAVELI therapy *[see Warnings and Precautions (5.1)]*.

Inform patients that vaccination may not prevent serious infection and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms include the following:

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

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

EMPAVELI REMS

EMPAVELI is available only through a restricted program called EMPAVELI 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 months following treatment with EMPAVELI.
- Patients must be instructed to complete or update vaccinations against encapsulated bacteria per ACIP recommendations as directed by the prescriber prior to treatment with EMPAVELI.
- Patients must receive antibiotics as directed by the prescriber if they are not up to date with vaccinations against encapsulated bacteria and have to start EMPAVELI right away.

Anaphylaxis and infusion-related reactions

Advise patients of the risk of anaphylaxis and infusion-related reactions. Inform patients that anaphylaxis is life-threatening and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms include the following:

- difficulty breathing including shortness of breath and wheezing
- swollen tongue or throat
- feeling faint
- rapid heart rate
- skin reactions, including hives and itching

- nausea or vomiting
- confusion and anxiety
- dizziness or fainting

Discontinuation

Inform patients with PNH that they may develop hemolysis due to PNH when EMPAVELI is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following discontinuation of EMPAVELI.

Inform patients who discontinue EMPAVELI to keep the Patient Safety Card with them for 2 months after the last dose of EMPAVELI, because the increased risk of serious infection persists for several weeks following discontinuation of EMPAVELI.

Manufactured for:
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For patent information: www.apellis.com/productpatent

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EMP-PI-DDMonthYYYY-X.0

MEDICATION GUIDE
EMPAVELI® (em-puh-vel-ee)
(pegcetacoplan)
injection, for subcutaneous use

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

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

- **EMPAVELI 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 cause death if not recognized and treated early.**
  - You must complete or be up to date with the vaccines against *Streptococcus pneumoniae* and *Neisseria meningitidis* at least 2 weeks before your first dose of EMPAVELI.
  - If you have not completed your vaccines and EMPAVELI must be started right away, you should receive the required vaccines as soon as possible.
  - If you have not been vaccinated and EMPAVELI 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 vaccines before starting EMPAVELI. Your healthcare provider will decide if you need additional vaccines.
  - Vaccines do not prevent all infections caused by encapsulated bacteria. **Call your healthcare provider or get emergency medical care right away if you get any of these signs and symptoms of a serious infection:**
    - fever with or without shivers or the 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 a 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 months after your last dose of EMPAVELI. Your risk of serious infections may continue for several weeks after your last dose of EMPAVELI. It is important to show this card to any healthcare provider who treats you. This will help them diagnose and treat you quickly.

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

- enroll in the EMPAVELI 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 EMPAVELI right away and you are not up to date on your vaccines
- 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 EMPAVELI?"**

What is EMPAVELI?

EMPAVELI is a prescription medicine used to:

- treat adults with a disease called paroxysmal nocturnal hemoglobinuria (PNH).
- treat adults and children 12 years of age and older with a kidney disease called complement 3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN), to reduce levels of protein in the urine (proteinuria).

It is not known if EMPAVELI is safe and effective in children with PNH.

It is not known if EMPAVELI is safe and effective in children under 12 years of age with C3G or primary IC-MPGN.

Do not take EMPAVELI if you:

- are allergic to pegcetacoplan or any of the ingredients in EMPAVELI. See the end of this Medication Guide for a complete list of ingredients in EMPAVELI.
- have a serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type B when you are starting EMPAVELI treatment.

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

- have an infection or fever.
- are pregnant or plan to become pregnant. EMPAVELI may harm your unborn baby.
  Females who are able to become pregnant:
  - should have a pregnancy test before starting treatment with EMPAVELI.
  - use an effective method of birth control (contraception) during treatment with EMPAVELI and for 40 days after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if EMPAVELI passes into your breast milk. You should not breastfeed during treatment with EMPAVELI and for 40 days after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. EMPAVELI and other medicines can affect each other, causing 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 EMPAVELI?

- **See the detailed Instructions for Use that comes with your EMPAVELI for information about how to prepare and infuse your dose of EMPAVELI with your infusion pump.**
- **See the detailed Instructions for Use that comes with your EMPAVELI Injector for information about how to prepare and inject your dose of EMPAVELI with your EMPAVELI Injector.**
- Your healthcare provider should show you how to prepare and administer EMPAVELI before you use it for the first time.
- Use EMPAVELI exactly as your healthcare provider tells you. Do not use more or less than your healthcare provider tells you to.
- If you miss a dose of EMPAVELI, take the missed dose as soon as possible. Take your next dose at your regularly scheduled time.

For adults with PNH:

- EMPAVELI is given under the skin (subcutaneously) 2 times each week. If there is an increase in your LDH, an enzyme in your blood, your healthcare provider may tell you to take EMPAVELI every 3 days.
- **If you are changing treatment from eculizumab to EMPAVELI, you should continue eculizumab for 4 weeks after your first dose of EMPAVELI. After 4 weeks, you should stop treatment with eculizumab.**
- **If you are changing treatment from ravulizumab to EMPAVELI, you should take your starting dose of EMPAVELI no more than 4 weeks after your last dose of ravulizumab.**
- **If you have PNH and you stop taking EMPAVELI, your healthcare provider will need to monitor you closely for at least 8 weeks after stopping EMPAVELI. Stopping treatment with EMPAVELI may cause a breakdown of red blood cells due to PNH.**

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

  - decreased hemoglobin level in your blood
  - blood in your urine
  - shortness of breath
  - trouble swallowing
  - tiredness
  - pain in the stomach (abdomen)
  - blood clots
  - erectile dysfunction (ED)

For adults and children 12 years of age and older with C3G or primary IC-MPGN:

- EMPAVELI is given under the skin (subcutaneously) 2 times each week.

What are the possible side effects of EMPAVELI?

EMPAVELI can cause serious side effects including:

- See **"What is the most important information I should know about EMPAVELI?"**
- **Allergic reactions.** Allergic reactions can happen during your EMPAVELI infusion and can be life-threatening. Stop your EMPAVELI infusion and get emergency medical care right away if you get any of these symptoms during your EMPAVELI infusion:

- chest pain
- trouble breathing or shortness of breath
- wheezing
- swelling of your face, tongue, or throat
- feel dizzy or faint or pass out
- fast heart rate
- nausea or vomiting
- feel confused or anxious
- skin reactions, including rash, hives, and itching

The most common side effects in adults with PNH treated with EMPAVELI include:

- injection-site reactions
- infections
- diarrhea
- pain in the stomach (abdomen)
- respiratory tract infection
- pain in the arms, hands, legs or feet
- low potassium in blood
- tiredness
- viral infection
- cough
- joint pain
- dizziness
- headache
- rash

The most common side effects in adults and children 12 years of age and older with C3G or primary IC-MPGN treated with EMPAVELI include:

- injection-site reactions
- fever
- common cold
- flu
- cough
- nausea

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 EMPAVELI.

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 EMPAVELI?

- Store vials of EMPAVELI in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.
- Do not use EMPAVELI past the expiration date stamped on the carton.

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

General information about the safe and effective use of EMPAVELI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use EMPAVELI for a condition for which it was not prescribed. Do not give EMPAVELI 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 EMPAVELI that is written for health professionals.

What are the ingredients in EMPAVELI?

Active ingredient: pegcetacoplan

Inactive ingredients: sorbitol, glacial acetic acid, sodium acetate trihydrate, Water for Injection USP. EMPAVELI may also contain sodium hydroxide and/or additional glacial acetic acid for pH adjustment.

Manufactured for:

Apellis Pharmaceuticals, Inc. 100 Fifth Avenue Waltham, MA 02451
For patent information: www.apellis.com/productpatent
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EMPAVELI is a registered trademark of Apellis Pharmaceuticals, Inc.
For more information, go to www.EMPAVELI.com or call 1-866-692-7527.
EMP-MG-DDMonthYYYY-X.0

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 7/2025

INSTRUCTIONS FOR USE
EMPAVELI® Injector
(pegcetacoplan)
injection, for subcutaneous use
Single-use on-body injector

Important Information
This Instructions for Use is for the EMPAVELI Injector only.

Read **this** Instructions for Use before you start using the Injector and each time you get a refill as there may be new information. The EMPAVELI Injector is placed on your body to give medicine under the skin. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. Your healthcare provider should show you or your caregiver how to inject EMPAVELI the right way before you use it for the first time. It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider. Ask your healthcare provider about any instructions you do not understand.

If you have questions, concerns, or need of help, please call ApellisAssist® at 1-866-MY-APL-ASSIST (1-866-692-7527).

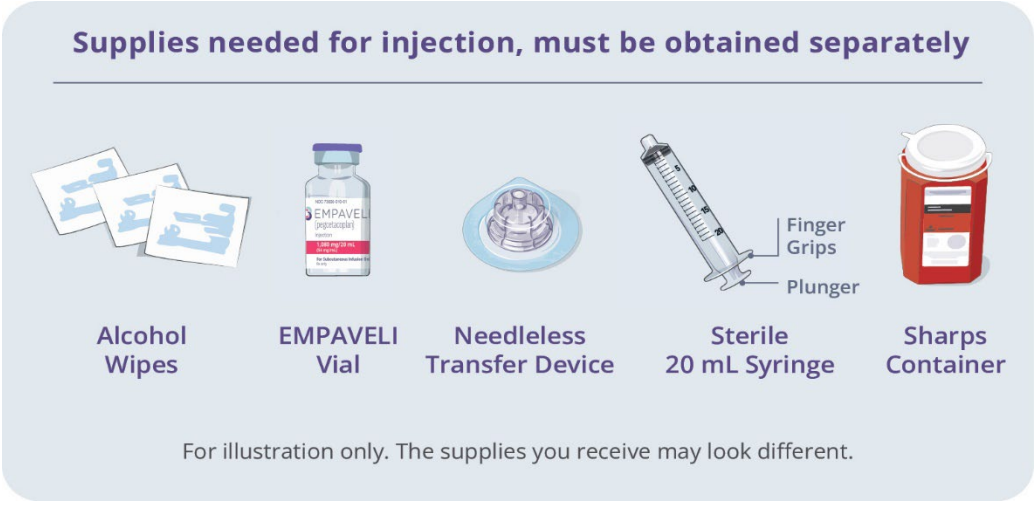
SIDE 1:
Filling the Syringe

Start Here
Complete these instructions on how to prepare EMPAVELI before completing EMPAVELI Injector administration instructions on the back of this page.

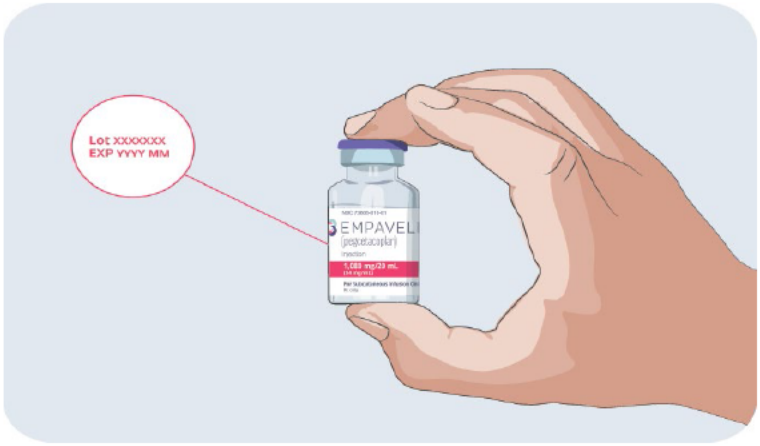
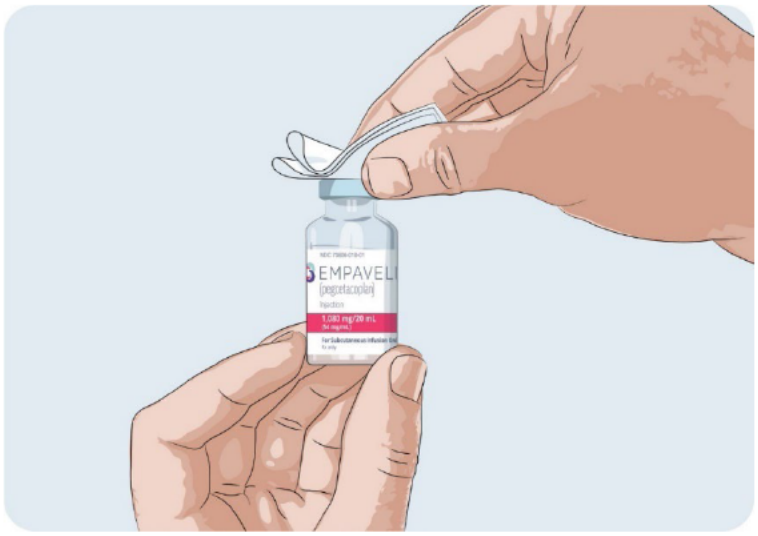
How should I store EMPAVELI?

- Store vials of EMPAVELI in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.
- **Do not** use EMPAVELI past the expiration date stamped on the carton.

Keep EMPAVELI, EMPAVELI Injector, and all medicines out of the reach of children.



Prepare for injection
1 Before you start: • Find a well-lit, flat work surface area, like a table. • Remove a single vial carton of EMPAVELI from the refrigerator. Keep the vial in the carton at room temperature 68°F to 77°F (20°C to 25°C) and allow it to warm up for about **30 minutes**. ⚠ **Do not** try to speed up the warming process.
2 • Wash your hands well with soap and water. • Dry your hands.

Check the vial and liquid	
3 	• Remove the vial from the carton. Carefully look at the liquid in the vial of EMPAVELI. • EMPAVELI is a clear, colorless to slightly yellowish liquid. Check for particles or color changes. ⚠ **Do not** use and call ApellisAssist if: — The liquid looks cloudy, contains particles, or is dark yellow. — The protective flip cap is missing from the top of the vial or damaged. — The expiration date on the label has passed.
4 	• Flip up to remove the protective flip cap from the top of the vial to show the exposed middle part of the gray rubber stopper of the EMPAVELI vial. • Throw away the protective flip cap.
5 	• Clean the gray rubber stopper on the top of the EMPAVELI vial with a new alcohol wipe. • Allow the gray rubber stopper to dry for at least 30 seconds. ⚠ **Do not** touch the exposed gray rubber stopper after wiping.

Prepare and fill the syringe with EMPAVELI using a needleless transfer device (such as a vial adapter)

6

Always follow the Instructions for Use provided by the needleless transfer device's manufacturer (as they may differ from the following steps).

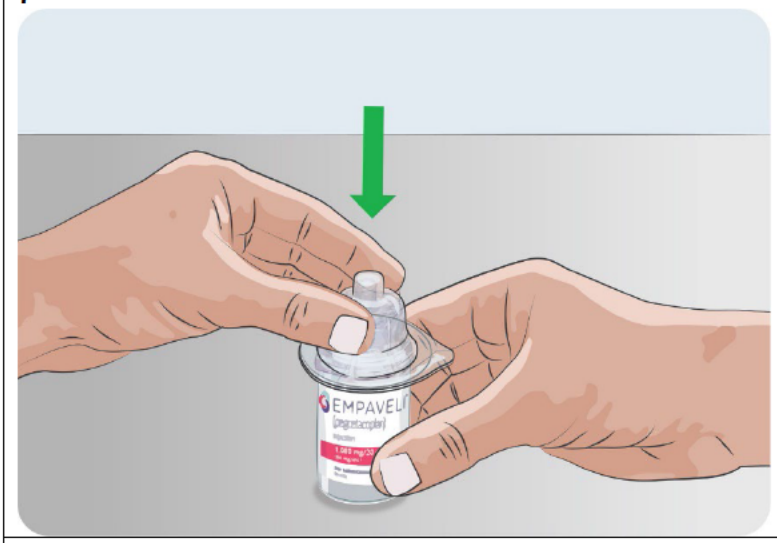
⚠ **Do not** remove the needleless transfer device from the blister package.

⚠ **Do not** touch the spike or the inside of the needleless transfer device.

⚠ **Do not** use the needleless transfer device if it comes out or is dropped out of the package.

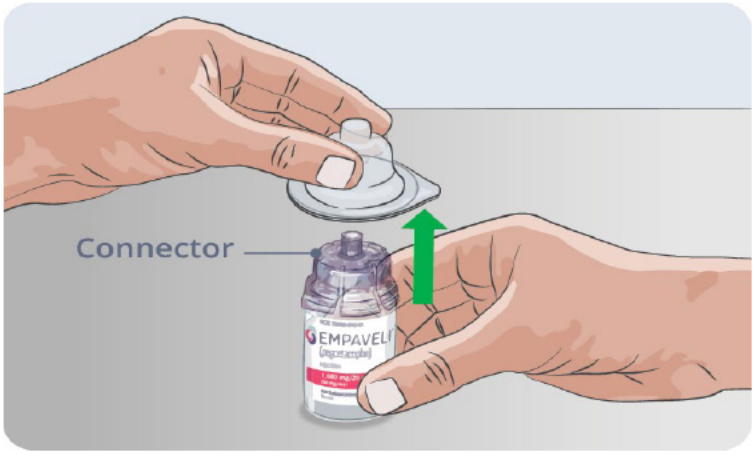
⚠ **Do not** use the needleless transfer device if the package is opened.

7



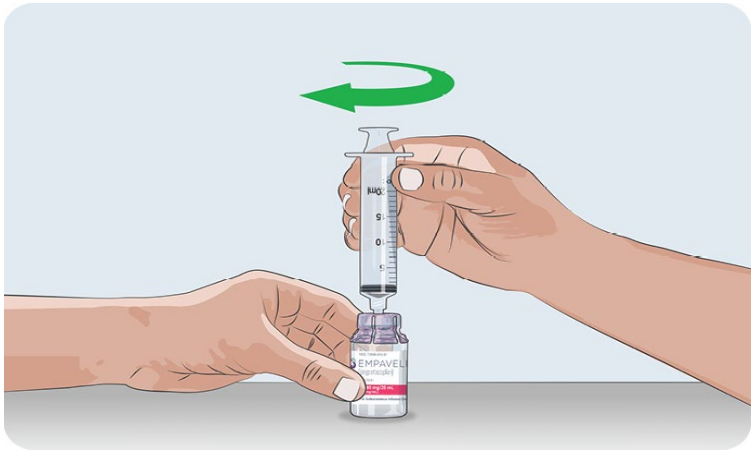
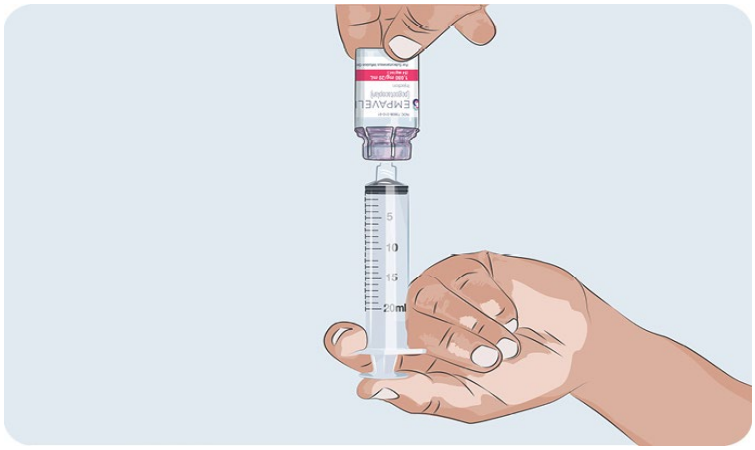
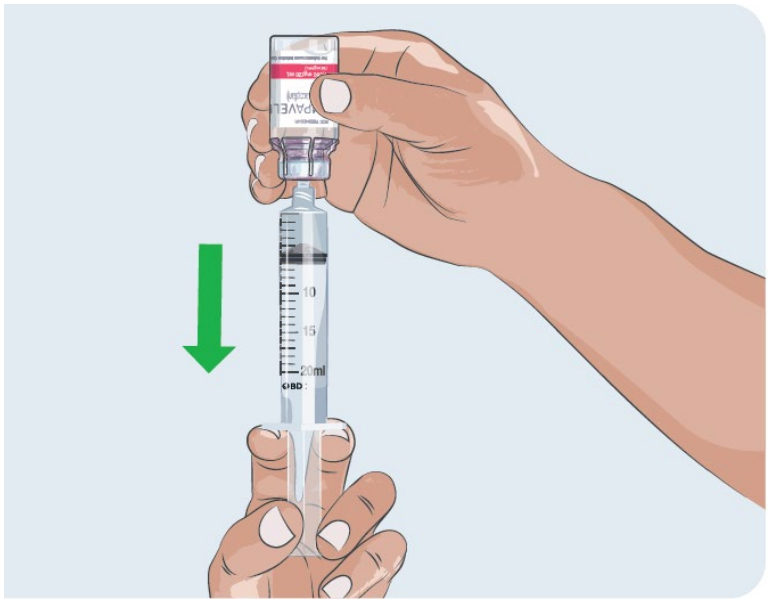
- Remove the cover of the needleless transfer device package.
- Place the vial on a clean, flat surface and hold the vial by the base with one hand.
- Using the outside of the blister package to firmly hold the needleless transfer device, push needleless transfer device straight down onto the vial top until it snaps securely into place.

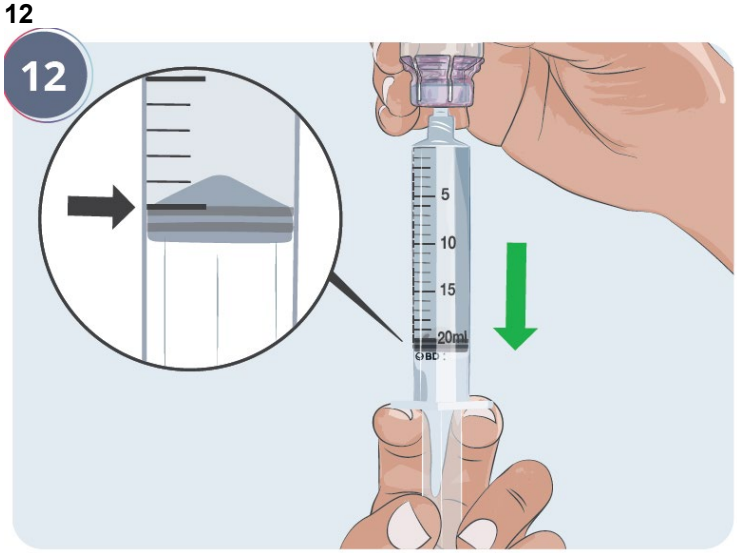
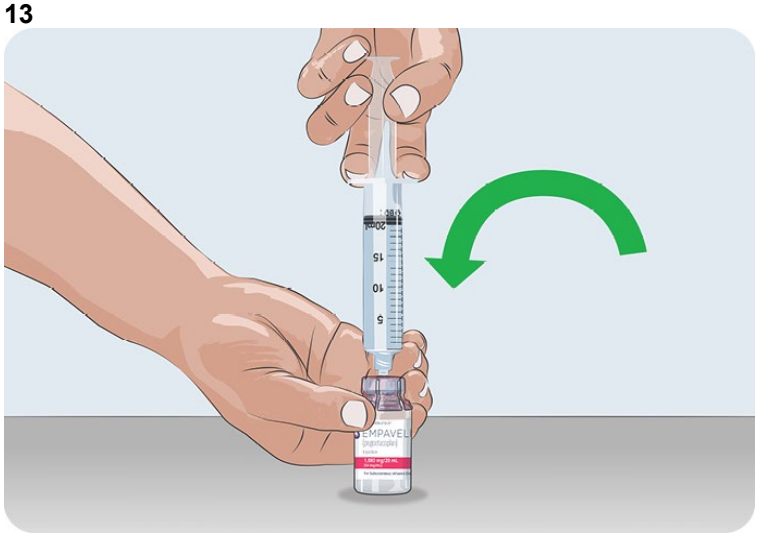
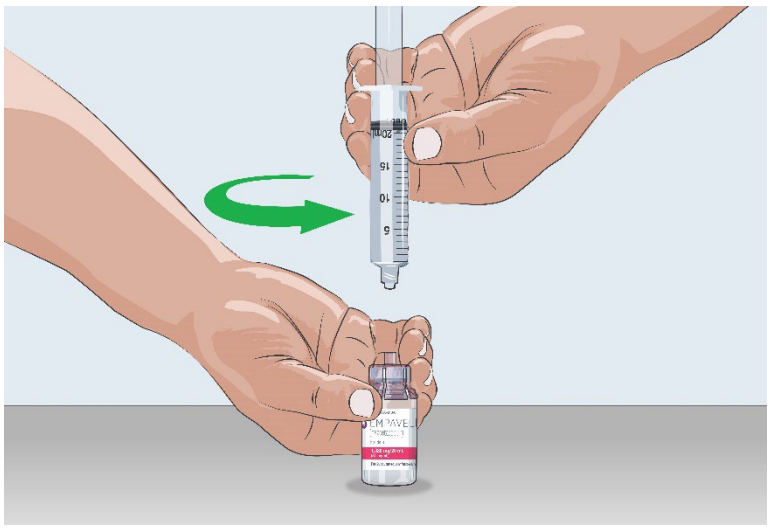
8

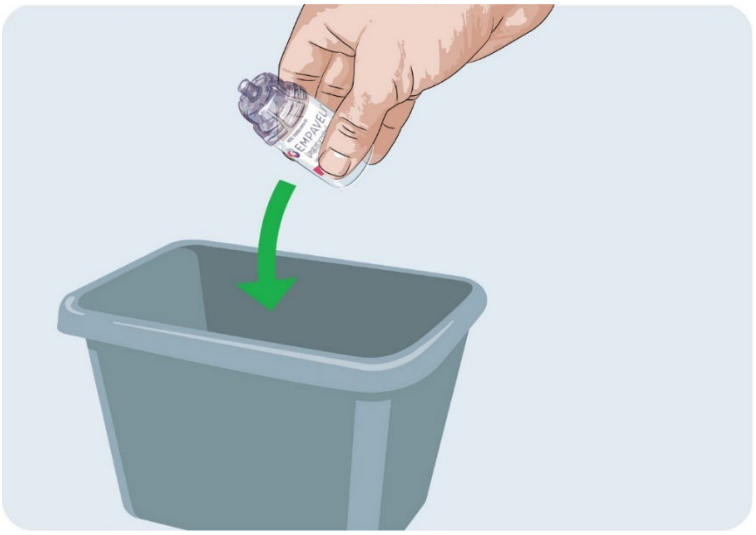


- Remove the blister package from the needleless transfer device and throw the blister package away.

⚠ **Do not** touch the connector at the top of the transfer device.

9 	• Remove the syringe from its packaging. ⚠ **Do not** touch the tip of the syringe. • Attach the syringe to the needleless transfer device by twisting the tip of the syringe to the right (clockwise) onto the top of the needleless transfer device.
10 	• Turn the EMPAVELI vial upside down.
11 	• Slowly pull the syringe plunger down to about the 5 mL mark to partially fill the syringe. • Remove air from the syringe by gently pushing on the plunger.

12 	• **Double check** your prescribed dose. — Your first dose, second dose and maintenance dose may be different. • Slowly pull the syringe plunger down to withdraw your prescribed dose of EMPAVELI to the correct marking amount (mL) of medicine that matches the dose your healthcare provider prescribed. Your dose may be different than the example shown. • **Double check** that you have withdrawn your prescribed dose. Your dose cannot be changed after it is filled in the EMPAVELI injector.
13 	• While holding the EMPAVELI vial and syringe, turn the EMPAVELI vial and filled syringe upright and place the bottom of the EMPAVELI vial on a flat surface.
14 	• Remove the filled syringe from the needleless transfer device with one hand while holding the EMPAVELI vial with the other hand and twisting the filled syringe to the left (counterclockwise).

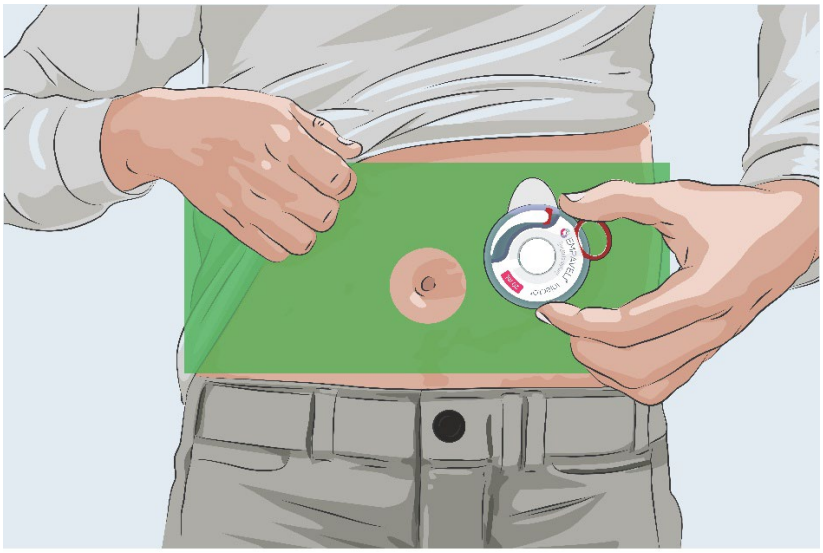
15 	• Place the syringe on a clean, flat surface while you prepare the EMPAVELI Injector. The syringe will not leak when set down. ⚠ **Do not** touch the tip of the filled syringe.
16 	⚠ **Do not** remove the needleless transfer device from the vial. • Throw away the vial with the needleless transfer device attached and any remaining EMPAVELI solution into the household trash.

TURN OVER
to continue

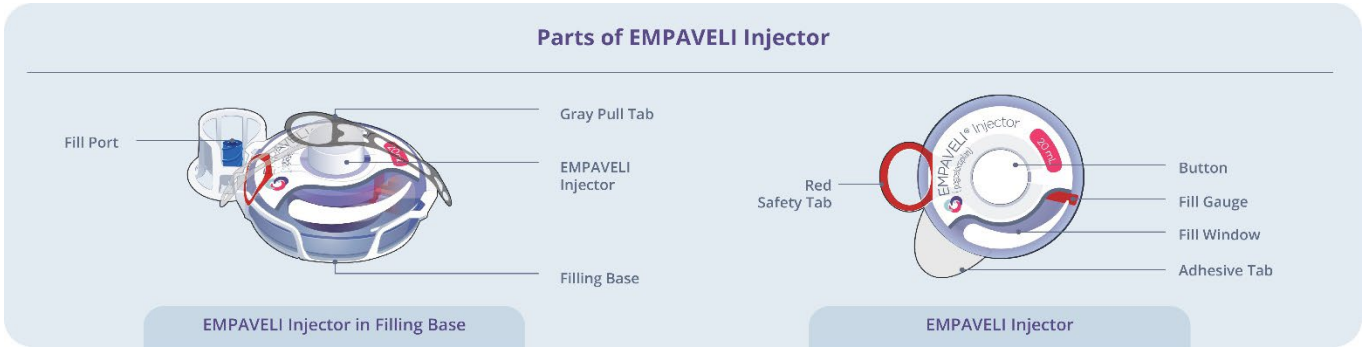
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SIDE 2:
Injector Administration

Complete these instructions for administering the EMPAVELI Injector after completing syringe filling instructions on the front of this page.



Once you complete the steps below, the **end result** is to attach the EMPAVELI Injector on your stomach.



Important information for administration with EMPAVELI Injector

General use:	**Using EMPAVELI Injector:**	**During injection:**
• **Do not** use EMPAVELI Injector if tamper-proof label has been broken. • **Do not** use EMPAVELI Injector if you have a skin condition on your stomach (injection site). • **Do not** use if you dropped EMPAVELI Injector. • **Do not** use if the sealed plastic tray is open or damaged.	• **Do not** apply EMPAVELI Injector along the belt line or on areas where the injector will be affected by folds in the skin. • **Do not** touch the white adhesive on the bottom of EMPAVELI Injector before attaching to stomach. • **Do not** let your clothes touch the clean site.	• **Do not** remove EMPAVELI Injector from the skin during injection. • **Do not** bathe, shower, exercise, use hot tubs, whirlpools, or saunas. Avoid getting your stomach wet. The EMPAVELI Injector is not waterproof. Water or sweat may loosen EMPAVELI Injector from skin.

• **Do not** use if the expiration date on the box has passed. • **Do not** use if you have an acrylic allergy. Tell your healthcare provider if you are allergic to acrylic. • **Do not** reuse EMPAVELI Injector. • **Do not** store the filled EMPAVELI Injector. • Wear loose clothes so that they **do not** get in the way of the EMPAVELI Injector. • **Do not** store the EMPAVELI Injector in direct sunlight. If the EMPAVELI Injector is stored in direct sunlight, **do not** use it and call ApellisAssist at 1-866-MY-APL-ASSIST (1-866-692-7527).	• **Do not** remove the Red Safety Tab until EMPAVELI Injector is attached to body. • **Do not** remove EMPAVELI Injector from the skin until the button pops out. • **Do not** throw away (dispose of) the EMPAVELI Injector into household trash. See the section “Remove and Dispose of EMPAVELI Injector” for information on how to dispose of the EMPAVELI Injector. • Choose an injection site at least 1 inch from the edge of your belly button and the edge of the EMPAVELI Injector, and 1 inch from last injection site. • Use the EMPAVELI Injector on stomach only.	• **Do not** sleep or bathe during injection. • Avoid intense physical activity. • **Do not** bump or knock the EMPAVELI Injector. • **Do not** bump the EMPAVELI Injector Button. • **Do not** use anything to hold the EMPAVELI Injector in place.

Supplies needed for injection



Alcohol Wipe



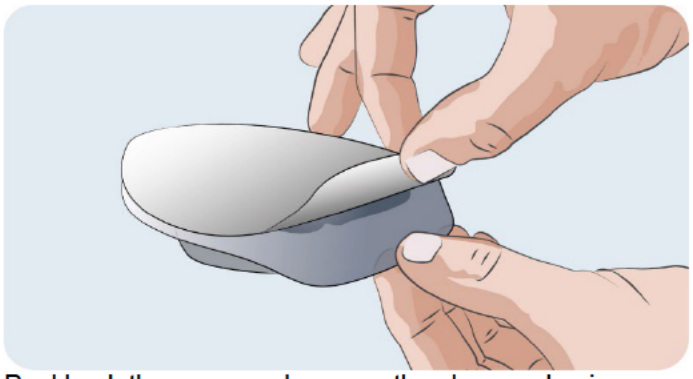
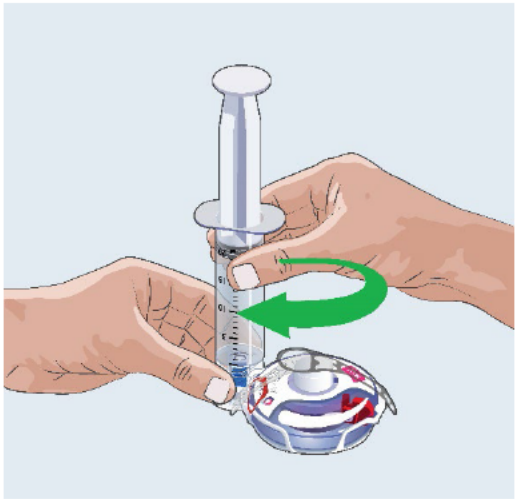
Syringe Filled With EMPAVELI



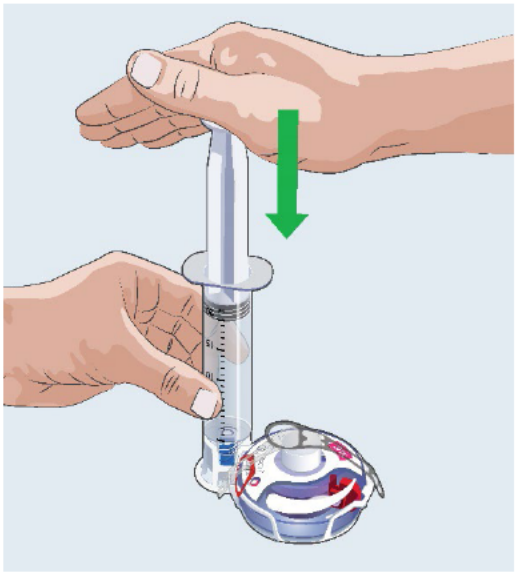
EMPAVELI Injector Package



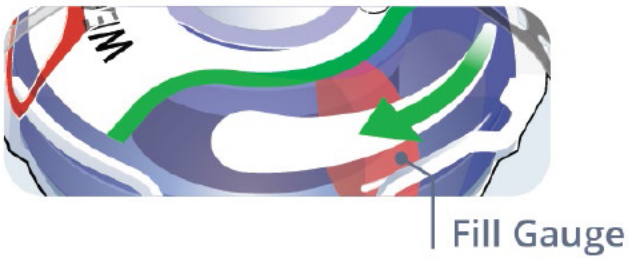
Sharps Container

Fill injector with EMPAVELI liquid	
17  Peel back the cover and remove the clear packaging insert.	 Remove the EMPAVELI Injector and the surrounding Filling Base from the packaging. Place it on a clean, flat surface.
18 	• Pick up the syringe filled with EMPAVELI. • Twist the filled syringe tip to the right (clockwise) into the Fill Port until it is tight.

19



- Firmly push the syringe plunger down.
- The syringe plunger may be hard to push.
- Watch the Fill Gauge move as EMPAVELI is pushed into the injector.



20



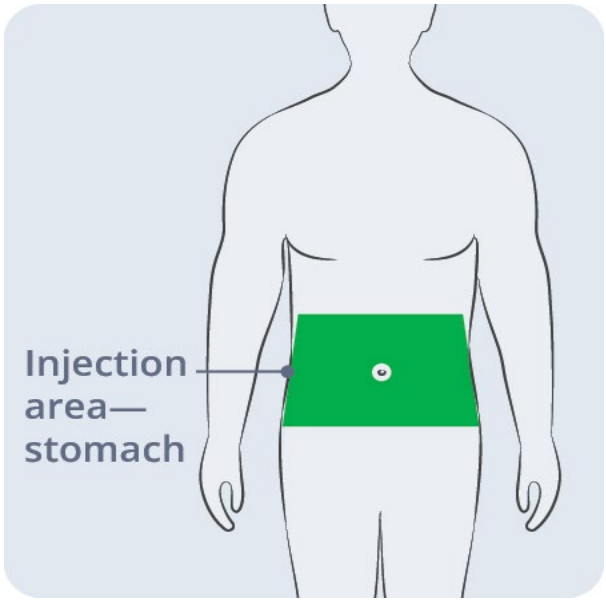
- Make sure the syringe is empty. If needed, press firmly down on the syringe plunger again.

⚠ **Do not** remove syringe from Filling Base. After the EMPAVELI Injector is filled, continue with the preparation and injection.

⚠ **Do not** store filled EMPAVELI Injector.

Attach EMPAVELI Injector to stomach

21



- Select an area on your stomach to place the EMPAVELI Injector.

⚠ Use the EMPAVELI Injector on your stomach only.

- Choose an injection site at least:
  - 1 inch from the edge of your belly button and the edge of the EMPAVELI Injector.

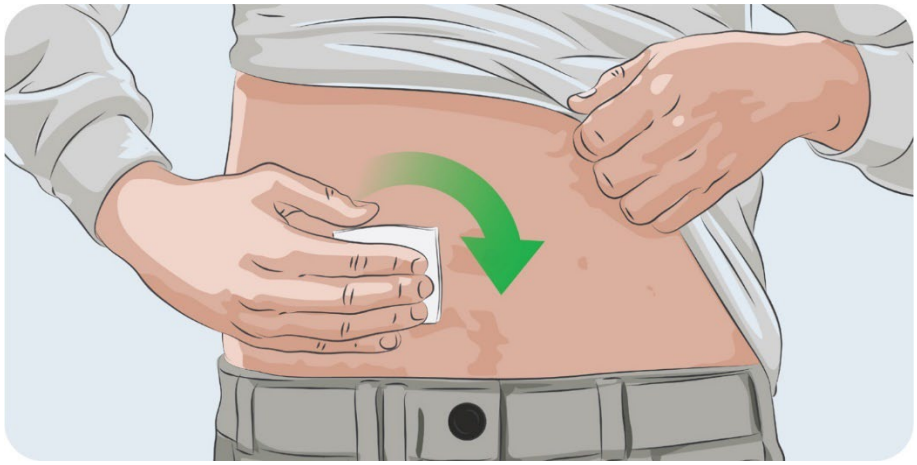
    and
  - 1 inch from your last injection site.

⚠ Avoid an injection site that is tender, bruised, red, hard, irritated, scarred, tattooed, or has stretch marks.

⚠ **Do not** apply the EMPAVELI Injector along the belt line or on areas where the EMPAVELI injector will be affected by folds in the skin.

⚠ Wear loose clothes so that they **do not** get in the way of the EMPAVELI Injector.

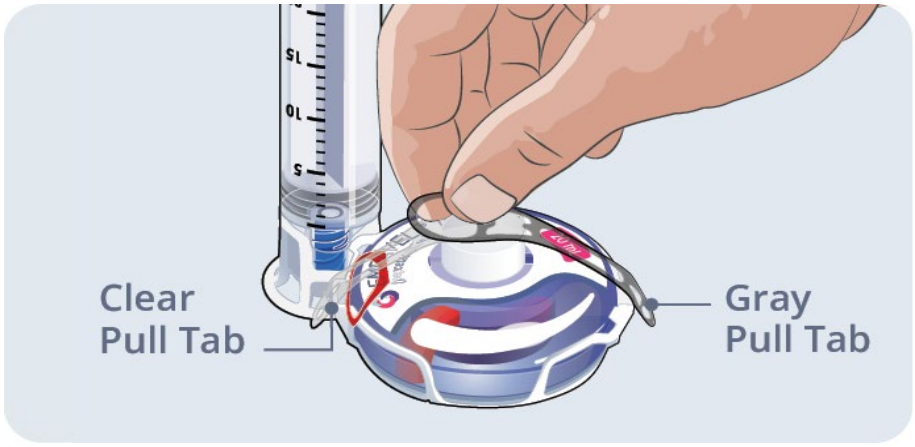
22



- Clean the injection site with an alcohol wipe.
- Allow the injection site to dry for at least 30 seconds.

⚠ **Do not** let your clothes touch the clean injection site.

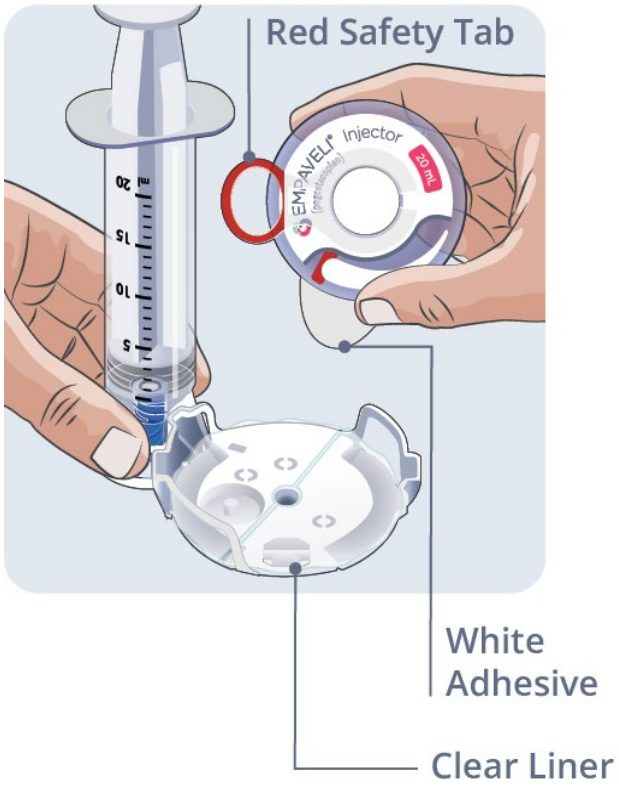
23



- Hold the Gray Pull Tab and pull. Allow both the Gray and Clear Pull Tabs to fall to the side.
- Both tabs may fall to the side or come off completely.

⚠ **Do not** remove the Red Safety Tab until the EMPAVELI Injector is attached to the body.

24



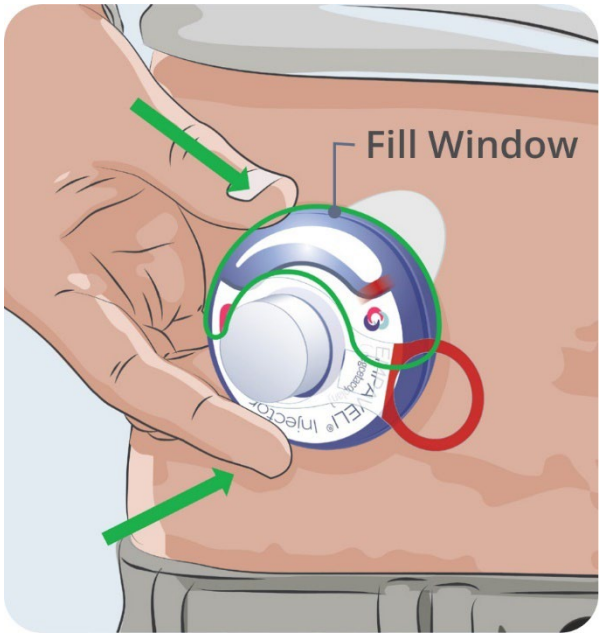
- Hold the sides of the EMPAVELI Injector and pull it straight up to remove it from the Filling Base.

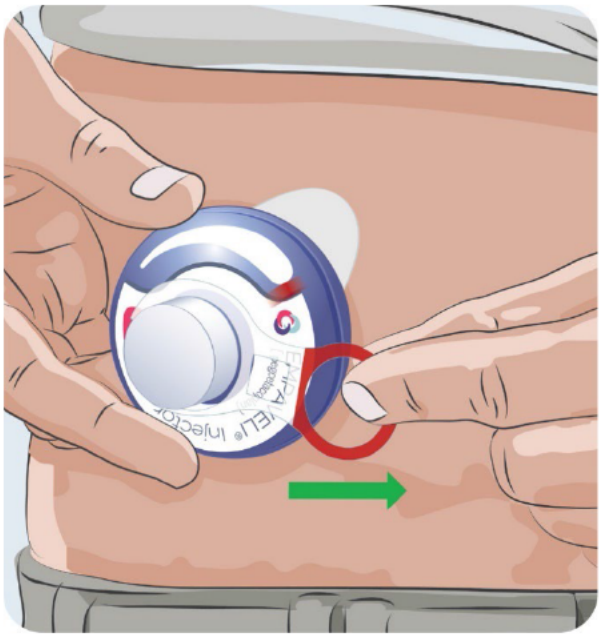
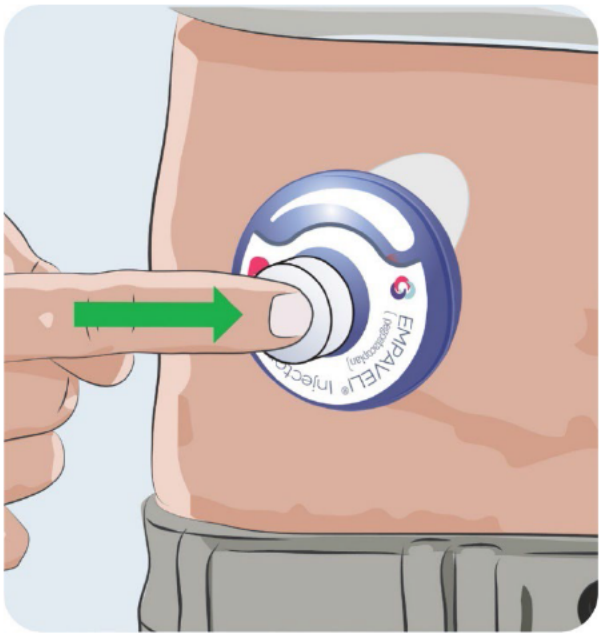
⚠ **Do not** touch the adhesive on the bottom of the EMPAVELI Injector or fold the adhesive onto itself.

- The White Adhesive will stay attached to the EMPAVELI Injector and the Clear Liner will stay attached to the Filling Base.

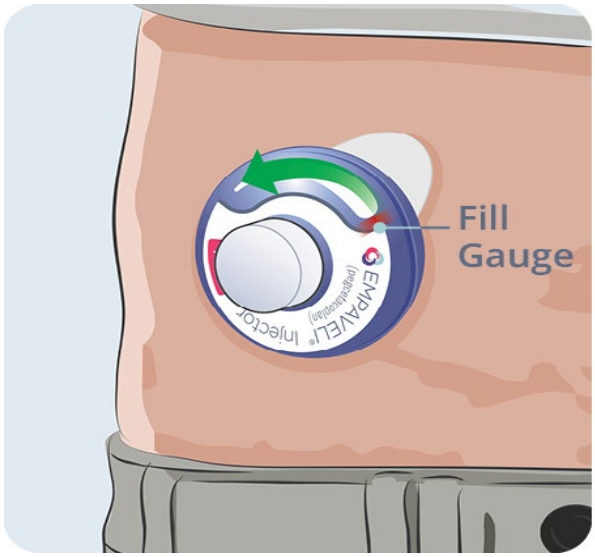
⚠ **Do not** remove the Red Safety Tab until the EMPAVELI Injector is attached to your body.

⚠ Ensure the injection site has been cleaned before attaching EMPAVELI Injector.

25 	• Position the EMPAVELI Injector so that the Fill Window is pointed up toward your face. • Press firmly on the clear portion of the EMPAVELI Injector to attach to stomach. ⚠ **Do not** use anything to hold the EMPAVELI Injector in place.

Start Injection	
26 	• Hold the EMPAVELI Injector with 1 hand. Use the other hand to pull the Red Safety Tab off. • The EMPAVELI injection will not start until the Red Safety Tab is removed. .
27 	• Right away, Press the button in firmly until it stays in place to start the EMPAVELI injection. ⚠ Pushing the Button in will insert the needle into your skin. You may feel the needle go into your skin. • Light daily activities can be done during the EMPAVELI injection. ⚠ Be careful not to bump or knock the EMPAVELI Injector or button during the EMPAVELI injection. ⚠ Keep your stomach dry. Avoid intense physical activity. **Do not** sleep or bathe during your EMPAVELI injection.

28



- Your EMPAVELI injection will continue as long as the button is pushed in. It may take about 30 to 60 minutes to complete.
- To track progress, watch the Fill Gauge move across Fill Window toward empty. It may take some time to move and may move slowly.

⚠ **Do not** remove the EMPAVELI Injector until the button pops out.

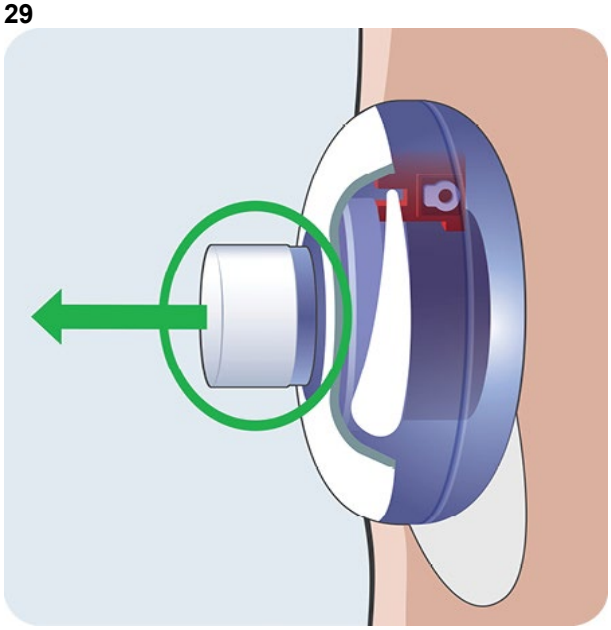
⚠ If the button does not pop out after 2 hours (120 minutes), refer to Questions and Answers.

⚠ If the EMPAVELI Injector falls off of your body, refer to Questions and Answers.

⚠ **Caution:** Holding down the button will stop the flow of medicine. Injection will begin again when the button is released.

⚠ If you have an allergic reaction to the adhesive, call your healthcare provider right away.

29



- When the button pops out, the EMPAVELI injection is done. The needle will be pulled out of the skin and back into the EMPAVELI Injector.

⚠ The button popping out is the only way to know if the EMPAVELI injection is complete. **Do not** remove the EMPAVELI Injector until the Button pops out.

Remove and dispose of EMPAVELI Injector

30



- Use your thumb to lift the Adhesive Tab. Hold the Adhesive Tab against the EMPAVELI Injector.
- Slowly peel the EMPAVELI Injector away from your skin.

31



- Put your used EMPAVELI Injector in an FDA-cleared sharps disposal container right away after use.

⚠ **Do not** throw away the EMPAVELI Injector in the household trash.

⚠ The Filling Base with the syringe attached, alcohol wipe, and packaging may be placed in your household trash.

- If you **do not** have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

- For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: **http:/www.fda.gov/safesharpsdisposal**.
- **Do not** throw away (dispose of) your used sharps disposal container in your household trash unless your community guidelines permit this.
- **Do not** recycle your used sharps disposal container.
- Keep the used EMPAVELI Injector and sharps disposal container out of the reach of children.

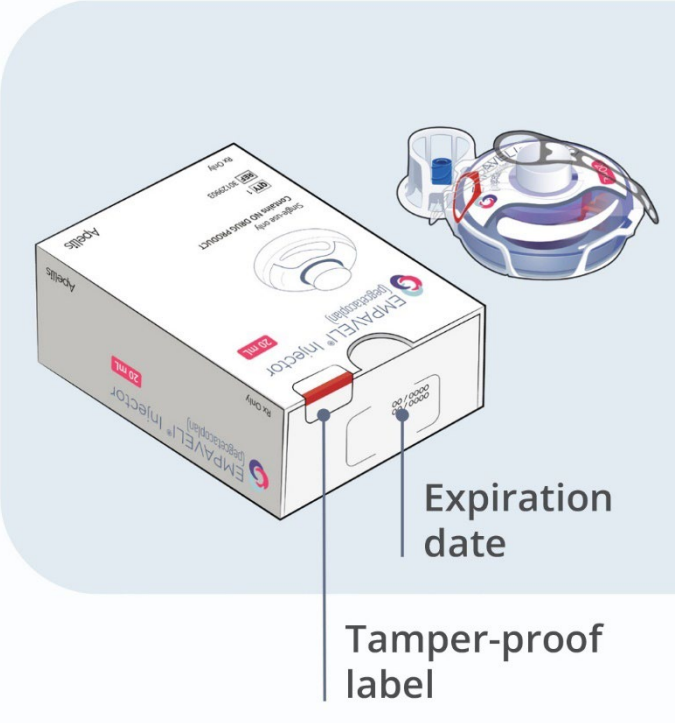
Symbol	Symbol Title	Symbol Definition
	Manufacturer	Indicates the medical device manufacturer
	Date of manufacture	Indicates the date when the medical device was manufactured
REF	Catalogue number	Indicates the manufacturer's catalogue number so that the medical device can be identified
LOT	Batch code	Indicates the manufacturer's batch code so that the batch or lot can be identified
	Use by date	Indicates the date after which the medical device is not to be used
	Consult instructions for use	Indicates the need for the user to consult the instructions for use
	Caution	Indicates the need for the user to consult the instructions for use for important cautionary information such as warnings and precautions that cannot, for a variety of reasons, be presented on the medical device itself
	Storage temperature range	Indicates the temperature limits to which the medical device can be safely exposed
	Keep dry	Indicates a medical device that needs to be protected from moisture
UDI	Unique device identifier	Indicates the manufacturer's device identifier so that a specific medical device can be identified
	Do not re-use	Indicates a medical device that is intended for one use, or for use on a single patient during a single procedure
	Do not resterilize	Indicates a medical device that is not to be resterilized
STERILE R	Sterilized using irradiation	Indicates a medical device that has been sterilized using irradiation
	Non-pyrogenic	Indicates a medical device that is non-pyrogenic
	Do not use if package is damaged	Indicates a medical device that should not be used if the package has been damaged or opened
Rx Only	Prescription only	Requires prescription in the United States

Reference ID: 5632481

How to store the EMPAVELI Injector

- Keep the EMPAVELI Injector in unopened tray inside the original box.
- **Do not** open the tray until ready for EMPAVELI injection.
- **Store** the EMPAVELI Injector unit in clean, dry area away from heat and sunlight, at a temperature between 36°F to 86°F (2°C to 30°C).
- **Use** the EMPAVELI Injector where the temperature is between 41°F to 104°F (5°C to 40°C).

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Questions and answers

Can I use more than 1 syringe to fill the EMPAVELI Injector?

No, use only 1 syringe per EMPAVELI Injector.

What should I do if the syringe plunger will not push down to fill the EMPAVELI Injector?

You must firmly press down on the plunger to fill the EMPAVELI Injector. It will feel like there is resistance.

Can I remove the EMPAVELI Injector from my stomach and put it on later to finish injection?

No. The EMPAVELI Injector cannot be reattached. If you take it off, you may not get your full dose.

How long should the injection take?

The injection time is about 30 to 60 minutes.

After 2 hours (120 minutes):

- If the button has not popped out, press and hold the button while you remove the EMPAVELI Injector from your skin. **Do not** touch the bottom of the EMPAVELI Injector as the needle will be exposed. Set the EMPAVELI Injector aside
- If you forgot to start the injection, **do not** push the button. Remove the EMPAVELI Injector and set it aside.

⚠ Call ApellisAssist at 1-866-MY-APL-ASSIST (1-866-692-7527) right away after putting your device aside.

What if the Button will not push in and lock?

Make sure that you have taken off the Red Safety Tab. If the Red Safety Tab is removed, make sure you have tried to push the Button in all the way. If you still cannot push the button all the way in, then the EMPAVELI Injector is damaged. Remove your EMPAVELI Injector and set aside. Open a new EMPAVELI Injector and start over. Call ApellisAssist at 1-866-MY-APL-ASSIST (1-866-692-7527).

What if the EMPAVELI Injector falls off of my body?

If the EMPAVELI Injector falls off of your body, pick it up carefully. Do not touch the needle or any medicine that may be on the EMPAVELI Injector. Set the EMPAVELI Injector aside and out of the reach of children. Call ApellisAssist at 1-866-MY-APLASSIST (1-866-692-7527) right away.

Is it normal for skin to be bumpy or irritated during an injection?

No. Your body may be sensitive to the adhesive on the EMPAVELI Injector or to the medicine. Call your healthcare provider right away.

Is it normal for skin to be red after an injection?

Your skin may be slightly red after adhesive removal. If the redness does not go away after 1 to 2 days, call your healthcare provider.

Manufactured for:
Apellis Pharmaceuticals, Inc. 100 Fifth Avenue Waltham, MA 02451

Manufactured by:
Enable Injections, Inc. 2863 E. Sharon Road Cincinnati, OH 45421, USA
10130600 Rev 04

Patent: EnableInjections.com/patent

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This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 7/2025

EMP INJ-IFU-DDMMMYYYY-X.0

INSTRUCTIONS FOR USE
EMPAVELI® (em-puh-vel-ee)
(pegcetacoplan)
injection, for subcutaneous use
infusion pump

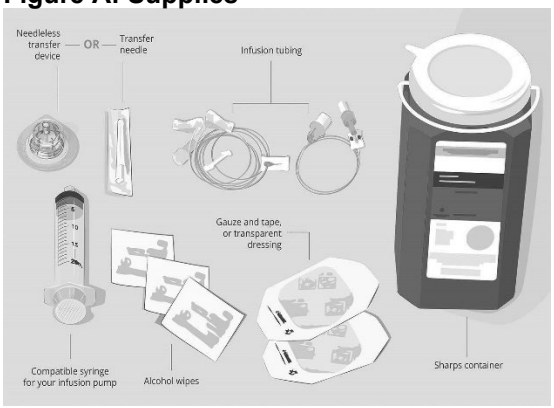
Important Information
This Instructions for Use is for the infusion pump only. If using EMPAVELI Injector, follow the Instructions for Use that comes with the EMPAVELI Injector.

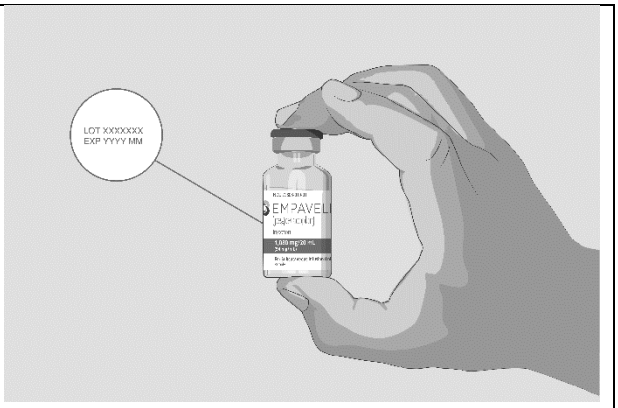
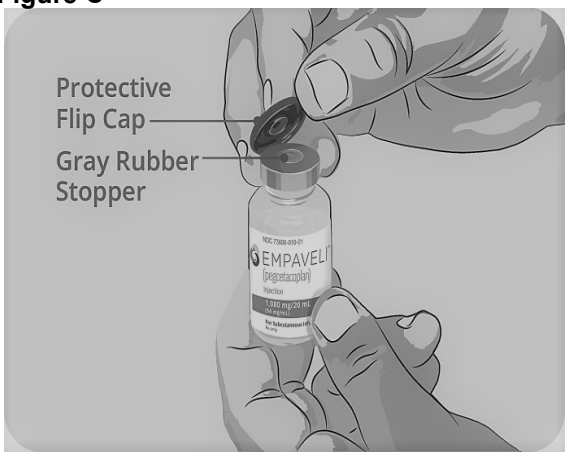
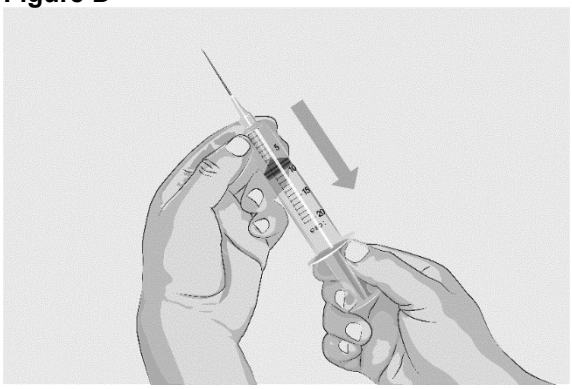
Read **this** Instructions for Use before you start using EMPAVELI with an infusion pump and each time you get a refill as there may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. Your healthcare provider should show you or your caregiver how to infuse EMPAVELI the right way before you use it for the first time. Ask your healthcare provider about any instructions you do not understand.

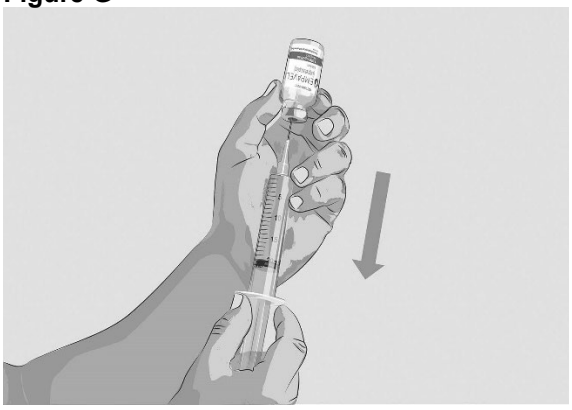
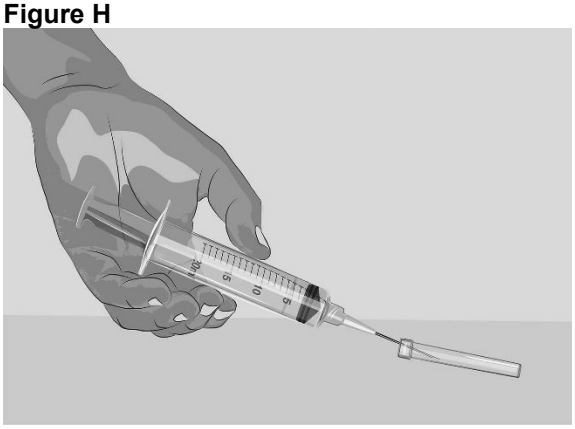
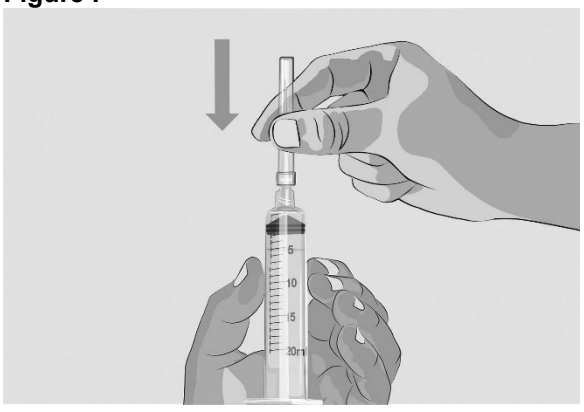
How should I store EMPAVELI?
- Store vials of EMPAVELI in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.
- Do not use EMPAVELI past the expiration date stamped on the carton.

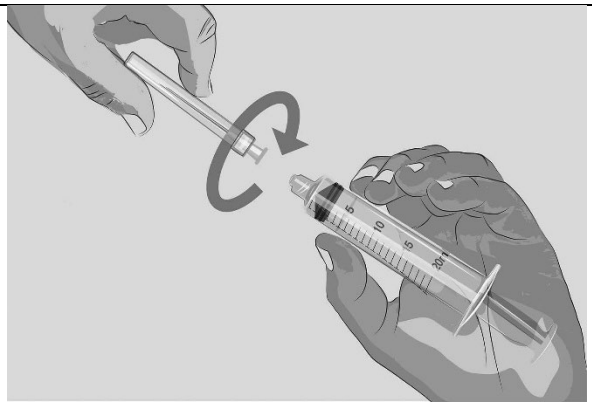
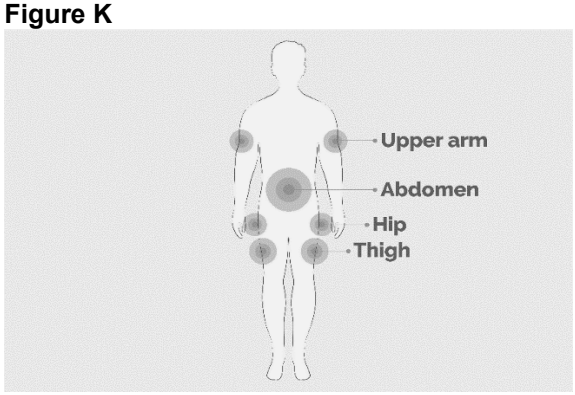
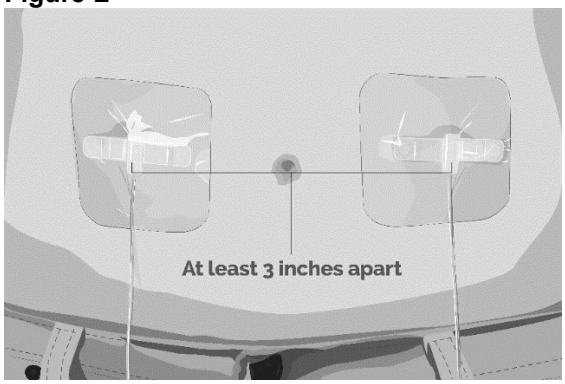
Keep EMPAVELI and all medicines out of the reach of children.

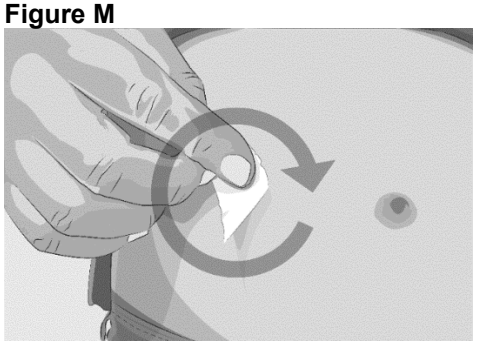
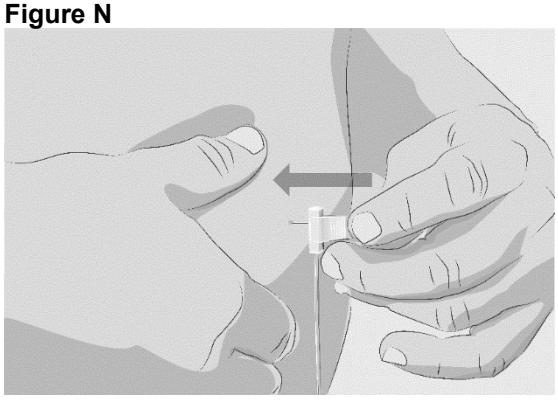
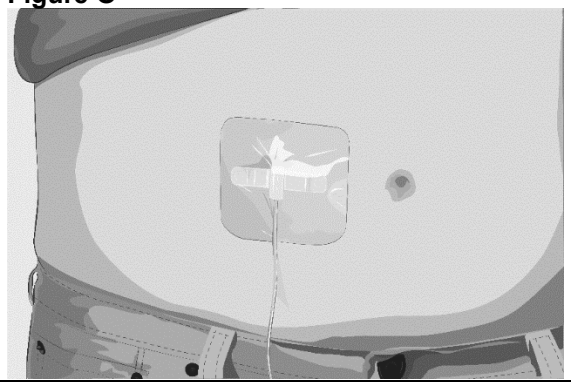
<table>
<tr><td>Step 1</td><td>Prepare for infusion
Before you start:
• Find a well-lit, flat work surface area, like a table.
• Remove a single vial carton from the refrigerator. Keep the vial in the carton at room temperature 68°F to 77°F (20°C to 25°C) and allow it to warm up for about 30 minutes.
• Do not try to speed up the warming process.

Gather your supplies (See Figure A):
• Infusion pump and manufacturer’s instructions (not shown)
• Compatible syringe for your infusion pump
• Transfer needle OR
• Needleless transfer device to draw up the medicine from the vial
• Infusion set (not shown; varies according to device manufacturer’s instructions)
• Infusion tubing
• Sharps container
• Alcohol wipes
• Gauze and tape, or transparent dressing</td><td rowspan="3">Figure A: Supplies

</td></tr>
<tr><td></td><td>Clean your work surface well using an alcohol wipe.</td></tr>
<tr><td></td><td>Wash your hands well with soap and water. Dry your hands.</td></tr>
<tr><td>Step 2</td><td>Check the vial and liquid
• Remove the vial from the carton. Carefully look at the liquid in the vial of EMPAVELI.
o EMPAVELI is a clear, colorless to slightly yellowish liquid. Check for particles or color changes (See Figure B).
Do not use the vial and call ApellisAssist at 1-866-MY-APL-ASSIST (1-866-692-7527) if:
• The liquid looks cloudy, contains particles, or is dark yellow.
• The protective flip cap is missing or damaged.</td><td>Figure B</td></tr>
</table>

	• The expiration date on the label has passed.	
Step 3	**Prepare and fill syringe** • Remove the protective flip cap from the top of the vial to show the middle part of the gray rubber stopper of the EMPAVELI vial (See **Figure C**). Throw away the protective flip cap. • Clean the gray rubber stopper with a new alcohol wipe and allow the gray rubber stopper to dry for at least 30 seconds. **Do not** touch the exposed gray rubber stopper after wiping. **Option 1:** If using a needleless transfer device (such as a vial adapter), follow the instructions provided by the device manufacturer. OR **Option 2:** If transfer is done using a transfer needle and a syringe, follow the instructions below: • Attach a sterile transfer needle to a sterile syringe. • Pull back the plunger to the 20-mL mark to fill the syringe with air (See **Figure D**). • Push the air-filled syringe with transfer needle attached down through the center of the vial gray rubber stopper. • The tip of the transfer needle should not be in the solution to avoid creating air bubble(s) (See **Figure E**). • Gently push the air from the syringe into the vial. This will inject the air from the syringe into the vial.	**Figure C**  **Figure D**  **Figure E**  **Figure F**

	• Turn the vial upside down and insert the transfer needle in the EMPAVELI solution (See **Figure F**).	
	• With the transfer needle tip in the EMPAVELI solution, slowly pull the plunger back to fill the syringe with your prescribed dose (See **Figure G**). Your first dose, second dose, and maintenance dose may be different. • Double check that you have withdrawn your prescribed dose. • Remove the filled syringe with EMPAVELI and the transfer needle from the vial. • Throw away the vial with the needleless transfer device attached and any remaining EMPAVELI solution into the household trash. • Remove the transfer needle by **using 1 hand** to slide the needle into the needle cap and **scoop upwards** to cover the needle (See **Figure H**). • After the needle is covered, push the needle cap down towards the syringe to fully attach it **with 1 hand** to prevent an accidental stick with the needle (See **Figure I**).	**Figure G**  **Figure H**  **Figure I**  **Figure J**

	• Twist off and remove the transfer needle (See **Figure J**).	
Step 4	**Prepare infusion pump and tubing** • Gather the infusion pump supplies and follow the device manufacturer's instructions to prepare the pump and tubing.	
Step 5	**Prepare the infusion site(s)** • Select an area on your stomach (abdomen), thighs, hips, or upper arms for the infusion(s) (See **Figure K**). **Avoid the following infusion areas:** o Do not infuse into areas where the skin is tender, bruised, red, or hard. o Avoid infusing into tattoos, scars, or stretch marks. • Use a different site(s) from the last time you infused EMPAVELI. If there are multiple infusion sites, they should be at least 3 inches apart. Change (rotate) infusion sites in between each infusion (See **Figure L**).	**Figure K**  **Figure L** 

	• Clean the skin at each infusion site(s) with a new alcohol wipe, starting at the center of each infusion site and working outward in a circular motion (See **Figure M**). • Let the skin dry.	**Figure M** 
Step 6	**Insert and secure the infusion needle(s)** • Pinch the skin between your thumb and forefinger around the infusion site (where you plan to insert the needle). • Insert the needle into the skin (See **Figure N**). • Secure the needle(s) using gauze and tape or a transparent dressing placed over the infusion site(s) (See **Figure O**).	**Figure N**  **Figure O** 
Step 7	**Start infusion** • Follow the device manufacturer's instructions to start the infusion. • Start the infusion right away after drawing EMPAVELI into the syringe. • EMPAVELI infusion takes about 30 minutes (if using 2 infusion sites) or about 60 minutes (if using 1 infusion site) to complete.	
Step 8	**Complete infusion** • Follow the device manufacturer's instructions to complete the infusion.	
Step 9	**Record infusion** • Record your treatment as directed by your healthcare provider.	

<table>
<tr><td>Step 10</td><td>Clean up
After the infusion is complete, remove the dressing and slowly take out the needle(s). Cover the infusion site with a new dressing.
Remove the infusion set from the pump and throw it away into the sharps container (See Figure P).
Clean and store the infusion pump according to the device manufacturer’s instructions.</td><td></td></tr>
<tr><td>Step 11</td><td>Dispose of (throw away) used needles and syringes and EMPAVELI infusion tubing.
Put the used needles, syringes, and EMPAVELI infusion tubing in an FDA-cleared sharps disposal container right away after use (See Figure P).
Do not dispose of (throw away) the used needles, syringes, and EMPAVELI infusion tubing in your household trash.
If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
made of heavy-duty plastic,
can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
upright and stable during use,
leak-resistant, and
properly labeled to warn of hazardous waste inside the container.
When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.
For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal.
Do not throw away your used sharps disposal container in your household trash unless your community guidelines permit this.
Do not recycle your used sharps disposal container.</td><td>Figure P
</td></tr>
</table>

Call 1-866-692-7527 to speak with an Apellis representative.
Manufactured for:
Apellis Pharmaceuticals, Inc. 100 Fifth Avenue Waltham, MA 02451
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EMPAVELI is a registered trademark of Apellis Pharmaceuticals, Inc.

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised 7/2025

EMP-IFU-DDMMMYYYY-X.0

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

ASPAVELI 1 080 mg solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 1 080 mg of pegcetacoplan.
Each mL contains 54 mg of pegcetacoplan.

Excipients with known effect
Each mL contains 41 mg of sorbitol.
Each vial contains 820 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless to slightly yellowish aqueous solution with pH 5.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ASPAVELI is indicated for the treatment of adult and adolescent patients aged 12 to 17 years with C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN) in combination with a renin-angiotensin system (RAS) inhibitor, unless RAS inhibitor treatment is not tolerated or contraindicated.

4.2 Posology and method of administration

Therapy should be initiated under the supervision of a healthcare professional experienced in the management of patients with haematological or renal disorders. Self-administration and home infusion should be considered for patients who have tolerated treatment well in experienced treatment centres. The decision of a possibility of self-administration and home infusions should be made after evaluation and recommendation from the treating physician.

Posology

Pegcetacoplan can be given by a healthcare professional or administered by the patient or caregiver following proper instruction.

PNH

Adult patients with PNH

Pegcetacoplan is administered twice weekly as a 1 080 mg subcutaneous infusion with a commercially available syringe system infusion pump or on-body delivery system, that can deliver doses up to 20 mL. The twice weekly dose should be administered on Day 1 and Day 4 of each treatment week.

PNH is a chronic disease and treatment with ASPAVELI is recommended to continue for the patient's lifetime, unless the discontinuation of this medicinal product is clinically indicated (see section 4.4).

Patients with PNH switching to ASPAVELI from a C5 inhibitor

For the first 4 weeks, pegcetacoplan is administered as twice weekly subcutaneous doses of 1 080 mg in addition to the patient's current dose of C5 inhibitor treatment to minimise the risk of haemolysis with abrupt treatment discontinuation. After 4 weeks, the patient should discontinue C5 inhibitor before continuing on monotherapy with ASPAVELI.

Switches from complement inhibitors other than eculizumab have not been studied. Discontinuing other complement inhibitors before reaching steady-state of pegcetacoplan should be done with caution (see section 5.2).

Dose adjustment in PNH

The dosing regimen may be changed to 1 080 mg every third day (e.g., Day 1, Day 4, Day 7, Day 10, Day 13, and so forth) if a patient has a lactate dehydrogenase (LDH) level greater than 2 x upper limit of normal (ULN). In the event of a dose increase, LDH should be monitored twice weekly for at least 4 weeks (see section 4.4).

C3G and primary IC-MPGN

Pegcetacoplan is administered twice weekly as a subcutaneous infusion with a commercially available syringe system infusion pump or on-body delivery system, that can deliver doses up to 20 mL. The twice weekly dose should be administered on Day 1 and Day 4 of each treatment week.

C3G and primary IC-MPGN are chronic diseases. Discontinuation of this medicinal product is not recommended unless clinically indicated.

Adult patients with C3G or primary IC-MPGN

Pegcetacoplan is administered twice weekly as a 1 080 mg subcutaneous infusion.

Adolescent patients with C3G or primary IC-MPGN

For adolescent patients, the dosing regimen is based on the patient´s body weight and consists of the following:

Body weight	**First dose (infusion volume)**	**Second dose (infusion volume)**	**Maintenance dose (infusion volume)**
≥ 50 kg	1 080 mg twice weekly (20 mL)		
35 to < 50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
30 to < 35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

Missed dose

If a dose of pegcetacoplan for treatment of PNH, C3G or primary IC-MPGN is missed, it should be administered as soon as possible, then the regular schedule should be resumed even if this results in an interval of less than 3 days between the replacement dose and the subsequent dose.

Patients with post-transplant recurrent C3G or primary IC-MPGN
Diagnosis of post-transplant recurrent C3G or primary IC-MPGN should be made based on a renal allograft biopsy. C3G or primary IC-MPGN recurrence may be detected in a routine post-transplant biopsy; otherwise, a biopsy should be performed when clinical signs indicate recurrent disease. As done in study APL2-C3G-204 (see section 5.1), treatment with pegcetacoplan can be started before the onset of clinical signs such as estimated glomerular filtration rate (eGFR) decrease or urine to protein-to-creatine ratio (uPCR) increase. There is limited experience with the use of pegcetacoplan in patients with recurrent C3G or primary IC-MPGN after transplantation in clinical studies (see section 5.1).

Special populations

Elderly
Although there were no apparent age-related differences observed in clinical studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients. There is no evidence indicating any special precautions are required for treating an elderly population.

Renal impairment
Severe renal impairment (creatinine clearance <30 mL/min) had no effect on the pharmacokinetics (PK) of pegcetacoplan; therefore, pegcetacoplan dose adjustment in patients with renal impairment is not necessary. There are no data available for the use of pegcetacoplan in patients with end-stage renal disease (ESRD) requiring dialysis (see section 5.2).

Hepatic impairment
The safety and efficacy of pegcetacoplan have not been studied in patients with hepatic impairment; however, no dose adjustment is recommended, as hepatic impairment is not expected to impact clearance of pegcetacoplan.

Paediatric population
The safety and efficacy of ASPAVELI in children with PNH aged 0 to <18 years have not yet been established. No data are available.

The safety and efficacy of ASPAVELI in children with C3G or primary IC-MPGN aged below 12 years have not been established. No data are available.

This medicinal product should not be used in children <12 years of age, as non-clinical safety data are not available for this age group.

Method of administration

ASPAVELI should only be administered via subcutaneous administration using a commercially available syringe system infusion pump or on-body delivery system.

This medicinal product can be self-administered. When self-administration is initiated, the patient will be instructed by a qualified healthcare professional in infusion techniques, the use of a syringe system infusion pump or an on-body delivery system, the keeping of a treatment record, the recognition of possible adverse reactions, and measures to be taken in case these occur.

- When using a syringe system infusion pump, ASPAVELI should be infused in the abdomen, thighs, hips, or upper arms. Infusion sites should be at least 7.5 cm apart from each other. The infusion sites should be rotated between administrations. The infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site).

- When using an on-body delivery system, ASPAVELI should be infused at a site on the abdomen. The infusion site should be rotated between administrations following the device manufacturer´s instructions. The infusion time varies by patient and typically ranges from 30 to 60 minutes.

Infusion into areas where the skin is tender, bruised, red, or hard should be avoided. Infusion into tattoos, scars, or stretch marks should be avoided. The infusion should be started promptly after drawing this medicinal product into the syringe. Administration should be completed within 2 hours after preparing the syringe. For instructions on the preparation and infusion of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to pegcetacoplan or to any of the excipients listed in section 6.1.

Pegcetacoplan therapy must not be initiated in patients:

- with unresolved infection caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* (see section 4.4).
- who are not currently vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see section 4.4).

4.4 Special warnings and precautions for use

Serious infections caused by encapsulated bacteria

The use of pegcetacoplan may predispose individuals to serious infections caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. To reduce the risk of infection, all patients must be vaccinated against these bacteria according to applicable local guidelines at least 2 weeks prior to receiving pegcetacoplan, unless the risk of delaying therapy outweighs the risk of developing an infection.

Patients with known history of vaccination

Before receiving treatment with pegcetacoplan, in patients with a known history of vaccination, it should be ensured that patients have received vaccines against encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae* Type B within 2 years prior to starting pegcetacoplan.

Patients without known history of vaccination

For patients without known history of vaccination, the required vaccines should be administered at least 2 weeks prior to receiving the first dose of pegcetacoplan. If immediate therapy is indicated, the required vaccines should be administered as soon as possible and the patient treated with appropriate antibiotics until 2 weeks after vaccination.

Monitoring patients for serious infections

Vaccination may not be sufficient to prevent serious infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. All patients should be monitored for early signs of infections caused by encapsulated bacteria including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, evaluated immediately if infection is suspected, and treated with appropriate antibiotics if necessary. Patients should be informed of these signs and symptoms, and steps taken to seek medical care immediately. Physicians must discuss the benefits and risks of pegcetacoplan therapy with patients.

Hypersensitivity

Hypersensitivity reactions have been reported. If a severe hypersensitivity reaction (including anaphylaxis) occurs, infusion with pegcetacoplan must be discontinued immediately, and appropriate treatment instituted.

Injection site reactions

Injection site reactions have been reported with the use of subcutaneous pegcetacoplan (see section 4.8). Patients should be trained appropriately in proper injection technique.

PNH laboratory monitoring
Patients with PNH receiving pegcetacoplan should be monitored regularly for signs and symptoms of haemolysis, including measuring LDH levels, and may require dose adjustment within the recommended dosing schedule (see section 4.2).

Effects on laboratory tests
There may be interference between silica reagents in coagulation panels and pegcetacoplan that results in artificially prolonged activated partial thromboplastin time (aPTT); therefore, the use of silica reagents in coagulation panels should be avoided.

Treatment discontinuation for PNH
If patients with PNH discontinue treatment with pegcetacoplan, they should be closely monitored for signs and symptoms of serious intravascular haemolysis. Serious intravascular haemolysis is identified by elevated LDH levels along with sudden decrease in PNH clone size or haemoglobin (Hb), or reappearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, dyspnoea, major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. If discontinuation of this medicinal product is necessary, alternate therapy should be considered. If serious haemolysis occurs after discontinuation, consider the following procedures/treatments: blood transfusion (packed RBCs), exchange transfusion, anticoagulation, and corticosteroids. Patients should be closely monitored for at least 8 weeks from the last dose, representing more than 5 half-lives of this medicinal product, to allow for medicinal product washout (see section 5.2) to detect serious haemolysis and other reactions. In addition, slow weaning should be considered.

Contraception in women of childbearing potential
It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with pegcetacoplan and for at least 8 weeks after the last dose of pegcetacoplan (see section 4.6).

Polyethylene glycol (PEG) accumulation
ASPAVELI is a PEGylated medicinal product. The potential long-term effects of PEG accumulation in the kidneys, the choroid plexus of the brain, and other organs are unknown (see section 5.3). Regular laboratory testing of renal function is recommended.

Educational materials
All physicians who intend to prescribe ASPAVELI must ensure they have received and are familiar with the physician educational material. Physicians must explain and discuss the benefits and risks of ASPAVELI therapy with the patient and provide them with the patient information pack and the patient card. The patient should be instructed to seek prompt medical care if they experience any sign or symptom of serious infection or hypersensitivity during therapy with ASPAVELI, especially if indicative of infection with encapsulated bacteria.

Excipients with known effect
Sorbitol content
ASPAVELI 1 080 mg contains 820 mg sorbitol in each vial.

Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say, essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on *in vitro* data, pegcetacoplan has low potential for clinical drug-drug interactions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with pegcetacoplan and for at least 8 weeks after the last dose of pegcetacoplan. For women planning to become pregnant, the use of pegcetacoplan may be considered following an assessment of the risks and benefits (see Pregnancy).

Pregnancy
There is a limited amount of data from the use of pegcetacoplan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Pegcetacoplan is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether pegcetacoplan is excreted in human milk. The potential for absorption and harm to the breastfed infant is unknown. Animal data suggest a low excretion (less than 1%, not pharmacologically significant) of pegcetacoplan in monkey milk (see section 5.3). It is unlikely that a breastfed infant would have clinically relevant exposure.

It is recommended to discontinue breast-feeding during pegcetacoplan treatment.

Fertility
No animal or human data on the effect of pegcetacoplan on fertility are available. In toxicity studies, there were no microscopic abnormalities in male or female reproductive organs in monkeys (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
PNH
The most commonly reported adverse reactions in patients with PNH treated with pegcetacoplan were injection site reactions: injection site erythema, injection site pruritus, injection site swelling, injection site pain, injection site bruising. Other adverse reactions reported in more than 10% of patients during clinical studies were upper respiratory tract infection, diarrhoea, haemolysis, abdominal pain, headache, fatigue, pyrexia, cough, urinary tract infection, vaccination complication, pain in extremity, dizziness, arthralgia and back pain. The most commonly reported serious adverse reactions were haemolysis and sepsis.

C3G and primary IC-MPGN
The most commonly reported adverse drug reactions in patients with C3G or primary IC-MPGN treated with pegcetacoplan were infusion site reactions and upper respiratory tract infections. The most commonly reported serious adverse reactions were acute kidney injury and pneumonia.

Tabulated list of adverse reactions
Table 1 gives the adverse reactions observed from the clinical studies and postmarketing experience with pegcetacoplan in patients with PNH, C3G and primary IC-MPGN. 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) or rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions from clinical trials[1] and postmarketing experience

MedDRA System Organ Class Adverse reaction	Frequency in PNH	Frequency in C3G or primary IC-MPGN
Infections and infestations		
Influenza		Very common
Upper respiratory tract infections[2]	Very common	Very common
Urinary tract infection	Very common	Common
Sepsis	Common[3]	
Opportunistic infections		Common[4]
COVID-19, Gastrointestinal infection, Fungal infection, Skin infection, Oral infection	Common	
Ear infection	Common	Common
Infection, Respiratory tract infection[5], Viral infection, Bacterial infection, Vaginal infection, Eye infection	Common	
Cervicitis, Groin infection	Uncommon	
Pneumonia	Uncommon	Common
Nasal abscess, Tuberculosis, Oesophageal candidiasis, COVID-19 pneumonia, Anal abscess	Uncommon	
Immune system disorders		
Hypersensitivity reaction		Very common[6]
Blood and lymphatic system disorders		
Haemolysis	Very common	
Thrombocytopenia	Common	Common[7]
Neutropenia	Common	Common
Metabolism and nutrition disorders		
Hypokalaemia	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	
Vascular disorders		
Hypertension	Common	
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Common
Dyspnoea, Oropharyngeal pain, Nasal congestion	Common	
Epistaxis	Common	Common
Gastrointestinal disorders		
Abdominal pain	Very common	
Diarrhoea	Very common	Very common
Nausea	Common	Very common
Skin and subcutaneous tissue disorders		
Erythema, Rash, Urticaria	Common	
Musculoskeletal and connective tissue disorders		
Arthralgia, Back pain	Very common	
Pain in extremity	Very common	Common
Myalgia	Common	Common
Muscle spasms	Common	
Renal and urinary disorders		
Acute kidney injury	Common	Very common
Chromaturia	Common	
General disorders and administration site conditions		
Pyrexia	Very common	Very common
Fatigue	Very common	Common
Infusion site reactions[8]	Very common	Very common

MedDRA System Organ Class Adverse reaction	Frequency in PNH	Frequency in C3G or primary IC-MPGN
Investigations		
Alanine aminotransferase increased, Bilirubin increased	Common	
Injury, poisoning and procedural complications		
Vaccination complication	Very common	

[1]Studies APL2-308, APL2-302, APL2-202, APL2-CP-PNH-204, and APL-CP0514 in PNH patients and Study APL2-C3G-310, APL2-C3G-314, APL2-201 and APL2-C3G-204 in C3G and primary IC-MPGN patients. Medically similar terms are grouped, where appropriate, on the basis of similar medical concept.
[2]Include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis and sinusitis.
[3]Sepsis includes one case of septic shock and one case with non-encapsulated *Neisseria meningitidis*.
[4]*Herpes zoster* (including *Herpes zoster meningoencephalitis*), and *Pneumocystis jirovecii* infection.
[5]Include respiratory tract infection and respiratory tract infection viral.
[6]Include rash and eczema.
[7]Includes platelet count decreased.
[8]PTs included in Infusion site reactions: infusion site erythema, infusion site pruritus, infusion site swelling, infusion site bruising, infusion site pain, infusion site induration.

Description of selected adverse reactions

Infections
No serious infection caused by encapsulated bacteria was reported during PNH Study APL2-302. Forty-eight patients experienced an infection during the study. The most frequent infections in patients treated with pegcetacoplan during PNH Study APL2-302 were upper respiratory tract infection (28 cases, 35%). Most infections reported in patients treated with pegcetacoplan during PNH Study APL2-302 were nonserious, and predominantly mild in intensity. Ten patients developed infections reported as serious including one patient who died due to COVID-19. The most frequent serious infections were sepsis (3 cases) (leading to discontinuation of pegcetacoplan in one patient) and gastroenteritis (3 cases); all of which resolved.

In C3G and primary IC-MPGN clinical studies, four serious respiratory tract infections caused by encapsulated bacteria were reported in patients treated with pegcetacoplan: an epiglottitis, a pneumococcal pneumonia and an atypical pneumonia that led to drug interruption, and a pneumonia *Haemophilus* with no dose adjustment. Events recovered and resolved except for the events of pneumonia *Haemophilus* and the atypical pneumonia that resolved with sequelae. In addition, one serious *Escherichia* urinary tract infection was reported, the event recovered and resolved with no dose adjustment.

Haemolysis
Nineteen patients reported haemolysis during PNH Study APL2-302 in patients treated with pegcetacoplan. Seven cases were reported as serious, and 5 cases led to discontinuation of pegcetacoplan and the dose of pegcetacoplan was increased in 10 patients. There were 3 cases of haemolysis during PNH Study APL2-308 in patients treated with pegcetacoplan. None of these cases were reported as serious or led to discontinuation of pegcetacoplan. The dose of pegcetacoplan was increased in all 3 patients.

Acute kidney injury
In C3G and primary IC-MPGN clinical studies, 10 serious events of acute kidney injury were reported in 8 patients (5.7%) treated with pegcetacoplan, of which 5 events were observed in 4 post-transplant patients. Of these serious events, only 1 led to drug withdrawal and 1 to dose interruption. All events recovered and resolved, except the single event that led to drug withdrawal.

Patients with post-transplant recurrent C3G or primary IC-MPGN
In the patients with post-transplant recurrent C3G or primary IC-MPGN (N=22), included in Studies APL2-C3G-310 and APL2-C3G-204, the safety profile appeared consistent with that of the overall population, although with higher frequencies of severe and serious adverse events, as expected in this patient population.

Paediatric population
In adolescent patients with C3G or primary IC-MPGN (N=28, aged 12 years to 17 years) included in Study APL2-C3G-310, the safety profile appeared consistent with the overall results. The most common adverse reaction reported in this patient population were infusion site reactions.
The safety of pegcetacoplan has not been studied in paediatric patients less than 12 years of age.

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

In the postmarketing setting, cases of overdose have been reported, with no new safety events observed. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Complement inhibitors, ATC code: L04AJ03

Mechanism of action
Pegcetacoplan is a symmetrical molecule comprised of two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa PEG molecule. The peptide moieties bind to complement C3 and C3b and exert a broad inhibition of the complement cascade. The 40-kDa PEG moiety imparts improved solubility and longer residence time in the body after administration of the medicinal product.

Pegcetacoplan binds to complement protein C3 and its activation fragment C3b with high affinity, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH, extravascular haemolysis (EVH) is facilitated by C3b opsonisation while intravascular haemolysis (IVH) is mediated by the downstream membrane attack complex (MAC). Pegcetacoplan exerts broad regulation of the complement cascade by acting proximal to both C3b and MAC formation, thereby controlling the mechanisms that lead to EVH and IVH.

In C3G and primary IC-MPGN, there is excessive deposition of C3 breakdown products in the glomeruli of the kidney leading to renal parenchymal damage and impairment of kidney function. Pegcetacoplan targets upstream effectors of complement activation (C3 and C3b), thereby inhibiting activation initiated by all (alternative, classical and lectin) complement pathways. By inhibiting C3, pegcetacoplan directly addresses the inappropriate C3 activation and modifies the underlying disease by reducing the excessive deposition of C3 breakdown products in the glomeruli of the kidney. By targeting C3b, pegcetacoplan also inhibits the activity of the alternative pathway (AP) C3 convertase through an additional mechanism of action in the complement cascade. This further prevents deposition of C3 breakdown products in the glomeruli.

Pharmacodynamic effects

PNH
In Study APL2-302, the mean serum C3 concentration increased from 0.94 g/L at baseline to 3.83 g/L at Week 16 in the pegcetacoplan group and sustained through Week 48. In Study APL2-308, the mean serum C3 concentration increased from 0.95 g/L at baseline to 3.56 g/L at Week 26.

In Study APL2-302, the mean percentage of PNH Type II + III RBCs increased from 66.80% at baseline, to 93.85% at Week 16 and sustained through Week 48. In Study APL2-308, the mean percentage of PNH Type II + III RBCs increased from 42.4% at baseline to 90.0% at Week 26.

In Study APL2-302, the mean percentage of PNH Type II + III RBCs with C3 deposition was decreased from 17.73% at baseline to 0.20% at Week 16 and sustained through Week 48. In Study APL2-308, the mean percentage of PNH Type II + III RBCs with C3 deposition decreased from 2.85% at baseline to 0.09% at Week 26.

C3G and primary IC-MPGN
In Study APL2-C3G-310, the mean serum C3 concentration increased from 0.62 g/L at baseline to 3.71 g/L at Week 26 in the pegcetacoplan group and the effect was sustained up to Week 52. In the placebo group, C3 concentrations remained stable up to Week 26 (0.57 g/L at baseline; 0.58 g/L at Week 26) and increased upon switch to pegcetacoplan to 3.59 g/L at Week 52.

Mean serum sC5b-9 concentration decreased from 902.5 ng/mL at baseline to 290.2 ng/mL at Week 26 in the pegcetacoplan group and the effect was sustained up to Week 52. In the placebo group, sC5b-9 concentrations remained stable (768.3 ng/mL at baseline; 759.9 ng/mL at Week 26) and decreased upon switch to pegcetacoplan to 272.9 ng/mL at Week 52.

Clearance of glomerular C3 deposits at 6 months was observed based on a greater proportion of patients achieving a staining score of zero in the pegcetacoplan (71.4%) as compared to the placebo (8.8%) group.

Clinical efficacy and safety

PNH
The efficacy and safety of pegcetacoplan in patients with PNH was assessed in two open-label, randomised-controlled phase 3 studies: in complement inhibitor-experienced patients in Study APL2-302 and in complement inhibitor-naïve patients in Study APL2-308. In both studies the dose of pegcetacoplan was 1 080 mg twice weekly. If required, the dose could be adjusted to 1 080 mg every 3 days.

Study in complement inhibitor-experienced adult patients (APL2-302)
Study APL2-302 was an open-label, randomised study with an active comparator-controlled period of 16 weeks followed by a 32-week open label period (OLP). This study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with Hb levels <10.5 g/dL. Eligible patients entered a 4-week run-in period during which they received pegcetacoplan 1 080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomised in a 1:1 ratio to receive either 1 080 mg of pegcetacoplan twice weekly or their current dose of eculizumab through the duration of the 16-week randomised controlled period (RCP). Randomisation was stratified based on the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day -28 (<4; ≥4) and platelet count at screening (<100 000/mm^3; ≥100 000/mm^3). Patients who completed the RCP entered the OLP during which all patients received pegcetacoplan for up to 32 weeks (patients who received eculizumab during the RCP entered a 4-week run-in period before switching to pegcetacoplan monotherapy).

The primary and secondary efficacy endpoints were assessed at Week 16. The primary efficacy endpoint was change from baseline to Week 16 (during RCP) in Hb level. Baseline was defined as the average of measurements prior to the first dose of pegcetacoplan (at the beginning of the run-in period). Key secondary efficacy endpoints were transfusion avoidance, defined as the proportion of patients who did not require a transfusion during the RCP, and change from baseline to Week 16 in absolute reticulocyte count (ARC), LDH level, and functional assessment of chronic illness therapy (FACIT)-Fatigue scale score.

A total of 80 patients entered the run-in period. At the end of the run-in period, all 80 were randomised, 41 to pegcetacoplan and 39 to eculizumab. Demographics and baseline disease

characteristics were generally well balanced between treatment groups (see Table 2). A total of 38 patients in the group treated with pegcetacoplan and 39 patients in the eculizumab group completed the 16-week RCP and continued into the 32-week open-label period. In total, 12 of 80 (15%) patients receiving pegcetacoplan discontinued due to adverse events. Per protocol 15 patients had their dose adjusted to 1 080 mg every 3 days. Twelve patients were evaluated for benefit and 8 of the 12 patients demonstrated benefit from the dose adjustment.

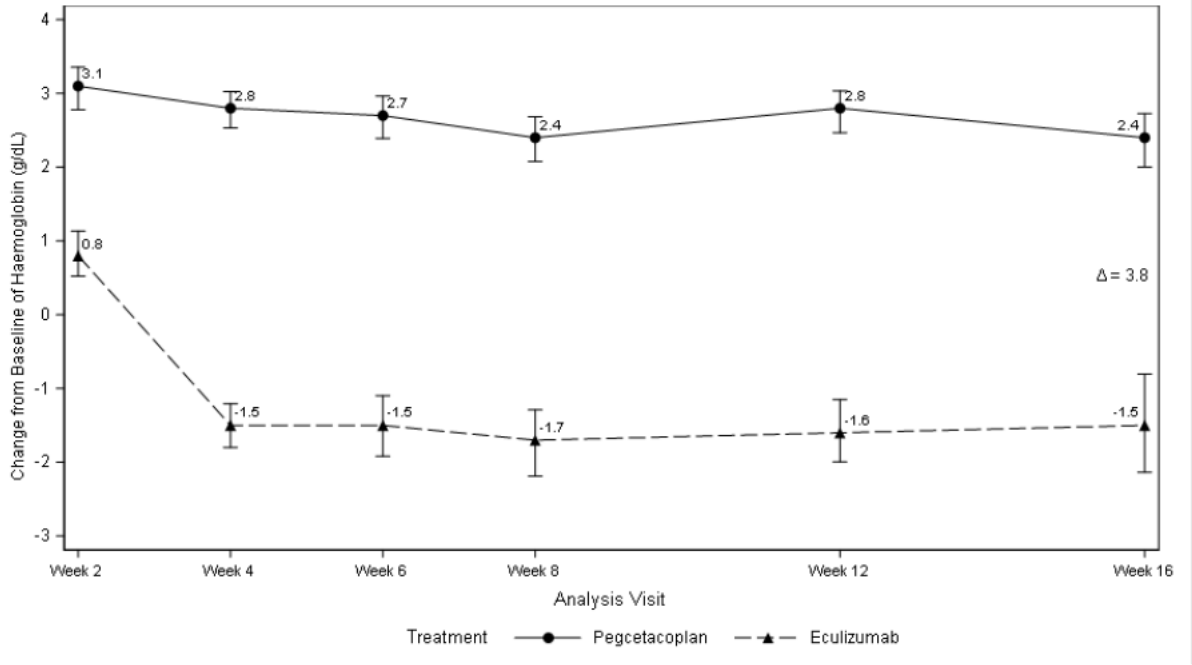
Table 2: Patient baseline demographics and characteristics in Study APL2-302

Parameter	**Statistics**	**Pegcetacoplan (N=41)**	**Eculizumab (N=39)**
Age (years)	Mean (SD)	50.2 (16.3)	47.3 (15.8)
18-64 years	n (%)	31 (75.6)	32 (82.1)
≥65 years	n (%)	10 (24.4)	7 (17.9)
Dose level of eculizumab at baseline			
Every 2 weeks IV 900 mg	n (%)	26 (63.4)	29 (74.4)
Every 11 days IV 900 mg	n (%)	1 (2.4)	1 (2.6)
Every 2 weeks IV 1 200 mg	n (%)	12 (29.3)	9 (23.1)
Every 2 weeks IV 1 500 mg	n (%)	2 (4.9)	0
Female	n (%)	27 (65.9)	22 (56.4)
Time since diagnosis of PNH (years) to Day -28	Mean (SD)	8.7 (7.4)	11.4 (9.7)
Haemoglobin level (g/dL)	Mean (SD)	8.7 (1.1)	8.7 (0.9)
Reticulocyte count (10^9/L)	Mean (SD)	218 (75.0)	216 (69.1)
LDH level (U/L)	Mean (SD)	257.5 (97.6)	308.6 (284.8)
Total FACIT-Fatigue*	Mean (SD)	32.2 (11.4)	31.6 (12.5)
Number of transfusions in last 12 months prior to Day -28	Mean (SD)	6.1 (7.3)	6.9 (7.7)
<4	n (%)	20 (48.8)	16 (41.0)
≥4	n (%)	21 (51.2)	23 (59.0)
Platelet count at screening (10^9/L)	Mean (SD)	167 (98.3)	147 (68.8)
Platelet count at screening <100 000/mm^3	n (%)	12 (29.3)	9 (23.1)
Platelet count at screening ≥100 000/mm^3	n (%)	29 (70.7)	30 (76.9)
History of aplastic anaemia	n (%)	11 (26.8)	9 (23.1)
History of myelodysplastic syndrome	n (%)	1 (2.4)	2 (5.1)

*FACIT-Fatigue is measured on a scale of 0-52, with higher values indicating less fatigue.

Pegcetacoplan was superior to eculizumab for the primary endpoint of the haemoglobin change from baseline (P<0.0001).

Figure 1. Adjusted mean change in haemoglobin (g/dL) from baseline to Week 16 in APL2-302



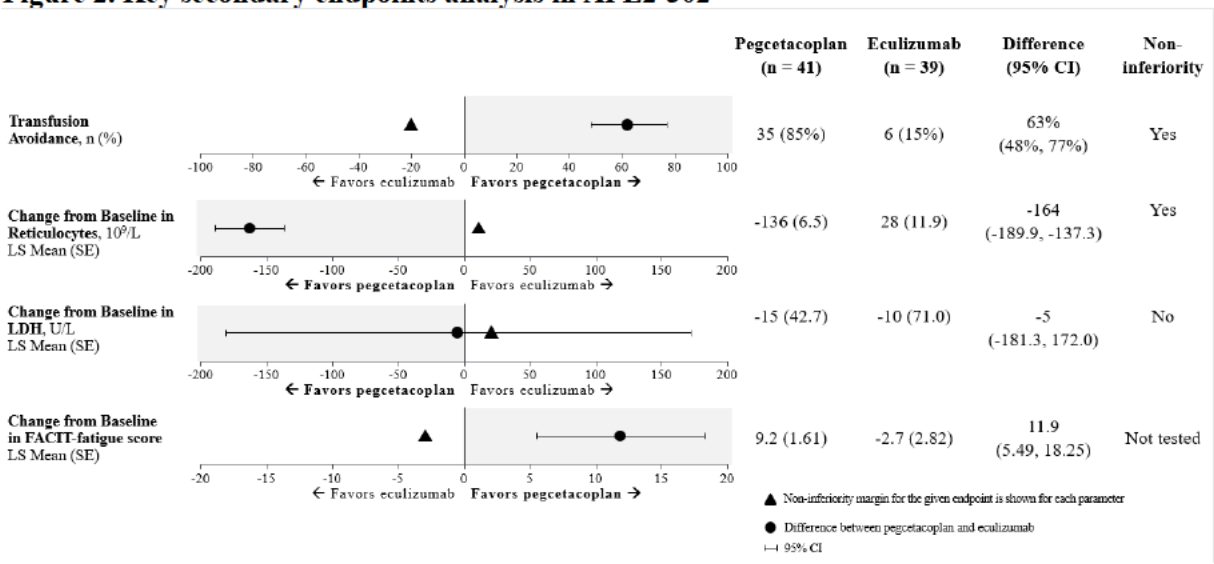
Non-inferiority was demonstrated in key secondary endpoints of transfusion avoidance and change from baseline in ARC.

Non-inferiority was not met in change from baseline in LDH.

Due to hierarchical testing, statistical testing for change from baseline for FACIT-Fatigue score was not formally tested.

The adjusted means, treatment difference, confidence intervals, and statistical analyses performed for the key secondary endpoints are shown in Figure 2.

Figure 2. Key secondary endpoints analysis in APL2-302



Results were consistent across all supportive analyses of the primary and key secondary endpoints, including all observed data with post transfusion data included.

Hb normalisation was achieved in 34% of patients in the pegcetacoplan group versus 0% in the eculizumab group at Week 16. LDH normalisation was achieved in 71% of patients in the group treated with pegcetacoplan versus 15% in the eculizumab group.

A total of 77 patients entered the 32-week OLP, during which all patients received pegcetacoplan, resulting in a total exposure of up to 48 weeks. The results at Week 48 were generally consistent with those at Week 16 and support sustained efficacy.

Study in complement inhibitor-naïve adult patients (APL2-308)

Study APL2-308 was an open-label, randomised, controlled study that enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrolment and with Hb levels less than the lower limit of normal (LLN). Eligible patients were randomised in a 2:1 ratio to receive pegcetacoplan or supportive care (e.g., transfusions, corticosteroids, supplements such as iron, folate, and vitamin B12), hereafter referred to as the control arm through the duration of the 26-week treatment period.

Randomisation was stratified based on the number of PRBC transfusions within the 12 months prior to Day -28 (<4; ≥4). At any point during the study, a patient assigned to the control arm who had Hb levels ≥2 g/dL below baseline or presented with a PNH associated thromboembolic event was per protocol able to transition to pegcetacoplan for the remainder of the study.

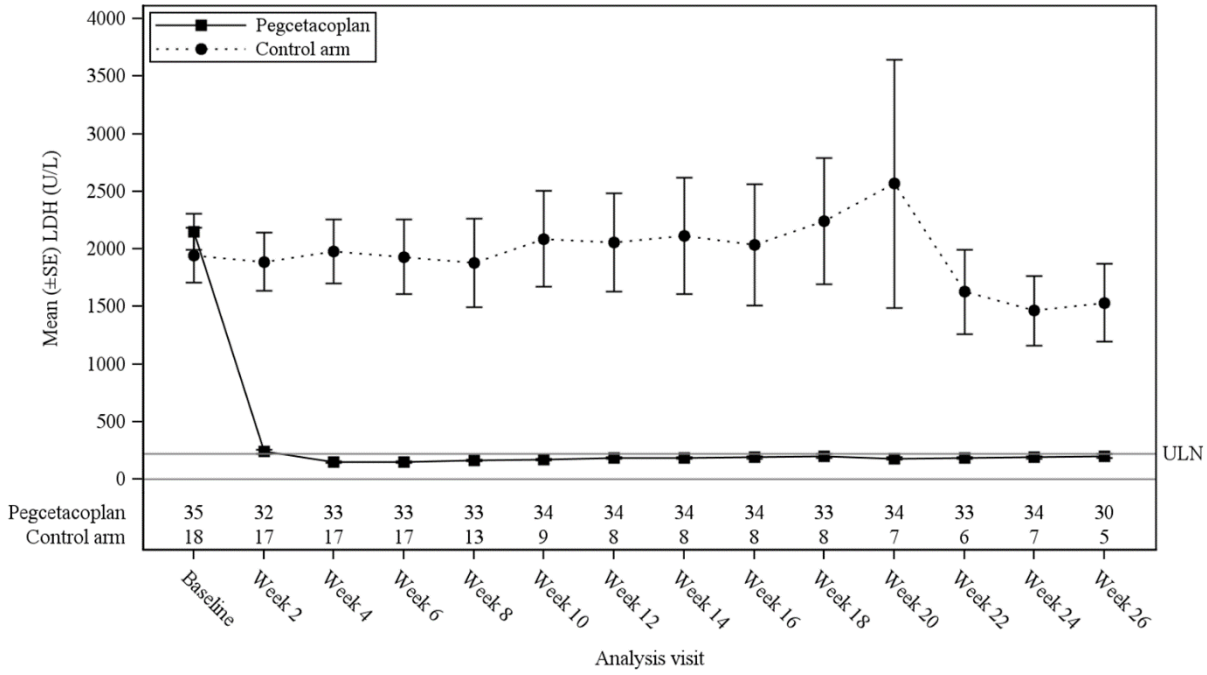
A total of 53 patients were randomised, 35 to pegcetacoplan and 18 patients to the control arm. Demographics and baseline disease characteristics were generally well balanced between treatment arms. The mean age was 42.2 years in the pegcetacoplan arm and 49.1 years in the control arm. The mean number of PRBC transfusions in the 12 months prior to screening was 3.9 in the pegcetacoplan arm and 5.1 in the control arm. Five patients in each arm (14.3% in the pegcetacoplan arm and 27.8% in the control arm) had a history of aplastic anaemia. Further baseline values were as follows: mean baseline Hb levels (pegcetacoplan arm: 9.4 g/dL vs. control arm; 8.7 g/dL), ARC (pegcetacoplan arm: 230.2×10^9/L vs. control arm: 180.3×10^9/L), LDH (pegcetacoplan arm: 2 151.0 U/L vs. control arm: 1 945.9 U/L) and platelet count (pegcetacoplan arm: 191.4×10^9/L vs. control arm: 125.5×10^9/L). Eleven of 18 patients randomised to the control arm transitioned to pegcetacoplan because their Hb levels decreased by ≥2 g/dL below baseline. Of the 53 randomised patients, 52 (97.8%) received prophylactic antibiotic therapy according to local prescribing guidelines.

The primary and secondary efficacy endpoints were assessed at Week 26. The two co-primary efficacy endpoints were Hb stabilisation, defined as avoidance of a >1 g/dL decrease in Hb concentration from baseline in the absence of transfusion, and change in LDH concentration from baseline.

In the group treated with pegcetacoplan, 30 out of 35 patients (85.7%) achieved Hb stabilisation versus 0 patients in the control arm. The adjusted difference between pegcetacoplan and the control arm was 73.1% (95% CI, 57.2% to 89.0%; p<0.0001).

The least-square (LS) mean (SE) changes from baseline in LDH concentration at Week 26 were -1 870 U/L in the group treated with pegcetacoplan versus -400 U/L in the control arm (p<0.0001). The difference between pegcetacoplan and the control arm was -1 470 (95% CI, -2 113 to -827). Treatment differences between the pegcetacoplan and the control arm were evident at Week 2 and were maintained through Week 26 (Figure 3). LDH concentrations in the control arm remained elevated.

Figure 3. Mean (±SE) LDH concentration (U/L) over time by treatment group in study APL2-308



For the selected key secondary efficacy endpoints of haemoglobin response in the absence of transfusions, change in haemoglobin level, and change in ARC, the group treated with pegcetacoplan demonstrated a significant treatment difference versus the control arm (Table 3).

Table 3: Key secondary endpoints analysis in study APL2-308

Parameter	**Pegcetacoplan (N=35)**	**Control arm (N=18)**	**Difference (95% CI) p-value**
Haemoglobin response in the absence of transfusions[a] n (%)	25 (71%)	1 (6%)	54% (34%, 74%) p < 0.0001
Change from baseline to Week 26 in haemoglobin level (g/dL) LS Mean (SE)	2.9 (0.38)	0.3 (0.76)	2.7 (1.0, 4.4)
Change from baseline to Week 26 in ARC (10^9/L) LS Mean (SE)	-123 (9.2)	-19 (25.2)	-104 (-159, -49)

[a] Haemoglobin response was defined as a ≥1 g/dL increase in haemoglobin from baseline at Week 26.
ARC = Absolute reticulocyte count, CI = Confidence interval, LS = Least square, SE = Standard error

C3G and primary IC-MPGN

The efficacy and safety of pegcetacoplan in patients with C3G or primary IC-MPGN was assessed in the randomised, placebo-controlled, double- blinded phase 3 Study APL2-C3G-310, including adults and adolescents with native kidney or post-transplant recurrent C3G or primary IC-MPGN.

The dose of pegcetacoplan was 1 080 mg twice weekly for adults or adolescents with body weights ≥50 kg, or weight-based for adolescents with body weights <50 kg.

Study in adult and adolescent patients with C3G or primary IC-MPGN (APL2-C3G-310)

Study APL2-C3G-310 was a randomised, double-blinded study with a placebo-controlled period of 26-weeks, followed by a 26-week OLP. This study enrolled adolescents from 12 years to 17 years of age, and adults with C3G or primary IC-MPGN. This study enrolled patients with native kidney or post-transplant recurrent disease who presented with proteinuria ≥1 g/day and eGFR ≥30 mL/min/1.73 m^2. Patients were on a stable and optimised dose regimen for C3G/primary

IC-MPGN treatment (e.g., RAS inhibitors, sodium-glucose cotransporter-2 [SGLT-2] inhibitors, immunosuppressants, systemic corticosteroids no higher than 20 mg/day of prednisone equivalent) for at least 12 weeks prior to randomisation.

Eligible patients were randomised in a 1:1 ratio to receive pegcetacoplan or placebo subcutaneously twice weekly during the 26-week RCP. Two stratification factors were applied to the randomisation; patients with post-transplant recurrence versus native kidney disease patients, and patients with baseline renal biopsies (either collected during screening or within 28 weeks prior to randomisation) versus patients without baseline renal biopsies. During the RCP, changes to the baseline treatment regimens for C3G/primary IC-MPGN were minimised and only made when required for the well-being of the patient. Patients who completed the RCP, entered the 26-week OLP, in which all participants were treated with pegcetacoplan twice weekly.

A total of 124 patients were randomised, 63 to pegcetacoplan and 61 to placebo. Demographics and baseline disease characteristics were generally balanced between the two groups (see Table 4). A total of 118 patients completed the 26-week RCP, of which 114 patients completed the OLP treatment period with pegcetacoplan (N=59 pegcetacoplan-to-pegcetacoplan; N=55 placebo-to-pegcetacoplan).

Table 4: Patient baseline demographics and disease characteristics in study APL2-C3G-310

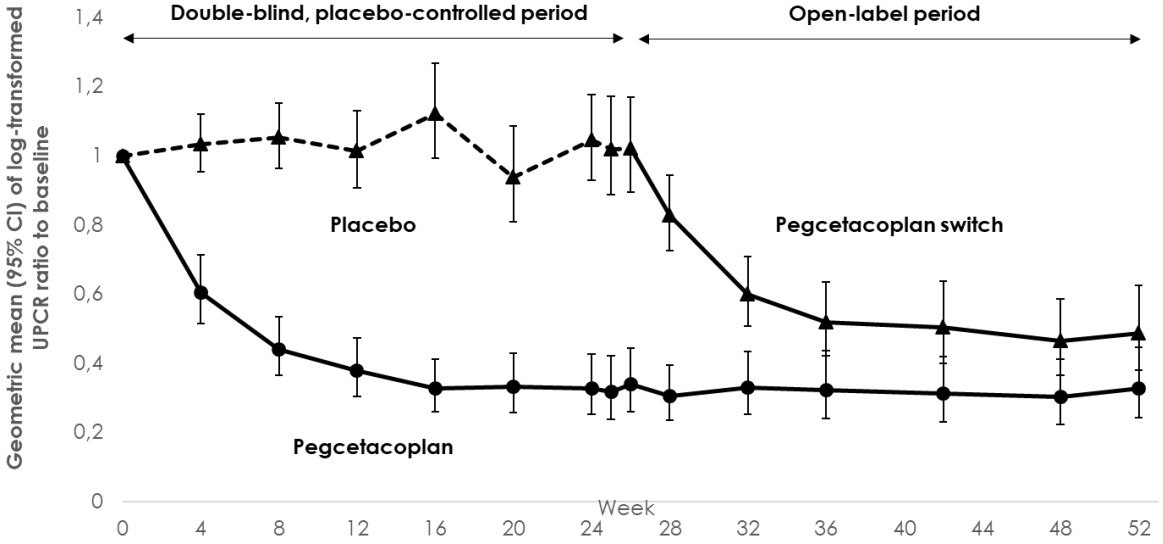
Parameter	**Statistics**	**Pegcetacoplan (N=63)**	**Placebo (N=61)**
Age (years)	Mean (SD)	28.2 (17.1)	23.6 (14.3)
Adolescents (12 – 17 years)	n (%)	28 (44.4)	27 (44.3)
Adults ≥18 years	n (%)	35 (55.6)	34 (55.7)
Sex			
Male	n (%)	26 (41.3)	28 (45.9)
Female	n (%)	37 (58.7)	33 (54.1)
Type of disease at Screening			
C3G	n (%)	51 (81.0)	45 (73.8)
C3GN	n (%)	45 (71.4)	41 (67.2)
DDD	n (%)	4 (6.3)	4 (6.6)
Undetermined	n (%)	2 (3.2)	0
IC-MPGN	n (%)	12 (19.0)	16 (26.2)
Time since diagnosis of C3G/IC-MPGN (years)	Mean (SD)	3.64 (3.47)	3.76 (3.62)
Prior kidney transplant	n (%)	5 (7.9)	4 (6.6)
Time since last kidney transplant (years)	Mean (SD)	11.4 (6.7)	5.8 (6.4)
Time since most recent post-transplant recurrence (years)	Mean (SD)	1.47 (1.49)	1.38 (1.64)
Baseline triplicate FMU uPCR (mg/g)	Mean (SD)	3124 (2408)	2541 (2015)
Baseline eGFR (mL/min/1.73 m^2)	Mean (SD)	78.5 (34.1)	87.2 (37.2)
C3c staining in baseline biopsy			
3+	n (%)	51 (81.0)	51 (83.6)
2+	n (%)	12 (19.0)	10 (16.4)
Baseline serum albumin (g/dL)	Mean (SD)	3.31 (0.61)	3.39 (0.70)
Baseline serum C3 (mg/dL)	Mean (SD)	60.6 (45.7)	56.3 (35.6)
Disease manifestations			
Oedema	n (%)	45 (71.4)	32 (52.5)
Fatigue	n (%)	16 (25.4)	8 (13.1)
Haematuria	n (%)	37 (58.7)	39 (63.9)
High Blood Pressure	n (%)	35 (55.6)	29 (47.5)
Nephrotic Syndrome	n (%)	32 (50.8)	27 (44.3)
Use of other treatments at baseline*			
Agents acting on the renin-angiotensin system	n (%)	59 (93.7)	54 (88.5)
Immunosuppressants	n (%)	49 (77.8)	45 (73.8)
Glucocorticoids	n (%)	29 (46.0)	27 (44.3)

*Within 12 weeks prior to study entry.
C3G = C3 glomerulopathy, C3GN = C3 glomerulonephritis, DDD = Dense-deposit disease, IC MPGN = Immune-complex membranoproliferative glomerulonephritis, FMU = First-morning urine, uPCR = Urine protein-to-creatinine ratio, eGFR = Estimated glomerular filtration rate, SD = Standard deviation

The primary and key secondary efficacy endpoints were assessed at Week 26. The primary efficacy endpoint was the log-transformed ratio of first-morning urine (FMU) uPCR at Week 26 compared with baseline.

Pegcetacoplan was superior to placebo, with a statistically significant 68.1% reduction (95% CI: 57.3% to 76.2%, p<0.0001) in uPCR from baseline compared to placebo after 26 weeks of treatment (-67.2% [95% CI: -74.9% to -57.2%] and + 2.9% [95% CI: -8.6% to 15.9%] for pegcetacoplan and placebo respectively. Efficacy of similar magnitude was observed in subgroups irrespective of age (adolescents vs. adults), disease type (C3G vs. primary IC-MPGN), disease status (native vs. post-transplant recurrent disease), and concomitant use of immunosuppressants/glucocorticoids (yes vs. no). The effect of pegcetacoplan on uPCR was sustained through Week 52 (-67.2 % from baseline). Patients who switched from placebo to pegcetacoplan at Week 26 (Figure 4) experienced a similar reduction (-51.3%) at Week 52.

Figure 4. Geometric mean ratio (95% CI) of FMU uPCR compared to baseline over time by treatment group from MMRM model in Study APL2-C3G-310



Note: Geometric mean ratio calculated from re-exponentiated LS Means.
CI = Confidence interval, LS = Least square, FMU = First-morning urine, uPCR = Urine protein-to-creatinine ratio, MMRM = Mixed model of repeated measure

Pegcetacoplan treatment for 26 weeks demonstrated statistically significant improvement in the key secondary endpoint related to proteinuria reduction, with 60.3% of patients treated with pegcetacoplan achieving a ≥50% reduction in uPCR compared to 4.9% in the placebo group, a difference of 52.7% (95% CI: 29.2%–76.2%; p<0.0001).

Pegcetacoplan treatment for 26 weeks resulted in a higher proportion of patients achieving a reduction of two orders of magnitude or greater, on a scale of 0-3, in renal C3 staining intensity with 26 (74.3%) patients on pegcetacoplan vs. 4 (11.8%) on placebo and a difference of 64.3% (95% CI: 41.4% - 87.2%, nominal p<0.0001).

Pegcetacoplan treatment for 26 weeks showed stabilisation in eGFR with a change from baseline of -1.497 (2.242) on pegcetacoplan vs. -7.808 (1.919) on placebo, and a treatment difference of 6.312 mL/min/1.73m^2 (95% CI: 0.501, 12.122, nominal p=0.0333). The effect of pegcetacoplan on eGFR was sustained through Week 52. Patients who switched from placebo to pegcetacoplan at Week 26 experienced a similar stabilisation at Week 52.

Efficacy of similar magnitude was broadly observed for proteinuria reduction ≥50%, C3 staining clearance and eGFR stabilisation in subgroups irrespective of age (adolescents vs. adults), disease type (C3G vs. primary IC-MPGN), disease status (native vs. post-transplant recurrent disease) and concomitant use of immunosuppressants/glucocorticoids (yes vs. no) at Week 26.

Study in adult post-transplant recurrent C3G or primary IC-MPGN (APL2-C3G-204)
Study APL2-C3G-204 was a phase 2 open-label, randomised study in 13 adult patients with post-transplant recurrent C3G (N=10) or primary IC-MPGN (N=3) for 52 weeks.

During the first 12 weeks of the study, 10 patients received pegcetacoplan, in addition to standard of care (SOC), and 3 only SOC. All patients received pegcetacoplan from Week 13 to Week 52.

The primary endpoint of reduction in C3 staining intensity on renal biopsy at Week 12 was observed in 50% of the patients treated with pegcetacoplan (5 of 10 patients; 4 of which, achieved a staining score of zero), and 33.3% of the patients in the control group (1 of 3 patients; with this patient achieving a staining score of 1).

In general, changes and percentage changes from baseline in eGFR (secondary endpoint) were small. Mean (SD) eGFR changed from 52.3 (12.11) mL/min/1.73 m^2 at baseline to 57.3 (25.12) mL/min/1.73 m^2 at Week 52, and median eGFR changed from 50.5 mL/min/1.73 m^2 at baseline to 58.5 mL/min/1.73 m^2 at Week 52. Most patients (9 of 13 patients [69.2%]) across groups achieved stabilisation or improvement in eGFR by Week 52.

Immunogenicity
Two different assays for the detection of anti-pegcetacoplan peptide anti-drug antibody (ADA) were used in PNH and C3G or primary IC-MPGN clinical studies, respectively. The assay used for C3G or primary IC-MPGN was more sensitive. Differences in assays preclude meaningful comparisons of the incidence of ADAs in the studies described below.

In PNH clinical studies, ADA incidence (treatment-emergent ADA or boosted ADA from pre-existing level) was low, and when present, had no noticeable impact on the PK/PD, efficacy, or safety profile of pegcetacoplan. Throughout studies APL2-302 and APL2-308, 3 out of 126 patients who were exposed to pegcetacoplan had confirmed positive anti-pegcetacoplan peptide antibodies. All 3 patients also tested positive for neutralising antibody (NAb). NAb response had no apparent impact on PK or clinical efficacy. Eighteen out of 126 patients developed anti-PEG antibodies; 9 were treatment-emergent and 9 were treatment-boosted.

In C3G and primary IC-MPGN clinical studies, ADA incidence (treatment-emergent ADA or boosted ADA from pre-existing level) in study APL2-C3G-310 was 23.6% for anti-PEG and 16.3% for anti-pegcetacoplan peptide. Based on population PK and PD analysis, ADAs had no clinically meaningful impact on efficacy or PK/PD in a pooled analysis population. Five patients also tested positive for NAb. NAb response had no apparent impact on PK or clinical efficacy. Twenty-nine out of 123 patients developed anti-PEG antibodies;14 were treatment-emergent and 15 were treatment-boosted. In patients with post-transplant recurrent disease in study APL2-C3G-204, no patient developed a positive ADA response (treatment-emergent ADA or boosted ADA from pre-existing level) to pegcetacoplan peptide or PEG. During the 26-week placebo-controlled period in study APL2-C3G-310, there was no detectable impact of ADAs on the safety of pegcetacoplan treatment.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ASPAVELI in one or more subsets of the paediatric population in PNH and C3G or primary IC-MPGN, respectively (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Pegcetacoplan is administered by subcutaneous infusion and gradually absorbed into the systemic circulation with a median T_{max} between 108 and 144 hours (4.5 to 6.0 days) following a single subcutaneous dose to healthy volunteers.

Steady-state serum concentrations following twice weekly dosing at 1 080 mg in patients with PNH were achieved approximately 4 to 6 weeks following the first dose. In complement inhibitor-experienced patients (Study APL2-302) the geometric mean (%CV) steady-state serum concentrations ranged between 655 (18.6%) and 706 (15.1%) µg/mL in patients treated for 16 weeks. Steady-state concentrations in the patients (n=22) that continued to receive pegcetacoplan up to Week 48 were 623 µg/mL (39.7%), indicating sustainable therapeutic concentrations of pegcetacoplan through Week 48. In complement inhibitor-naïve patients (Study APL2-308) the geometric mean (%CV) steady-state serum concentration at Week 26 was 744 µg/mL (25.5%) with twice weekly dosing. The bioavailability of a subcutaneous dose of pegcetacoplan is estimated to be 76% based on population PK analysis.

Steady-state serum concentrations following twice weekly dosing at 1 080 mg in C3G or primary IC-MPGN patients were achieved approximately 4 to 8 weeks following the first dose and therapeutic concentrations of pegcetacoplan were maintained through Week 52. In patients of study APL2-C3G-310, the steady-state mean (%CV) serum concentrations ranged between 715.8 (31.2%) and 765.7 (23.2%) µg/mL up to Week 26 and remained between 670.1 (30.1%) and 726.6 (30.5%) µg/mL up to Week 52.

Distribution
The mean (%CV) volume of distribution of pegcetacoplan is approximately 3.98 L (32%) in patients with PNH based on population PK analysis.

The mean (%CV) of central volume of distribution of pegcetacoplan is approximately 4.31 L (32.1%) in adult patients with C3G or primary IC-MPGN.

Metabolism/elimination
Based on its PEGylated peptide structure, the metabolism of pegcetacoplan is expected to occur via catabolic pathways and be degraded into small peptides, amino acids, and PEG. Results of a radiolabelled study in cynomolgus monkeys suggest the primary route of elimination of the labelled peptide moiety is via urinary excretion. Although the elimination of PEG was not studied, it is known to undergo renal excretion.

Pegcetacoplan showed no inhibition or induction of the CYP enzyme isoforms tested as demonstrated from the results of *in vitro* studies. Pegcetacoplan was neither a substrate nor an inhibitor of the human uptake or efflux transporters.

Following multiple subcutaneous dosing of pegcetacoplan in patients with PNH, the mean (%CV) clearance is 0.015 L/h (30%) and median effective half-life of elimination ($t_{1/2}$) is 8.6 days as estimated by the population PK analysis.

The estimated mean (CV%) of clearance is 0.012 L/hour (43%) in adult patients with C3G or primary IC-MPGN. The median terminal $t_{1/2}$ is 10.1 days in adult patients with C3G or primary IC-MPGN.

Linearity/non-linearity
Exposure of pegcetacoplan increases in a dose proportional manner from 45 to 1 440 mg.

Special populations
No impact on the pharmacokinetics of pegcetacoplan was identified with age (12-81 years), race or sex based on the results of population PK analysis in patients with PNH, C3G or primary IC-MPGN.

Compared with a reference 70 kg patient, the steady-state average concentration is predicted to be approximately 20% higher in patients with a body weight of 50 kg. PNH patients weighing 40 kg are predicted to have a 45% higher average concentration. Minimal data are available on the safety profile of pegcetacoplan for PNH patients with a body weight below 50 kg.

Elderly
Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 years and over is not sufficient to determine whether they respond differently from younger patients. See section 4.2.

Paediatric population
Based on population PK analysis, body weight in adolescent patients (12-17 years) has an impact on clearance and volume of distribution. The dosing regimen for adolescents with C3G or primary IC-MPGN is based on the patient´s body weight. See section 4.2. The model-predicted exposure for adolescents with C3G or primary IC-MPGN is adequately matched to the adult reference exposure.

Renal impairment
In a study of 8 patients with severe renal impairment, defined as creatinine clearance (CrCl) less than 30 mL/min using the Cockcroft-Gault formula (with 4 patients with values less than 20 mL/min), renal impairment had no effect on the pharmacokinetics of a single 270-mg dose of pegcetacoplan. There are minimal data on patients with PNH with renal impairment who have been administered the clinical dose of 1 080 mg twice weekly. Based on population PK analysis, eGFR had no clinically meaningful impact on pegcetacoplan exposure in a pooled analysis population. There are no available clinical data for the use of pegcetacoplan in patients with ESRD requiring dialysis. See section 4.2.

5.3 Preclinical safety data

In vitro and *in vivo* toxicology data reveal no toxicity of special concern for humans. Effects observed in animals at exposure levels similar to clinical exposure levels are described below. These effects were not observed in clinical studies.

Animal reproduction
Pegcetacoplan treatment of pregnant cynomolgus monkeys at a subcutaneous dose of 28 mg/kg/day (2.9 times the human steady-state C_{max}) from the gestation period through parturition resulted in a statistically significant increase in abortions or stillbirths. No maternal toxicity or teratogenic effects were observed in offspring delivered at term. Additionally, no developmental effects were observed in infants up to 6 months postpartum. Systemic exposure to pegcetacoplan was detected in foetuses from monkeys treated with 28 mg/kg/day from the period of organogenesis through the second trimester, but the exposure was minimal (less than 1%, not pharmacologically significant).

Carcinogenesis
Long term animal carcinogenicity studies of pegcetacoplan have not been conducted.

Genotoxicity
Pegcetacoplan was not mutagenic when tested in *in vitro* bacterial reverse mutation (Ames) assays and was not genotoxic in an *in vitro* assay in human TK6 cells or in an *in vivo* micronucleus assay in mice.

Animal toxicology
Repeat-dose studies were conducted in rabbits and cynomolgus monkeys with daily subcutaneous doses of pegcetacoplan up to 7 times the human dose (1 080 mg twice weekly). Histologic findings in both species included dose-dependent epithelial vacuolation and infiltrates of vacuolated macrophages in multiple tissues. These findings have been associated with large cumulative doses of long-chain

PEG in other marketed PEGylated drugs, were without clinical consequence, and were not considered adverse. Reversibility was not demonstrated in the pegcetacoplan animal studies after one month and was not evaluated for a longer duration. Data from literature suggest reversibility of PEG vacuoles.

Renal tubular degeneration was observed microscopically in both species at exposures (C_{max} and AUC) less than or comparable to those for the human dose and was minimal and nonprogressive between 4 weeks and 9 months of daily administration of pegcetacoplan. Although no overt signs of renal dysfunction were observed in animals, the clinical significance and functional consequence of these findings are unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E 420)
Glacial acetic acid
Sodium acetate trihydrate
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Store in the original carton to protect from light.

6.5 Nature and contents of container

A Type I glass vial with a stopper (chlorobutyl or bromobutyl), and a seal (aluminium) with a flip-off cap (polypropylene) containing 54 mg/mL of sterile solution.

Each single pack contains 1 vial.

Multipack containing 8 (8 packs of 1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

ASPAVELI comes as a ready-to-use solution in single-use vials. Because the solution contains no preservative, this medicinal product should be infused immediately after preparing the syringe.

ASPAVELI is a clear, colourless to slightly yellowish aqueous solution. Do not use if the liquid looks cloudy, contains particles, or is dark yellow.

Always bring the vial to the room temperature for approximately 30 minutes before use.

Remove the protective flip cap from the vial to expose the central portion of the gray rubber stopper of the vial. Clean the stopper with a new alcohol wipe and allow the stopper to dry. Do not use if the protective flip cap is missing or damaged.

Preparing the syringe:

Option 1: If using a needleless transfer device (such as a vial adapter), follow the instructions provided by the device manufacturer.

Option 2: If transfer is done using a transfer needle and a syringe, follow the instructions below:
- Attach a sterile transfer needle to a sterile syringe.
- Pull back the plunger to fill the syringe with air, which should be about 20 mL.
- Make sure the vial is in upright position. Do not turn the vial upside down.
- Push the air-filled syringe with transfer needle attached through the centre of the vial stopper.
- The tip of the transfer needle should not be in the solution to avoid creating bubbles.
- Gently push the air from the syringe into the vial. This will inject the air from the syringe into the vial.
- Invert the vial.
- With the transfer needle tip in the solution, slowly pull the plunger to fill the syringe with the prescribed dose of ASPAVELI.
- Remove the filled syringe and the transfer needle from the vial.
- Do not recap the transfer needle. Unscrew the needle and throw it away in the sharps container.

Administration:

ASPAVELI should only be administered via subcutaneous administration using either a syringe system infusion pump or an on-body delivery system:

- Follow the device manufacturer's instructions to prepare the infusion pump and tubing. When using an infusion pump, areas for infusion include the abdomen, thighs, hips, or upper arms. Rotate infusion sites from one infusion to the next. If there are multiple infusion sites, they should be at least 7.5 cm apart. The infusion time is approximately 30 minutes (if using two sites) or approximately 60 minutes (if using one site).

- Follow the device manufacturer's instructions to prepare the on-body delivery system. When using the on-body delivery system, ASPAVELI should be administered at a site on the abdomen. Rotate the infusion site from one infusion to the next. The infusion time varies by patient and typically ranges from 30 to 60 minutes.

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

7. MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/001
EU/1/21/1595/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 December 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

Swedish Orphan Biovitrum AB (publ)
Norra Stationsgatan 93
113 64 Stockholm
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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

The educational and controlled distribution programme is aimed at:

- Ensuring patients receive vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* at least 2 weeks before starting treatment with ASPAVELI
- Ensuring that patients who cannot wait 2 weeks before starting treatment with ASPAVELI receive broad-spectrum antibiotics until 2 weeks after receiving the vaccines

- Ensuring that ASPAVELI is only dispensed after written confirmation that the patient has received vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or is receiving prophylactic antibiotic according to national guidelines
- Ensuring prescribers or pharmacists receive annual reminders of mandatory revaccinations in accordance with current national vaccination guidelines (including *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*)
- Providing information about the signs and symptoms of serious infections to healthcare providers and patients
- Ensuring that prescribers provide patients with the package leaflet and patient card and explain the main risks of ASPAVELI using these materials
- Ensuring that patients who experience symptoms of serious infections seek emergency medical treatment and present their patient card to the emergency care provider
- Educate prescribers and patients about the risk of IVH after discontinuation of the medicinal product and postponement of administration and the need to maintain effective complement inhibitor treatment (PNH indication only).
- Educate prescribers about the risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.

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

- Physician educational material
- Patient information pack

Physician educational material:

- The SmPC
- Guide for healthcare professionals
- Patient card

- **Guide for healthcare professionals:**
  - Treatment with ASPAVELI may increase the risk of serious infections with encapsulated bacteria.
  - The need for patients to be vaccinated against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or receive antibiotic prophylaxis.
  - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
  - Risk of IVH after discontinuation and postponement of administration of the medicinal product, its criteria, the required post-treatment monitoring, and its proposed management (PNH indication only).
  - Risk of potential long-term effects of PEG accumulation and the recommendation to monitor as clinically indicated, including through laboratory testing.
  - The need to educate patients/carers of the following:
    - the risks of treatment with ASPAVELI
    - signs and symptoms of serious infections, hypersensitivity reactions, and what action to take
    - the patient/carer guides and its content
    - the need to carry the patient card and to tell any healthcare practitioner that he/she is receiving treatment with ASPAVELI
    - the requirement for vaccinations/antibiotic prophylaxis
    - the enrolment in the PASS (where available)
  - Instructions on how to handle possible adverse events.
  - Information about the PASS (where available), the importance of contributing to such a study, and how to enter patients.
  - Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.

- **Patient card:**
  - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using ASPAVELI.
  - Signs or symptoms of the serious infections and warning to seek immediate attention from a healthcare professional if above is present.
  - Contact details of the ASPAVELI prescriber.

The patient information pack:
- Patient information leaflet
- Patient/carer guide

- **Patient/carer guide:**
  - Treatment with ASPAVELI may increase the risk of serious infections with encapsulated bacteria, serious hypersensitivity reactions, and PNH-specific risk of IVH after discontinuation of the medicinal product.
  - A description of the signs and symptoms of serious infections, hypersensitivity reactions, IVH after discontinuation of the medicinal product, and the need to seek emergency care at the nearest hospital.
  - The importance of vaccination prior to treatment with ASPAVELI and/or to receive antibiotic prophylaxis.
  - Annual reminder of mandatory revaccinations (in accordance with current national vaccination guidelines).
  - Detailed description of the modalities used for the self-administration of ASPAVELI.
  - Recommendation for use of effective contraception in women of childbearing potential.
  - Remarks on the importance of reporting on specific adverse reactions, namely: serious infections, serious hypersensitivity reactions, and risk of IVH after discontinuation of the medicinal product.
  - Instructions on how to view the patient self-treatment video on any internet-connected device.
  - Enrolment in the PASS (where available).

Annual reminder of mandatory revaccinations
The MAH shall send annually to prescribers or pharmacists who prescribe/dispense ASPAVELI, a reminder in order that the prescriber/pharmacist checks if a re-vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* is required for his/her patients on treatment with ASPAVELI, in accordance with national vaccination guidelines.

System for controlled distribution
The MAH shall ensure that in each Member State where ASPAVELI is marketed, a system aimed to control distribution 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, or equivalent as permitted by national legislation, of the patient's vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* and/or prophylactic antibiotic treatment according to national vaccination guidelines.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING 1 VIAL

1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 20 mL vial contains 1 080 mg pegcetacoplan (54 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: sorbitol, glacial acetic acid, sodium acetate trihydrate, sodium hydroxide, and water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
For subcutaneous 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

Store in a refrigerator.
Store in the original carton in order to protect from light.

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

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ASPAVELI 1 080 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

CARTON CONTAINING 8 VIALS

1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 20 mL vial contains 1 080 mg pegcetacoplan (54 mg/mL)

3. LIST OF EXCIPIENTS

Excipients: sorbitol, glacial acetic acid, sodium acetate trihydrate, sodium hydroxide, and water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
8 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
For subcutaneous 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

Store in a refrigerator.
Store in the original carton in order to protect from light.

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

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ASPAVELI 1 080 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 INNER PACKAGING

INNER CARTON CONTAINING 1 VIAL

1. NAME OF THE MEDICINAL PRODUCT

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 20 mL vial contains 1 080 mg pegcetacoplan (54 mg/mL)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 vial. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
For subcutaneous use.

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

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original carton in order to protect from light.

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1595/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ASPAVELI 1 080 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan
For subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ASPAVELI 1 080 mg solution for infusion
pegcetacoplan

▼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 using 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 or nurse.
- 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ASPAVELI is and what it is used for
2. What you need to know before you use ASPAVELI
3. How to use ASPAVELI
4. Possible side effects
5. How to store ASPAVELI
6. Contents of the pack and other information

1. What ASPAVELI is and what it is used for

What is ASPAVELI
ASPAVELI is a medicine that contains the active substance pegcetacoplan. Pegcetacoplan has been designed to attach to the C3 complement protein, which is a part of the body's defence system called the 'complement system'.

What is ASPAVELI used for
Paroxysmal nocturnal haemoglobinuria (PNH)
ASPAVELI is used to treat adult patients with a disease called paroxysmal nocturnal haemoglobinuria (PNH) who have anaemia as a result of this disease.

In patients with PNH, the 'complement system' is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction, and blood clots. By attaching to and blocking the C3 protein, this medicine can stop the complement system from attacking red blood cells and so control symptoms of the disease. This medicine has been shown to increase the number of red blood cells (reduce anaemia), which may improve these symptoms.

C3 glomerulopathy (C3G) and primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN)
ASPAVELI is used to treat adult and adolescent patients (aged 12 to 17 years) with diseases called complement C3 glomerulopathy (C3G) or primary immune-complex membranoproliferative glomerulonephritis (primary IC-MPGN). For these diseases, ASPAVELI is used together with a renin-angiotensin-system inhibitor (RAS inhibitor), unless the use of a RAS inhibitor is not considered appropriate.

Glomerulonephritis is a kidney problem where there is inflammation in the kidney. C3G and primary IC-MPGN are types of glomerulonephritis. In patients with C3G or primary IC-MPGN, the 'complement system' is overactive and when this system is not well controlled, this can result in damage to the glomerulus, a network of small blood vessels in the kidney, which filters the blood. Over time, this stops the kidneys from removing waste in the blood. This waste, if not removed from the blood, builds up in the body and may lead to kidney inflammation, damage and failure. This can lead to blood in the urine (haematuria), excess protein in the urine (proteinuria), reduced kidney function (as measured by the glomerular filtration rate [GFR]), high blood creatinine levels, tiredness and swelling (oedema) of hands, feet or ankles. This medicine has been shown to reduce the amount of protein in the urine and can stabilise kidney function.

2. What you need to know before you use ASPAVELI

Do not use ASPAVELI
- if you are allergic to pegcetacoplan or any of the other ingredients of this medicine (listed in section 6).
- if you have an infection caused by so-called encapsulated bacteria.
- if you are not vaccinated against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using ASPAVELI.

Symptoms of infection
Before starting ASPAVELI, inform your doctor if you have any infections.

Because the medicine targets the complement system, which is part of the body's defences against infection, the use of this medicine increases your risk of infections, including those caused by the so-called encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. These are severe infections affecting your nose, throat and lungs or the linings of the brain and can spread throughout the blood and body.

Talk to your doctor before you start ASPAVELI to be sure that you receive vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* if you have not had these vaccines in the past. If you have had these vaccines in the past, you might still need additional vaccinations before starting this medicine. These vaccinations should be given at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection for 2 weeks after you have been vaccinated. Following vaccination, you may be more closely monitored by your doctor for symptoms of infection.

<u>Infection symptoms</u>
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache and a fever
- fever and a rash
- fever with or without shivers or chills
- shortness of breath
- high heart rate
- clammy skin
- headache with a stiff neck or stiff back
- headache with nausea (feeling sick) or vomiting
- eyes sensitive to light
- muscle aches with flu-like symptoms
- confusion
- extreme pain or discomfort

Make sure that you keep your vaccinations up to date. You should also be aware that vaccines reduce the risk of serious infections, but do not prevent all serious infections. In accordance with national recommendations, your doctor might consider that you need supplementary measures such as antibacterial medicines to prevent infection.

Allergic reactions
Allergic reactions may appear in some patients. In case of severe allergic reaction, discontinue ASPAVELI infusion and seek medical help immediately. Severe allergic reaction may present as difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing or collapse.

Injection site reactions
Injection site reactions have been observed with the use of ASPAVELI. You should undergo appropriate training in proper injection technique before self-administering.

Laboratory monitoring for PNH
During your treatment with ASPAVELI your doctor will perform regular check-ups, including blood tests for lactate dehydrogenase (LDH) levels and tests of renal function, and may adjust your dose if needed.

Effects on laboratory tests
Use of silica reagents in coagulation tests should be avoided as it can result in artificially prolonged activated partial thromboplastin time (aPTT).

Children and adolescents
Do not give this medicine to children with PNH under 18 years of age as no data are available on its safety and effectiveness in this group.

Do not give this medicine to children with C3G or primary IC-MPGN under 12 years of age as no data are available on its safety and effectiveness in this group.

Other medicines and ASPAVELI
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility
Women of childbearing potential
The effects of the medicine on an unborn child are not known. The use of effective contraception methods is recommended during treatment and up to 8 weeks after treatment by women who are able to get pregnant. Ask your doctor for advice before taking this medicine.

Pregnancy/breast-feeding
ASPAVELI is not recommended during 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.

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

ASPAVELI contains sorbitol
Sorbitol is a source of fructose. If your doctor has told you that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you take or receive this medicine.

ASPAVELI contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use ASPAVELI

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

At least 2 weeks before you start treatment with this medicine, your doctor will review your medical records and may give you one or more vaccinations. If you cannot be vaccinated at least 2 weeks before you start treatment with ASPAVELI, to reduce the risk of infection, your doctor will prescribe antibiotics for 2 weeks after you have been vaccinated.

If you use this medicine to treat PNH
Dose for adults:
The initial recommended dose for adults with PNH is 1 080 mg twice a week. You should take the twice weekly dose on Day 1 and Day 4 of each treatment week.

If you are switching to ASPAVELI from another type of PNH medicine, called a C5 inhibitor, you should take ASPAVELI in addition to your current dose of C5 inhibitor as prescribed for 4 weeks. After 4 weeks you should stop taking your C5 inhibitor.

The dose or dosing interval should not be changed without consulting your doctor. Your doctor may adjust your dose to 1 080 mg every third day (e.g., Day 1, Day 4, Day 7, Day 10, Day 13, and so forth) if appropriate. If you think you have missed a dose, speak to your doctor as soon as possible.

If you use this medicine to treat C3G or primary IC-MPGN
Dose for adults:
The initial recommended dose for adults with C3G or primary IC-MPGN is 1 080 mg twice a week. You should take the twice weekly dose on Day 1 and Day 4 of each treatment week.

Dose for adolescents:
The initial recommended twice a week dose for adolescents with C3G or primary IC-MPGN is based on the patient´s body weight. Your doctor will calculate your dose based on the below dosing table. You should take the twice weekly dose on Day 1 and Day 4 of each treatment week.

Body weight	**First dose (infusion volume)**	**Second dose (infusion volume)**	**Maintenance dose (infusion volume)**
50 kg and above	1 080 mg twice weekly (20 mL)		
35 to less than 50 kg	648 mg (12 mL)	810 mg (15 mL)	810 mg twice weekly (15 mL)
30 to less than 35 kg	540 mg (10 mL)	540 mg (10 mL)	648 mg twice weekly (12 mL)

Method and route of administration
ASPAVELI is intended to be given as an infusion under the skin using:
- an infusion pump or
- an on-body delivery system.

Your first doses of the medicine will be given to you by healthcare professionals in a clinic or treatment centre. If treatment goes well, your doctor may discuss with you the possibility of you giving the medicine yourself at home. If this is appropriate, a healthcare professional will train you or a caregiver how to give the infusion.

Infusion rate(s)
Using the infusion pump, the infusion time is approximately 30 minutes if you use 2 infusion sites or approximately 60 minutes if using 1 site.

Using the on-body delivery system, the infusion time typically ranges from 30 to 60 minutes (depending on how quickly the medicine flows into your body).

The infusion should be started promptly after drawing this medicinal product into the syringe and completed within 2 hours after preparing the syringe.

Instructions for use – preparing the syringe

<table>
<tr><td>Step 1</td><td>Prepare for infusion
Before you start:
1. Remove a single vial carton from the refrigerator. Keep the vial in the carton at room temperature and allow it to warm up for approximately 30 minutes. Do not try to speed up the warming process using a microwave or any other heat source.
2. Find a well-lit, flat work surface area, like a table.
3. Gather your supplies:
i) When using an infusion pump (Figure 1):
A. Syringe system infusion pump and manufacturer’s instructions (not shown)
B. Compatible syringe
C1. Transfer needle OR
C2. Needleless transfer device to draw up product from the vial
D. Infusion set (not shown; varies according to device manufacturer’s instructions)
E. Infusion tubing and Y connector (if required)
F. Sharps container
G. Alcohol wipes
H. Gauze and tape, or transparent dressing

OR

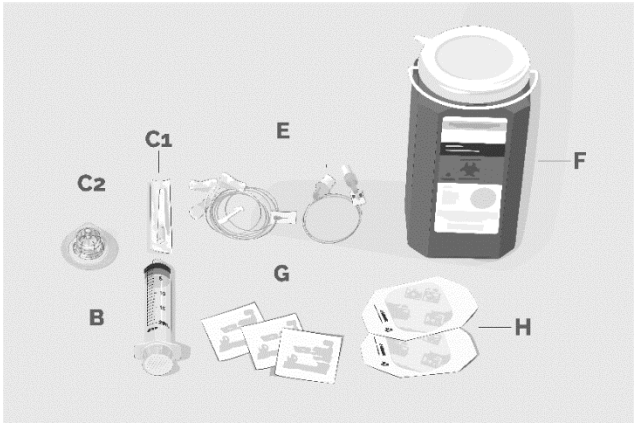
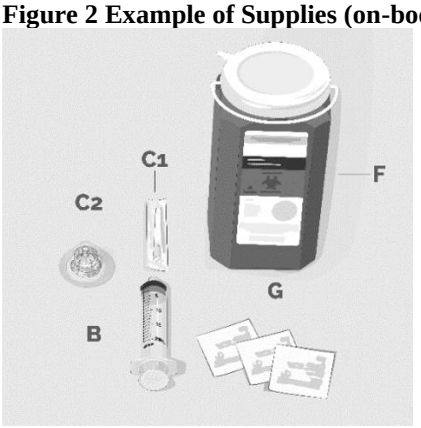
ii) When using an on-body delivery system (Figure 2):
A. On-body delivery system and manufacturer´s instructions (not shown)
B. Compatible syringe
C1. Transfer needle OR
C2. Needleless transfer device to draw up product from the vial
F. Sharps container
G. Alcohol wipes</td><td>Figure 1 Example of Supplies (infusion pump)


Figure 2 Example of Supplies (on-body delivery system)

</td></tr>
<tr><td></td><td>Thoroughly clean your work surface using an alcohol wipe.</td><td></td></tr>
<tr><td></td><td>Wash your hands thoroughly with soap and water. Dry your hands.</td><td></td></tr>
</table>

Step 2	**Check the vial and liquid** Remove the vial from the carton. Carefully look at the liquid in the vial. ASPAVELI is a clear, colourless to slightly yellowish liquid. Check for particles or colour changes (Figure 3). **Do not use the vial if:** • The liquid looks cloudy, contains particles, or is dark yellow. • The protective flip cap is missing or damaged. • The expiry date (EXP) on the label has passed.	**Figure 3** 

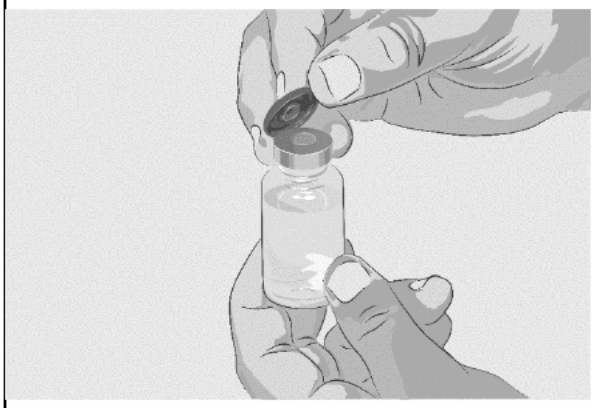
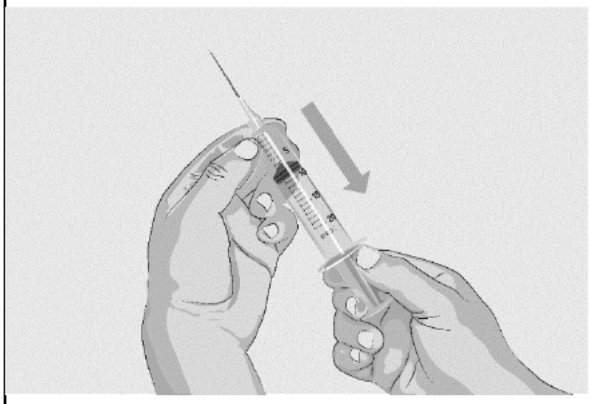
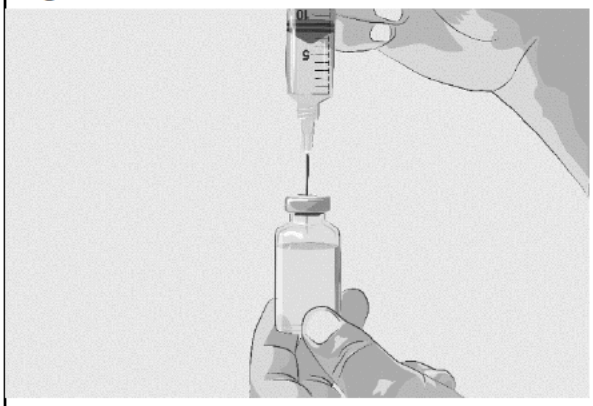
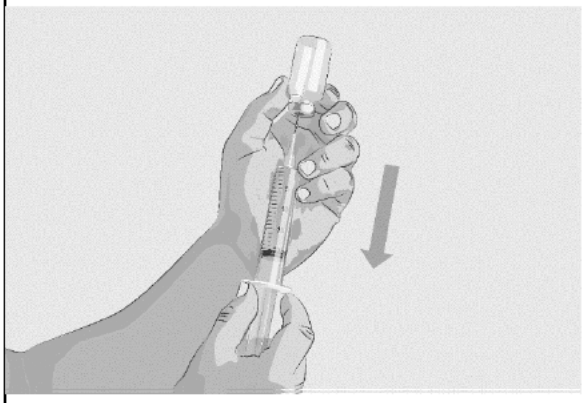
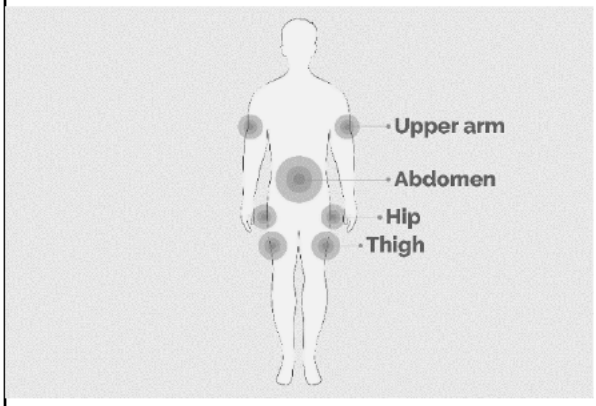
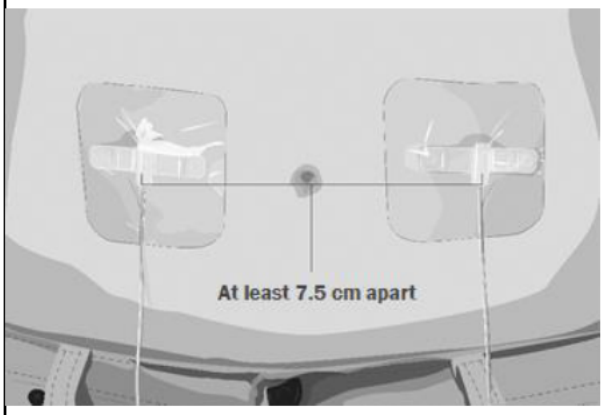
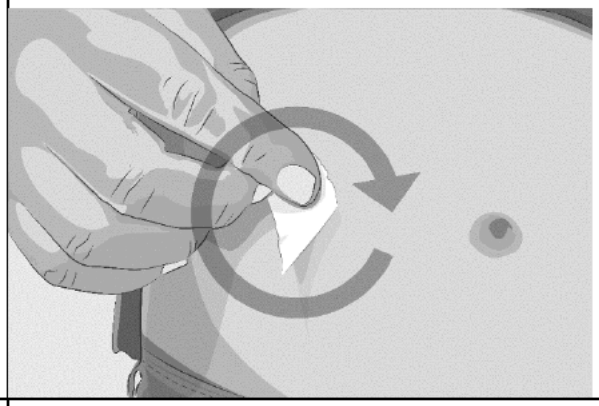
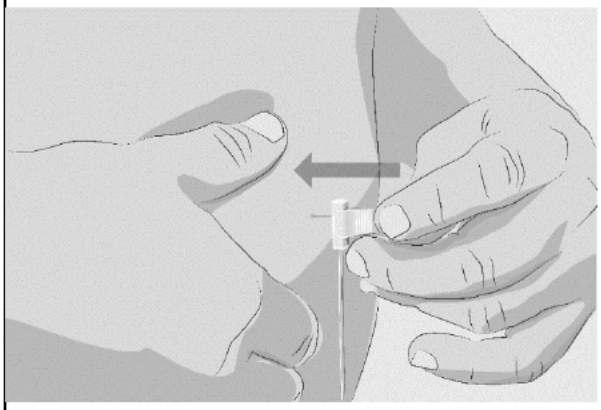
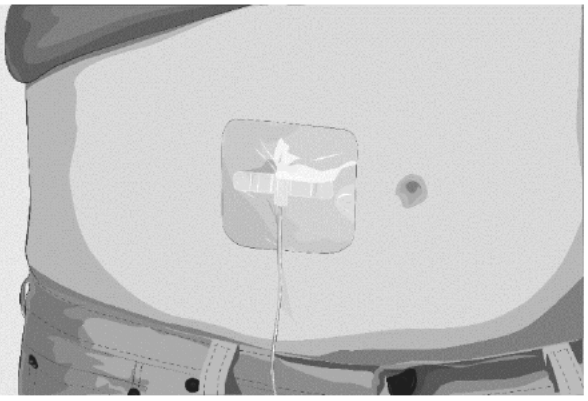
Step 3	**Prepare and fill syringe** Remove the protective flip cap from the vial to expose the central portion of the grey rubber stopper of the vial (Figure 4). Throw the cap away. Clean the stopper with a new alcohol wipe and allow the stopper to dry. Option 1: If using a needleless transfer device (such as a vial adapter), follow the instructions provided by the device manufacturer. OR Option 2: If using a transfer needle and a syringe, follow the instructions below: A. Attach a sterile transfer needle to a sterile syringe. B. Pull back the plunger to fill the syringe with air, which should be about 20 mL (Figure 5). C. Make sure the vial is in upright position. Do NOT turn the vial upside down. Push the air-filled syringe with the transfer needle attached through the centre of the vial stopper. D. The tip of the transfer needle should not be in the solution to avoid creating bubbles. (Figure 6). E. Gently push the air from the syringe into the vial. This will inject the air from the syringe into the vial. F. Turn the vial upside down (Figure 7). G. With the transfer needle tip in the solution slowly pull the plunger to fill the syringe with the prescribed dose of ASPAVELI (Figure 8). H. Double check that you have withdrawn your prescribed dose. Any excess volume should be disposed. I. Remove the filled syringe and the transfer needle from the vial. J. **Do not recap the transfer needle.** Unscrew the needle and throw it away in the sharps container.	**Figure 4**  **Figure 5**  **Figure 6**  **Figure 7** 

		Figure 8 

For infusion of the product using an on-body delivery system, follow the device manufacturer's instructions. Throw away all used disposable supplies as well as any unused product and the empty vial as recommended by your healthcare professional.

For infusion of the product using a syringe system infusion pump, follow the steps below.

Step 4	**Prepare syringe system infusion pump and tubing** Gather the infusion pump supplies and follow the device manufacturer's instructions to prepare the pump and tubing.	
Step 5	**Prepare the infusion site(s)** A. Select an area on your abdomen (except for the five centimetres area around the belly button), thighs, hips, or upper arms region for the infusion(s) (Figure 9). B. Use a different site(s) from the one you used for your last infusion. If there are multiple infusion sites, they should be at least 7.5 cm apart. Rotate infusion sites in between each infusion (Figure 10). **C. Avoid the following infusion areas:** **a. Do not infuse into areas where the skin is tender, bruised, red, or hard.** **b. Avoid tattoos, scars, or stretch marks.**	**Figure 9**  **Figure 10** 

	D. Clean the skin at each infusion site(s) with a new alcohol wipe, starting at the centre and working outward in a circular motion (Figure 11). E. Let the skin dry.	**Figure 11** 
Step 6	**Insert and secure the infusion needle(s)** A. Pinch the skin between your thumb and forefinger around the infusion site (where you intend to place the needle). Insert the needle into the skin (Figure 12). Follow the device manufacturer's instructions on the angle of the needle. B. Secure the needle(s) using sterile gauze and tape or a transparent dressing placed over the infusion site(s) (Figure 13).	**Figure 12**  **Figure 13** 
Step 7	**Start infusion** Follow the device manufacturer's instructions to start the infusion. Start the infusion promptly after drawing the solution into the syringe.	
Step 8	**Complete infusion** Follow the device manufacturer's instructions to complete the infusion.	
Step 9	**Record infusion** Record your treatment as directed by your healthcare professional.	

Step 10	**Clean up** A. After the infusion is complete, remove the dressing and slowly take out the needle(s). Cover the infusion site with a new dressing. B. Disconnect the infusion set from the pump and discard into the sharps container (Figure 14). C. Throw away all used disposable supplies as well as any unused product and the empty vial as recommended by your healthcare professional. D. Clean and store the syringe system infusion pump according to the device manufacturer's instructions.	**Figure 14** 

If you forget to use ASPAVELI
If you miss a dose, it should be taken as soon as possible; then take the next dose at the regularly planned time.

If you stop using ASPAVELI for treatment of PNH
PNH is a lifelong condition and so it is expected that you will use this medicine for a long time. If you wish to stop using the medicine, please speak to your doctor first. If you stop taking the medicine suddenly, you may be at risk of making your symptoms worse.

If your doctor decides to stop your treatment with this medicine, follow their instructions for how to stop. Your doctor will monitor you closely for at least 8 weeks after stopping treatment for any signs of the destruction of red blood cells (haemolysis) due to PNH. Symptoms or problems that can happen due to destruction of red blood cell include:
- tiredness
- shortness of breath
- blood in the urine
- stomach-area (abdomen) pain
- drop in the number of your red blood cell count
- blood clots (thrombosis)
- trouble swallowing
- erectile dysfunction in males

If you have any of these signs and symptoms, contact your doctor.

If you stop using ASPAVELI for treatment of C3G or primary IC-MPGN
C3G and primary IC-MPGN are lifelong conditions and so it is expected that you will use this medicine for a long time. If you wish to stop using the medicine, please speak to your doctor first.

4. Possible side effects

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

Your doctor will discuss the possible side effects with you and explain the risks and benefits of ASPAVELI with you before treatment.

The most serious side effect is serious infection.

If you experience any of the infection symptoms (see section 2 "Infection symptoms"), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Side effects reported in patients with PNH are listed below:

Very common (may affect more than 1 in 10 people):
- Reactions at the site of infusion: These include redness, swelling, itching, bruising and pain, or hardening of the skin. These reactions usually go away within a few days.
- Infection of the nose, throat, or airways (upper respiratory tract infection)
- Diarrhoea
- Destruction of red blood cells (haemolysis)
- Stomach pain (abdominal pain)
- Headache
- Tiredness (fatigue)
- Fever or high temperature (pyrexia)
- Cough
- Urinary tract infection
- Complications related to the mandatory vaccinations
- Arm and leg pain (pain in extremities)
- Dizziness
- Joint pain (arthralgia)
- Back pain

Common (may affect up to 1 in 10 people):
- Infection in the ear, mouth or skin
- Pain in the throat
- Fewer platelets in the blood (thrombocytopenia) which may cause bleeding or bruising more easily than normal
- Nausea (feeling sick)
- Decreased levels of potassium in the blood (hypokalaemia)
- Nose bleed (epistaxis)
- Skin redness (erythema)
- Muscle pain (myalgia)
- Infection of the stomach and intestines, which may cause symptoms of mild to severe nausea, vomiting, cramps, diarrhoea (gastrointestinal infection)
- Elevated liver tests
- Difficulty breathing (dyspnoea)
- Fewer number of white blood cells (neutropenia)
- Impaired kidney function
- Different colour of the urine
- High blood pressure
- Muscle spasms
- Stuffy nose (nasal congestion)
- Rash
- Infection in the blood (sepsis)
- Viral infection
- Fungal infection
- Respiratory tract infection
- Eye infection
- Hives
- COVID-19
- Bacterial infection
- Vaginal infection

Uncommon (may affect up to 1 in 100 people):
- Inflammation of the cervix
- Groin infection
- Pocket of pus in nose (nasal abscess)
- Pneumonia
- Tuberculosis
- Yeast infection in the oesophagus
- Pocket of pus in anus (anal abscess)

Side effects reported in patients with C3G or primary IC-MPGN are listed below:

Very common (may affect more than 1 in 10 people):
- Reactions at the site of infusion
- Infection of the nose, throat, or airways (upper respiratory tract infection)
- Allergic reaction (which includes rash and eczema)
- Fever or high temperature (pyrexia)
- Headache
- Diarrhoea
- Nausea (feeling sick)
- Impaired kidney function
- Influenza

Common (may affect up to 1 in 10 people):
- Cough
- Pneumonia
- Tiredness (fatigue)
- Opportunistic infections (which include shingles and other infections that occur when the immune system is weakened)
- Urinary tract infection
- Infection in the ear
- Fewer platelets in the blood (thrombocytopenia)
- Muscle pain (myalgia)
- Nose bleed (epistaxis)
- Fewer number of white blood cells (neutropenia)
- Decreased levels of potassium in the blood (hypokalaemia)
- Arm and leg pain (pain in extremities)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. 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 ASPAVELI

- 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 after “EXP”. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C – 8 °C).
- Keep the vial in the original carton in order to protect it from light.
- Do not throw away any medicines via wastewater. 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 ASPAVELI contains
The active substance is pegcetacoplan 1 080 mg (54 mg/mL in a 20 mL vial).

The other ingredients are: sorbitol (E 420) (see section 2 “ASPAVELI contains sorbitol”), glacial acetic acid, sodium acetate trihydrate (see section 2 “ASPAVELI contains sodium”), sodium hydroxide (see section 2 “ASPAVELI contains sodium”), and water for injection.

What ASPAVELI looks like and contents of the pack
ASPAVELI is a clear, colourless to slightly yellowish solution for subcutaneous infusion (54 mg/mL in a 20 mL vial). Solutions that are cloudy or have particles or colour change should not be used.

Pack sizes
ASPAVELI comes in a pack of 1 vial or a multipack of 1 x 8 vials.

Please note that alcohol swabs, needles, and other supplies or equipment are not contained in the pack.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

Manufacturer
Swedish Orphan Biovitrum AB (publ)
Norra Stationsgatan 93
113 64 Stockholm
Sweden

This leaflet was last revised in MM/YYYY.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

CORE DATA SHEET

pegcetacoplan

Version: Version [redacted]

2ページ～最終ページは新薬承認情報提供時に削除とした。

エムパベリ®皮下注 1080 mg

＜ペグセタコプラン＞

（C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎）

第 1 部（モジュール 1）
申請書等行政情報及び添付文書に関する情報

1.7　同種同効品一覧表

Swedish Orphan Biovitrum Japan 株式会社

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目次

1.7　同種同効品一覧表.....3

表目次

表 1.7-1　同種同効品一覧 3

1.7　同種同効品一覧表

「C3 腎症」の効能又は効果で承認されているファビハルタカプセル 200 mg（一般名：イプタコパン塩酸塩水和物）を同種同効品とした。なお、本申請品目の予定する効能又は効果は「C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎」であるが、「一次性免疫複合体型膜性増殖性糸球体腎炎」の効能又は効果を有する薬剤は、本邦では承認されていない。同種同効品について表 1.7-1 に示す。

表 1.7-1　同種同効品一覧

販売名	エムパベリ皮下注 1080 mg	ファビハルタカプセル 200 mg
一般的名称	ペグセタコプラン	イプタコパン塩酸塩水和物
会社名	Swedish Orphan Biovitrum Japan 株式会社	ノバルティスファーマ株式会社
効能又は効果	○発作性夜間ヘモグロビン尿症 ○C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎	○発作性夜間ヘモグロビン尿症 ○C3 腎症
添付文書改訂年月日	—	2025 年 5 月改訂（第 3 版、効能変更）

＊＊2025年5月改訂（第3版、効能変更）
＊2024年8月改訂（第2版）

貯法：室温保存

有効期間：36ヵ月

日本標準商品分類番号
873999

承認番号	30600AMX00147000
販売開始	2024年8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

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。[5.1、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〉

5.1 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、11.1.2、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］

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。

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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、5.1、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、5.1、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、5.1、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、5.1、9.1.2参照]

11.2 その他の副作用

	5%未満	頻度不明
＊＊血液およびリンパ系障害	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、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

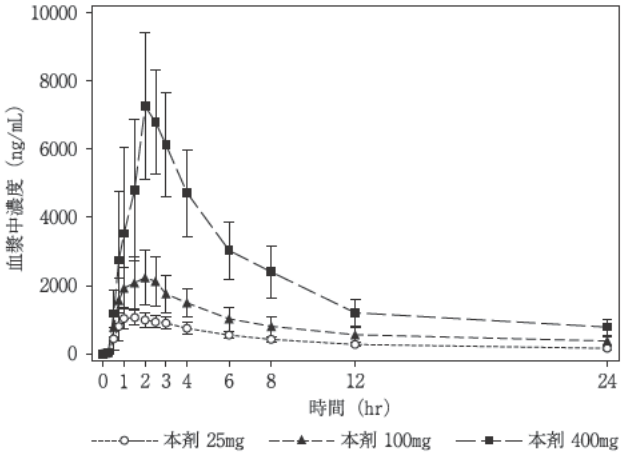
16.1.1 単回投与

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

二重盲検投与期の副次評価項目である投与6ヵ月時のeGFRのベースラインからの変化量［調整平均値（95%信頼区間）］は、本剤群で1.295（−2.136，4.726）mL/min/1.73m^2、プラセボ群で−0.861（−4.357，2.635）mL/min/1.73m^{2}であり、その群間差は2.156（−2.749，7.061）mL/min/1.73m^{2}であった（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のeGFRで調整したMMRM）［ベースライン時eGFR平均値±標準偏差:本剤群89.3±35.20mL/min/1.73m^2（38例）、プラセボ群99.2±26.88mL/min/1.73m^2（36例）］。

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〉

18.1.1 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〉

18.1.2 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〉

＊＊18.1.3 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）[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[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[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

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

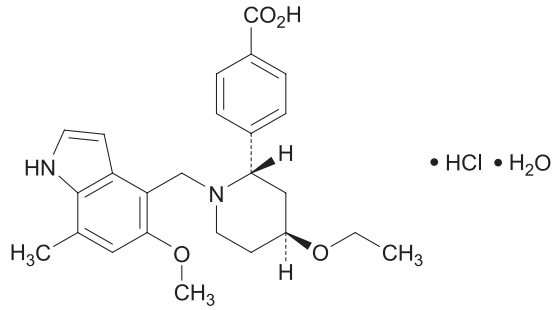
分子量

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。

〈発作性夜間ヘモグロビン尿症〉

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。

〈C3腎症〉

21.4 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。

21.5 本剤の投与が、C3腎症の診断、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）（2025年5月19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

NOVARTIS DIRECT
0120-003-293
受付時間：月～金 9：00～17：30
（祝日及び当社休日を除く）
www.novartis.co.jp

＊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

（03）

エムパベリ®皮下注 1080 mg

＜ペグセタコプラン＞

（C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎）

第 1 部（モジュール 1）

申請書等行政情報及び添付文書に関する情報

1.8　添付文書（案）

※この添付文書（案）は審査段階のものであるため、
最新の添付文書を参照すること

Swedish Orphan Biovitrum Japan 株式会社

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目次

略語・略号一覧.....3
1.8　添付文書（案）.....4
1.8.1　添付文書（案）.....4
1.8.2　効能又は効果（案）及びその設定根拠.....11
1.8.2.1　効能又は効果（案）.....11
1.8.2.2　設定根拠.....11
1.8.2.3　効能又は効果に関連する注意（案）.....12
1.8.2.4　設定根拠.....12
1.8.3　用法及び用量（案）及びその設定根拠.....13
1.8.3.1　用法及び用量（案）.....13
1.8.3.2　設定根拠.....13
1.8.3.3　用法及び用量に関連する注意（案）.....14
1.8.3.4　設定根拠.....14
1.8.4　使用上の注意（案）及びその設定根拠.....15

略語・略号一覧

略語・略号	略していない表現（英語）	略していない表現（日本語）
$AUC_{0-\infty}$	area under the drug concentration-time curve from time 0 to infinity	時間 0 から無限時間までの濃度–時間曲線下面積
C3G	C3 glomerulopathy	C3 腎症
CL	clearance	クリアランス
eGFR	Estimated glomerular filtration rate	推算糸球体濾過量
IC-MPGN	Immune complex membranoproliferative glomerulonephritis	免疫複合体型膜性増殖性糸球体腎炎
MPGN	membranoproliferative glomerulonephritis	膜性増殖性糸球体腎炎
PD	pharmacodynamic	薬力学
PEG	Polyethylene glycol	ポリエチレングリコール
uPCR	urine protein-to-creatinine ratio	尿中タンパク／クレアチニン比

1.8 添付文書（案）

1.8.1 添付文書（案）

エムパベリ皮下注 1080 mg の添付文書案を以下に示す。

最新の添付文書を参照すること

**20XX 年 XX 月改訂（第 X 版、効能変更、用法及び用量変更）
*20XX 年 XX 月改訂（第 X 版）

日本標準商品分類番号
873999

貯　　法：遮光下、2～8℃で保存
有効期間：30 ヵ月

承認番号	30500AMX00117000
販売開始	2023 年 9 月

補体（C3）阻害剤

ペグセタコプラン皮下注製剤

劇薬、処方箋医薬品(注)

エムパベリ®皮下注 1080mg

EMPAVELI® for Subcutaneous Injection

注）注意－医師等の処方箋により使用すること

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。[5.1、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投与すること。

1.1.4 髄膜炎菌等の感染症のリスクについて患者に説明し、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 適応疾患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。］［11.1.2 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。］［11.1.1 参照］

2.3 本剤の成分に対し過敏症の既往歴のある患者［11.1.3 参照］

3. 組成・性状

3.1 組成

1 バイアル（20mL）中

販売名	エムパベリ皮下注 1080mg	
有効成分	ペグセタコプラン	1080mg
添加剤	ソルビトール	820mg
	氷酢酸	7.7mg
	酢酸ナトリウム三水和物	9.8mg
	注射用水	適量

3.2 製剤の性状

販売名	エムパベリ皮下注 1080mg
剤形	注射剤（バイアル）
外観	無色～微黄色澄明な液
pH	約 5.0
浸透圧比	約 1
（日局生理食塩液に対する比）	

**4. 効能又は効果

○発作性夜間ヘモグロビン尿症

○C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎

5. 効能又は効果に関連する注意

〈効能共通〉

**5.1 本剤は、補体 C3 及び C3b に結合し、補体経路を阻害するため、髄膜炎菌、肺炎球菌及びインフルエンザ菌をはじめとする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。［1.1、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〉

5.2 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。

〈C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

**5.3 本剤は、国内外の最新の診療ガイドラインを参考に、C3 染色や免疫グロブリン染色の結果等に基づき、C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎と確定診断された患者にのみ使用すること。

**5.4 「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

〈発作性夜間ヘモグロビン尿症〉

通常、成人には、ペグセタコプランとして 1 回 1080mg を週 2 回皮下投与する。なお、十分な効果が得られない場合には、1 回 1080mg を 3 日に 1 回の間隔で皮下投与することができる。

〈C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

通常、18 歳以上の患者にはペグセタコプランとして 1 回 1080mg を週 2 回皮下投与する。

通常、12 歳以上 18 歳未満の患者にはペグセタコプランとして体重に基づいて下表に示す投与量を週 2 回皮下投与する。

投与量換算表

体重	初回投与量	2 回目投与量	3 回目以降投与量
50kg 以上	1080mg	1080mg	1080mg
35kg 以上 50kg 未満	648mg	810mg	810mg
30kg 以上 35kg 未満	540mg	540mg	648mg

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 投与を忘れた場合は、気づいた時点で速やかに本剤を投与し、その後はあらかじめ定めた投与日に投与すること。

〈発作性夜間ヘモグロビン尿症〉

7.2 補体（C5）阻害剤から本剤に切り替える際は、補体（C5）阻害剤中止による溶血を抑えるため、本剤投与開始後4週間は補体（C5）阻害剤を併用すること。

8. 重要な基本的注意

〈効能共通〉

**8.1 本剤の投与開始にあたっては、医療施設において、必ず医師によるか、医師の直接の監督の下で投与を行うこと。自己投与の適用については、医師がその妥当性を慎重に検討し、投与方法等について十分な教育訓練を実施した後、本剤投与による危険性と対処法について患者又はその保護者が理解し、患者又はその保護者が確実に投与できることを確認した上で、医師の管理指導の下で実施すること。自己投与の適用後、感染症等の本剤による副作用が疑われる場合や自己投与の継続が困難な状況となる可能性がある場合には、直ちに自己投与を中止させ、医師の管理下で慎重に観察するなど適切な処置を行うこと。また、本剤投与後に副作用の発現が疑われる場合は、医療施設へ連絡するよう患者又はその保護者に指導を行うこと。使用済みの注射器等を再使用しないように患者又はその保護者に注意を促し、すべての器具の安全な廃棄方法に関する指導を行うと同時に、使用済みの注射器等を廃棄する容器を提供すること。

〈発作性夜間ヘモグロビン尿症〉

8.2 本剤を中止した場合に重篤な溶血があらわれるおそれがある。本剤の投与を中止した患者に対しては、最低8週間、溶血及びそれに付随する臨床症状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。

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。

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）による感染症に罹患しやすくなるおそれがある。

9.4 生殖能を有する者

妊娠可能な女性には、本剤投与中及び投与終了後一定期間は適切な避妊を行うよう指導すること。[9.5参照]

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。妊娠カニクイザルに本剤28mg/kg/日（ヒトの定常状態におけるC_{max}の2.5倍）を皮下投与したとき、流産及び死産が増加した。サルで胎児への移行が認められている[1]。[9.4参照]

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。サルで乳汁移行が認められている[1]。

**9.7 小児等

〈発作性夜間ヘモグロビン尿症〉

小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。

〈C3腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

12歳未満の小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。

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 感染症（頻度不明）

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る。[1.1、2.2、5.1参照]

11.1.2 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、5.1参照]

11.1.3 過敏症（2.5%）

アナフィラキシー等の重度の過敏症があらわれることがある。[2.3参照]

11.2 その他の副作用

器官別大分類	5-10%	5%未満
胃腸障害		下痢
**一般・全身障害および投与部位の状態	注射部位紅斑、注射部位そう痒感、注入部位反応	注射部位硬結、注射部位腫脹、注射部位疼痛、注射部位内出血、注射部位反応、発熱
免疫系障害		過敏症[注]
**感染症および寄生虫症		上咽頭炎、インフルエンザ
**腎および尿路障害		急性腎障害

注）紅斑、蕁麻疹、そう痒症

12. 臨床検査結果に及ぼす影響

凝固検査パネルにシリカ試薬を使用すると、本剤との間に干渉作用が生じ、見かけ上、活性化部分トロンボプラスチン時間（aPTT）が延長するおそれがある。凝固検査パネルにはシリカ試薬を使用しないこと。

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 投与前に、微粒子、変色がないか目視にて確認し、異常が認められた場合は使用しないこと。

14.2 薬剤投与時の注意

14.2.1 注入部位は、腹部、大腿部、臀部、上腕部とし、順次変更すること。皮膚が敏感な部位、皮膚に異常のある部位（傷、発赤、硬結等）には注射しないこと。

14.2.2 注入部位が2ヵ所の場合は、注入部位の間隔を8cm以上あけること。

14.2.3 シリンジポンプを用いて、約15～30分（注入部位が2ヵ所の場合）又は約30～60分（注入部位が1ヵ所の場合）かけて注入すること。シリンジに本剤を充填後、直ちに注入を開始すること。薬剤の調製開始後2時間以内に投与を完了すること。

14.3 薬剤交付時の注意

14.3.1 患者が家庭で保存する場合においては、冷蔵庫内（2～8℃）で保存し、使用期限を超えない範囲で使用するよう指導すること。

15. その他の注意

**15.1 臨床使用に基づく情報

発作性夜間ヘモグロビン尿症患者を対象とした国際共同第Ⅲ相試験及び、C3腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者を対象とした国際共同第Ⅲ相試験において、本剤に対する抗体の産生が報告されている[2),3)]。[17.3.1参照]

15.2 非臨床試験に基づく情報

ウサギ及びカニクイザルを用いた反復投与毒性試験において、本剤の臨床最大用量投与時の0.06倍及び1.27倍の曝露量で、全身の器官・組織のマクロファージの空胞化、脳脈絡叢及び滑膜の上皮細胞の空胞化、並びに腎臓の尿細管変性が認められた。これらの空胞化形成は、長鎖ポリエチレングリコール（PEG）の蓄積に関連した変化と考えられ、回復性があり機能障害は認められなかった。また、腎臓の尿細管変性について、腎機能障害の徴候は認められず、臨床的意義及び機能的影響は不明である[4),5)]。

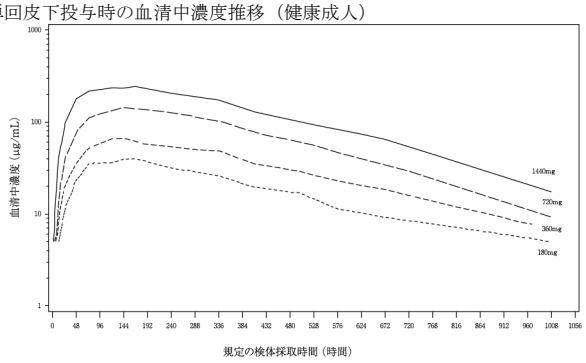
16. 薬物動態

16.1 血中濃度

16.1.1 単回投与

日本人健康被験者16例に本剤180～1440mg[注)]を単回皮下投与したときのペグセタコプランの血清中濃度推移及び薬物動態パラメータは以下のとおりであった。また、曝露量は概ね用量比例的に増加した[6)]。

単回皮下投与時の血清中濃度推移（健康成人）



定量限界未満の値（<5μg/mL）は5μg/mLとした。

単回皮下投与時の薬物動態パラメータ（健康成人）

本剤の用量（mg）	例数	C_{max}（μg/mL）	t_{max}[a)]（h）	$AUC_{0\text{-}inf}$（μg・h/mL）	$t_{1/2}$[a)]（h）	CL/F（mL/h）	V_z/F（L）
180	4	40（11.6）	144（120, 168）	18,380（8.9）	240.9（211, 268）	9.8（9.5）	3.38（15.1）
360	4	63（26.5）	192（120, 241）	31,980（11.7）	246（233, 257）	11.3（12.8）	3.98（16.0）
720	4	146（6.4）	132（120, 168）	67,150（11.1）	226（90, 287）	10.7（11.4）	2.94（33.2）
1440	4	242（25.6）	156（72, 168）	113,700（20.9）	211（197, 244）	12.7（23.0）	3.93（19.3）

幾何平均値（幾何変動係数%）
a）中央値（最小値，最大値）

16.1.2 反復投与

（1）健康成人

外国人健康被験者16例に本剤30～270mg[注)]を1日1回皮下投与したときのペグセタコプランの薬物動態パラメータは以下のとおりであった[7)]（外国人データ）。

1日1回反復皮下投与時の薬物動態パラメータ（健康成人）

測定時点	本剤の用量（mg/日）	例数	C_{max}（μg/mL）	t_{max}[a)]（h）	$AUC_{0\text{-}24h}$（μg・h/mL）	$t_{1/2}$（h）	CL/F（mL/h）
1日目	30	4	1.7（104）	24（24, 24）	18（119）	—	—
	90	4	3.5（69）	24（24, 24）	36（73）	—	—
	180	4	6.9（25）	24（24, 24）	73（24）	—	—
	270	4	17（37）	24（24, 24）	189（57）	—	—
28日目	30	4	77（7.1）	3（1, 8）	1,654（8.5）	198（13）	18（8.5）
	90	4	256（19）	24（2, 24）	5,741（18）	237（10）[b)]	16（18）
	180	4	470（13）	14（2, 24）	10,170（9.4）	211（16）[b)]	18（9.4）
	270	4	646（31）	8（1, 24）	13,020（13.4）	204（12）	21（13）

幾何平均値（幾何変動係数%）、—：算出せず
a）中央値（最小値，最大値）
b）3例

（2）発作性夜間ヘモグロビン尿症患者

エクリズマブ（遺伝子組換え）の効果が不十分な発作性夜間ヘモグロビン尿症患者80例（日本人患者10例を含む）に本剤1080mgを週2回皮下投与したときのペグセタコプランの血清中トラフ濃度は以下のとおりであり、初回投与から約4～6週間後に定常状態に達し、48週目まで維持された[2)]。

週2回反復皮下投与時の血清中トラフ濃度（μg/mL）
（発作性夜間ヘモグロビン尿症患者）

		本剤群	エクリズマブ群
導入期	-3週（Day -21）	272±65（39例）[b)]	267±72（38例）[b)]
	-2週（Day -14）	436±86（41例）[b)]	430±96（39例）[b)]
無作為化期	1日（Day 1）[a)]	594±106（41例）[b)]	588±111（37例）[b)]
	2週（Day 14）	666±118（41例）	—[c)]
	4週（Day 28）	676±115（40例）	—[c)]
	6週（Day 42）	677±132（39例）	—[c)]
	8週（Day 56）	692±106（37例）	—[c)]
	12週（Day 84）	708±124（38例）	—[c)]
	16週（Day 112）	714±109（36例）	—[c)]
継続期	24週（Day 168）	667±173（37例）	668±141（38例）[d)]
	48週（Day 336）	660±193（22例）	627±178（18例）[d)]

平均値±標準偏差（例数）、—：該当せず
a）無作為化期の治験薬投与前
b）本剤及びエクリズマブを併用投与
c）エクリズマブを投与
d）本剤を投与

** （3）C3腎症、一次性免疫複合体型膜性増殖性糸球体腎炎患者

C3腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者（日本人患者3例を含む）に年齢及び体重に応じた用量[注)]を週2回反復皮下投与したときのペグセタコプランの血清中トラフ濃度は以下のとおりであり、本剤投与開始後（プラセボ群では本剤への切替え後）4週目から8週目の間に定常状態に達した。また、定常状態の血清中ペグセタコプラン濃度は、52週目まで維持された[8)]。

週2回反復皮下投与時の血清中トラフ濃度（μg/mL）

（C3腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者）

		本剤群	プラセボ群
二重盲検期	4週	730±187（61）	< LLOQ
	8週	766±178（61）	< LLOQ
	12週	756±177（61）	< LLOQ
	16週	716±224（61）	< LLOQ
	20週	734±202（60）	< LLOQ
	24週	728±233（61）	< LLOQ
	26週	728±221（59）	< LLOQ
非盲検期	28週	710±225（60）	313±262（56）[a)]
	32週	700±260（60）	670±202（57）[a)]
	36週	727±222（59）	684±267（57）[a)]
	42週	706±289（60）	679±271（54）[a)]
	48週	721±243（60）	672±260（56）[a)]
	52週	677±303（60）	706±272（55）[a)]

平均値±標準偏差（例数）、<LLOQ：定量下限（10μg/mL）未満
a）本剤を投与

16.1.3 母集団薬物動態解析

（1）発作性夜間ヘモグロビン尿症

外国人及び日本人の健康成人、外国人腎機能障害患者並びに外国人及び日本人の発作性夜間ヘモグロビン尿症患者239例から得られた血清中ペグセタコプラン濃度データ（3,734時点）を用いて母集団薬物動態解析を行った。健康成人及び発作性夜間ヘモグロビン尿症患者に本剤を1日1回、週に2回又は3日に1回反復皮下投与したときのペグセタコプランの血清中薬物動態パラメータは以下のとおりであった[9)]。

反復皮下投与時の血清中薬物動態パラメータ（推定値）
（健康成人及び発作性夜間ヘモグロビン尿症患者）

本剤の投与レジメン	対象	$C_{max,\ ss}$（μg/mL）	$AUC_{week,\ ss}$（μg・h/mL）	$t_{1/2}$[a)]（h）	CL（L/day）	V2（L）
270mg 1日1回	健康成人	766（23）	128,589（23）	10（18）	0.270（21）	3.9（24）
	PNH患者	566（26）	95,009（26）	7.5（20）	0.366（24）	3.9（30）
360mg 1日1回	健康成人	1,021（23）	171,452（23）	10（18）	0.270（21）	3.9（24）
	PNH患者	755（26）	126,679（26）	7.5（20）	0.366（24）	3.9（30）
1080mg 週2回	健康成人	904（24）	147,549（24）	10（19）	0.269（22）	3.9（26）
	PNH患者	671（28）	108,541（28）	7.4（21）	0.366（25）	3.9（31）
1080mg 3日に1回	健康成人	1,026（23）	164,681（24）	10（18）	0.272（21）	3.9（26）
	PNH患者	765（27）	120,808（27）	7.4（21）	0.366（24）	3.9（31）

PNH=発作性夜間ヘモグロビン尿症
1,000例の幾何平均値（幾何変動係数%）
a）ln（2）/（投与16週時点のCL/V2）

**（2）C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎

12 歳以上の外国人及び日本人の C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者 140 例（日本人患者 3 例を含む）から得られた血清中ペグセタコプラン濃度データ（1,406 時点）を用いて母集団薬物動態解析を行った。C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者に年齢及び体重に応じた用量[注)]を週 2 回反復皮下投与したときのペグセタコプランの血清中薬物動態パラメータは以下のとおりであった[10)]。

反復皮下投与時の血清中薬物動態パラメータ（推定値）

（C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者）

対象	例数	C_{max} (μg/mL)	AUC_{1wk} (μg・h/mL)	$t_{1/2}$ (days)	CL (L/day)	VC (L)
12 歳以上 18 歳未満[a)]	55	841 (75.6)	137,400 (77.0)	11.5 (66.1)	0.270 (75.1)	4.46 (41.7)
18 歳以上[b)]	85	828 (41.5)	135,200 (42.6)	10.2 (43.4)	0.294 (43.1)	4.34 (31.5)

幾何平均値（変動係数%）

a）体重 50 kg 以上：1080 mg を週 2 回皮下投与、体重 35 kg 以上 50 kg 未満：初回は 648 mg、2 回目以降は 810 mg を週 2 回皮下投与、体重 30 kg 以上 35 kg 未満：初回及び 2 回目は 540 mg、3 回目以降は 648 mg を週 2 回皮下投与

b）1080 mg を週 2 回皮下投与

**16.3 分布

母集団薬物動態解析の結果、発作性夜間ヘモグロビン尿症患者におけるペグセタコプランの分布容積の平均値（幾何変動係数%）は約 3.9L（35%）であった[9)]。また、C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者におけるペグセタコプランの分布容積の平均値（変動係数%）は、12 歳以上 18 歳未満で 4.46L（41.7%）、18 歳以上で 4.34L（31.5%）であった[10)]。

16.4 代謝

ペグセタコプランは、その PEG 化ペプチド構造により異化経路を介してペプチドやアミノ酸に分解されると考えられる[11)]。

**16.5 排泄

母集団薬物動態解析の結果、発作性夜間ヘモグロビン尿症患者に本剤を反復皮下投与したとき、クリアランスの推定平均値（幾何変動係数%）は 0.015L/時間（28%）、消失の有効半減期（$t_{1/2}$）の中央値は 8.0 日であった[9)]。また、カニクイザルを用いた放射性標識体試験の結果から、標識ペプチド部分の排泄の主要経路は尿中排泄であることが示唆された[12)]。C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者に本剤を反復皮下投与したとき、12 歳以上 18 歳未満におけるクリアランスの推定平均値（変動係数%）は 0.0112L/時間（75.1%）、消失の半減期（$t_{1/2}$）の中央値は 10.5 日であり、18 歳以上ではそれぞれ 0.0122L/時間（43.1%）、10.1 日であった[10)]。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

重度の腎機能障害患者 8 例（クレアチニンクリアランスが 30mL/分未満）に本剤 270mg[注)]を単回皮下投与したときのペグセタコプランの C_{max} 及び $AUC_{0\text{-}inf}$ は対照被験者（クレアチニンクリアランスが 60mL/分以上等）と概ね同様であった[13)]（外国人データ）。

16.6.2 肝機能障害患者

肝機能障害患者におけるペグセタコプランの薬物動態に関する検討は行っていない。ペグセタコプランは主に異化経路を介して消失することから、肝機能障害がペグセタコプランのクリアランスに影響しないと考えられる。

16.7 薬物相互作用

薬物相互作用を検討した臨床試験は実施されていない。ペグセタコプランは CYP450 の阻害及び誘導を引き起こさないことが示された（*in vitro*）。また、ペグセタコプランは P 糖タンパク質（P-gp）及び乳がん耐性蛋白質（BCRP）の基質や阻害剤ではないことが示された（*in vitro*）[14)]。

注）本剤の用法及び用量は、ペグセタコプランとして発作性夜間ヘモグロビン尿症の患者には 1 回 1080mg を、C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者には 18 歳以上では 1 回 1080mg を、12 歳以上 18 歳未満では体重に基づいて設定した以下の投与量を週 2 回皮下投与である。

・体重 30 kg 以上 35 kg 未満：初回及び 2 回目は 540 mg、3 回目以降は 648 mg
・体重 35 kg 以上 50 kg 未満：初回は 648 mg、2 回目以降は 810 mg
・体重 50 kg 以上：1080 mg

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（APL2-302 試験）

エクリズマブ（遺伝子組換え）による治療を行ってもヘモグロビン（Hb）値が 10.5g/dL 未満である発作性夜間ヘモグロビン尿症患者（総症例 80 例、日本人 10 例を含む）を対象とした多施設共同無作為化非盲検実薬対照並行群間比較試験が実施された。なお、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（いずれも 1 回 0.5mL）を必須とした。また、医師の判断で抗菌薬の予防投与も可能とされた。［5.1 参照］

本剤の用法・用量は、1 回 1080mg を週 2 回皮下投与し、乳酸脱水素酵素（LDH）値が正常値上限の 2 倍超の場合は投与間隔を 3 日に 1 回とすることが可能とされた。

試験は 4 週間の導入投与期間（本剤とエクリズマブ（遺伝子組換え）を併用投与）、16 週間の無作為化投与期間（本剤又はエクリズマブ（遺伝子組換え）を投与）及び 32 週間の非盲検投与期間（本剤を投与、ただし、無作為化投与期間でエクリズマブ（遺伝子組換え）が投与されていた症例は 4 週間は投与を継続）で構成された。

主要評価項目である無作為化投与期間の 16 週時点の Hb 値のベースラインからの変化量は以下のとおりであり、本剤群のエクリズマブ（遺伝子組換え）群に対する優越性が示された。

	本剤群 (41 例)	エクリズマブ群 (39 例)
ベースライン[a)] の Hb 値 (平均値±標準偏差)	8.69±1.08	8.68±0.89
16 週時点の Hb 値のベースラインからの変化量[b)] (平均値±標準偏差（評価例数）)	2.79±2.03 (36 例)	0.03±0.44 (6 例)
16 週時点の Hb 値のベースラインからの変化量[c)] (最小二乗平均値±標準誤差)	2.37±0.36	-1.47±0.67
群間差（本剤群－エクリズマブ群）［95%信頼区間］[c)]	3.84［2.33, 5.34］	
p 値[c) d)]	<0.0001	

Hb 値（g/dL）

a）導入期開始時点

b）被験者が輸血を受けた場合、輸血後のすべてのデータを欠測として取り扱った

c）投与群、評価時点、投与群と評価時点の交互作用及び層別変数（治療開始前 1 年間の濃厚赤血球輸血回数［4 回未満、4 回以上］とベースラインの血小板数［100,000/mm³ 未満、100,000/mm³ 以上］）を固定効果、ベースラインの Hb 値を共変量、被験者を変量効果とした反復測定混合効果モデル、被験者内相関に無構造の共分散行列を仮定、輸血による打切りあり

d）両側有意水準 5%

副作用は、導入投与期間で 53.8%（43/80 例）、無作為化投与期間の本剤群で 34.1%（14/41 例）、非盲検投与期間で 46.8%（36/77 例）に認められ、主な副作用は、注射部位紅斑（導入投与期間、無作為化投与期間の本剤群、非盲検投与期間でそれぞれ 27.5%、14.6%、13.0%）、注射部位腫脹（同 11.3%、9.8%、1.3%）、注射部位そう痒感（同 11.3%、2.4%、6.5%）であった[2)]。

〈C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

**17.1.2 国際共同第Ⅲ相試験（APL2-C3G-310 試験、jRCT：2041230022）

レニン-アンジオテンシン系阻害薬を含む支持療法又は免疫抑制療法を安定して受けているにもかかわらず尿中タンパク／クレアチニン比（uPCR）が 1 g/g 以上で eGFR が 30 mg/min/1.73m² 以上の C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎を有する 12 歳以上の患者（総症例 124 例、日本人 3 例を含む）を対象とした多施設共同無作為化二重盲検プラセボ対照試験が実施された。なお、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を必須とした。［5.1、5.4 参照］

本剤の用法・用量は、被験者の年齢及び体重に応じて以下の用量を週 2 回皮下投与とされた。

- 18 歳以上及び 12 歳以上 18 歳未満で体重 50 kg 以上の被験者：1080 mg、12 歳以上 18 歳未満で体重 35 kg 以上 50 kg 未満の被験者：初回は 648 mg、2 回目以降は 810 mg、12 歳以上 18 歳未満で体重 30 kg 以上 35 kg 未満の被験者：初回及び 2 回目は 540 mg、3 回目以降は 648 mg

試験は 26 週間の無作為化投与期間（本剤群又はプラセボ群のいずれかに 1：1 の比で無作為割付）、26 週間の非盲検投与期間（本剤を投与）で構成された。主要評価項目である 26 週時の uPCR のベースラインに対する比の対数変換値は以下のとおりであり、26 週時において本剤群はプラセボ群と比較して統計学的に有意な uPCR の減少が認められた。

	パラメータ	本剤群 (63 例)	プラセボ群 (61 例)
24-25-26 週時点[d)]	推定／比較[a)]		
	最小二乗平均値±標準誤差	-1.11±0.136	0.03±0.061
	最小二乗平均値の 95%信頼区間	[-1.38, -0.85]	[-0.09, 0.15]
	最小二乗平均値の差［95%信頼区間］（本剤対プラセボ）	-1.14［-1.44, -0.85］	
	p 値（本剤対プラセボ）[b)]	<0.0001	
	幾何平均値［95%信頼区間］[c)]	0.328［0.252, 0.428］	1.029［0.914, 1.159］
	幾何平均値の比［95%信頼区間］（本剤対プラセボ）[c)]	0.319［0.238, 0.427］	

a）投与群、時点、基礎疾患の種類、ベースラインの免疫抑制剤の使用、ベースラインの腎移植の有無、ベースラインの腎生検の有無、ベースラインの uPCR の対数変換値及び時点と投与群の交互作用を説明変数とした mixed-effect model for repeated measures（MMRM）で 26 週時の uPCR のベースラインに対する比の対数変換値を解析した。

b）両側有意水準 5%

c）幾何平均値及び幾何平均値の比は指数化した最小二乗平均値及び最小二乗平均値の差で推定した。

d）24、25、26 週時点の均等加重平均を 26 週時の最小二乗平均値とした。

注）ベースラインの uPCR はスクリーニング開始から 1 日目までに採取した 9 回の早朝第一尿の検体のうち、少なくとも 6 回の検体から得られた uPCR の平均を算出した。

また、ベースラインと比較した26週時点のeGFRの変化量（最小二乗平均値）は、本剤群で-1.497 mL/min/1.73 m^2及びプラセボ群で-7.808 mL/min/1.73 m^2であった。

副作用は、全試験期間で本剤投与例の40.8%（49/120例）に認められ、主な副作用は、注射部位そう痒感（4.2%）、そう痒症（4.2%）であった[3),15)]。

17.3 その他

17.3.1 免疫原性

〈発作性夜間ヘモグロビン尿症〉

（1）発作性夜間ヘモグロビン尿症患者を対象とした国際共同第Ⅲ相試験（APL2-302試験）において、本剤が投与された患者（総症例80例、日本人10例を含む）のうち、抗ペグセタコプラン ペプチド抗体産生が検出された患者の割合は2.5%（2/80例、日本人は0例）であった[2)]。［15.1参照］

〈C3腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

**（2）C3腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者を対象とした国際共同第Ⅲ相試験（APL2-C3G-310試験）において、本剤が投与された患者（総症例124例、日本人3例を含む）のうち、抗ペグセタコプラン ペプチド抗体の発現率は29.3%（36/123例）、抗ポリエチレングリコール抗体の発現率は26.8%（33/123例）であった。これら抗薬物抗体の発現は、本剤の薬物動態、薬力学、有効性[10)]及び安全性[16)]プロファイルに明らかな影響を及ぼさなかった。［15.1参照］

18. 薬効薬理

18.1 作用機序

〈効能共通〉

**18.1.1 ペグセタコプランは、補体C3タンパク質及びC3bに高親和性で結合し、C3の開裂、補体活性化の下流エフェクターの生成及び膜侵襲複合体（MAC）生成を阻害する。さらに、C5転換酵素の成分であるC3bを阻害することでC5転換活性も阻害し、C5b及びC5aの形成を防ぐ[17)]。

〈発作性夜間ヘモグロビン尿症〉

**18.1.2 C3b及びMAC生成を阻害することにより、発作性夜間ヘモグロビン尿症患者における血管外溶血及び血管内溶血を抑制する[17)]。

〈C3腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

**18.1.3 C3分解産物の糸球体への沈着を防ぎ、既存の沈着物を減少させる[15)]。

18.2 薬力学的作用

〈発作性夜間ヘモグロビン尿症〉

18.2.1 発作性夜間ヘモグロビン尿症患者に本剤1080mgを週2回投与した結果、血中C3濃度は増加し、Hb値の改善、網状赤血球数及びLDH値の低下が認められた[2)]。

〈C3腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

**18.2.2 C3腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎の患者に本剤1080mg（もしくはそれに相当する、体重に基づいて調整された用量）を週2回投与した結果、血中C3濃度は約6倍に上昇し、血漿中可溶性C5b-9濃度は約3分の1に低下した[18)]。

19. 有効成分に関する理化学的知見

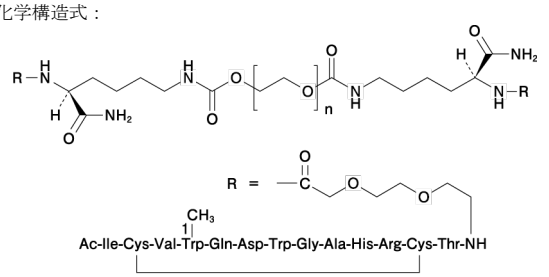
一般的名称：ペグセタコプラン

Pegcetacoplan（JAN）

分子式：$C_{170}H_{248}N_{50}O_{47}S_4$（$C_2H_4O$）$_n$

分子量：約43,500（ペプチド部分：3872.35）

化学構造式：



nは約800～1100である.

20. 取扱い上の注意

外箱開封後は遮光して保存すること。

21. 承認条件

〈効能共通〉

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。

〈発作性夜間ヘモグロビン尿症〉

21.2 国内での治験症例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。

〈C3腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

**21.4 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。

**21.5 本剤の投与が、C3腎症及び一次性免疫複合体型膜性増殖性糸球体腎炎の診断、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

エムパベリ皮下注1080mg　20mL［1バイアル］

23. 主要文献

1）社内資料：カニクイザルを用いた生殖発生毒性試験（18CATX-001試験）（2023年3月27日承認、CTD2.6.6.7）

2）社内資料：外国人及び日本人発作性夜間ヘモグロビン尿症患者を対象とした国際共同第Ⅲ相試験（APL2-302試験）（2023年3月27日承認、CTD2.7.6.9）

**3）社内資料：C3腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎を有する患者を対象とした第Ⅲ相試験（APL2-C3G-310試験）（20XX年XX月XX日承認、CTD2.7.6.2）

4）社内資料：ウサギを用いた反復投与毒性試験（13CATX-003及び15CATX-003試験）（2023年3月27日承認、CTD2.6.6.3）

5）社内資料：カニクイザルを用いた反復投与毒性試験（13CATX-004及び15CATX-004試験）（2023年3月27日承認、CTD2.6.6.3）

6）社内資料：日本人健康被験者を対象とした海外第Ⅰ相試験（APL2-102試験）（2023年3月27日承認、CTD2.7.6.8）

7）社内資料：外国人健康被験者を対象とした海外第Ⅰ相試験（APL-CP1014試験）（2023年3月27日承認、CTD2.7.6.2）

**8）社内資料：薬物動態（APL2-C3G-310試験）（20XX年XX月XX日承認、CTD2.7.6.2）

9）社内資料：母集団PK解析（APL-EX20-CP-002報告書）（2023年3月27日承認、CTD2.7.2.1）

**10）社内資料：母集団薬物動態（20XX年XX月XX日承認、CTD2.7.2.3）

11）Hydery T, Coppenrath VA. A Comprehensive Review of Pegvaliase, an Enzyme Substitution Therapy for the Treatment of Phenylketonuria. Drug Target Insights. 2019 Jun 21；13：1-8.

12）社内資料：カニクイザルを用いた放射性標識体試験（17MTX-001試験）（2023年3月27日承認、CTD2.6.4.6）

13）社内資料：外国人高度腎機能障害を有する被験者を対象とした海外第Ⅰ相試験（APL2-CP-PV-205試験）（2023年3月27日承認、CTD2.7.6.7）

14）社内資料：薬物動態学的薬物相互作用（17COTX-001、002、003試験）（2023年3月27日承認、CTD2.6.4.7）

**15）Fakhouri F, Bomback AS, Ariceta G, Delmas Y, Dixon BP, Gale DP, et al. Trial of Pegcetacoplan in C3 glomerulopathy and Immune-Complex MPGN. N Engl J Med. 2025;393(22):2210-2220.

**16）社内資料：抗薬物抗体の臨床的影響（20XX年XX月XX日承認、CTD2.5.5.9）

17）Mastellos DC, Reis ES, Yancopoulou D, Risitano AM, Lambris JD. Expanding complement therapeutics for the treatment of paroxysmal nocturnal hemoglobinuria. Semin Hematol. 2018；55（3）：167-175.

**18）社内資料：薬力学（補体バイオマーカー）（20XX年XX月XX日承認、CTD2.7.2.2）

*24. 文献請求先及び問い合わせ先

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フリーダイヤル 0120-114-936
（9：00～17：45/土日祝、休業日を除く）

26. 製造販売業者等

26.1 製造販売元

Swedish Orphan Biovitrum Japan株式会社
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*26.2 発売元

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1.8.2 効能又は効果（案）及びその設定根拠

1.8.2.1 効能又は効果（案）

効能又は効果（案）は、以下のとおり設定した。

〇発作性夜間ヘモグロビン尿症

〇C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎

（下線部：追記）

1.8.2.2 設定根拠

C3 腎症（C3G）又は一次性免疫複合体型膜性増殖性糸球体腎炎（IC-MPGN）を有する患者を対象とした、日本人被験者 3 例を含む国際共同第 3 相試験（APL2-C3G-310 試験）、海外第 2 相試験（APL2-C3G-204 試験）、APL2-C3G-310 試験の被験者を対象とした長期継続試験である国際共同第 3 相試験（APL2-C3G-314 試験）及び海外第 2 相非盲検試験（APL2-201 試験）において、C3G 及び一次性 IC-MPGN に対する有効性及び許容可能な安全性プロファイルが示されたことから、当該効能又は効果（案）を設定した。

APL2-C3G-310 試験では、ペグセタコプランを週 2 回皮下投与したとき、Week 26 にプラセボ群と比較して統計学的に有意かつ臨床的に意味のあるタンパク尿の減少（68.1%）が認められ、主要評価項目を達成した。主要評価項目の結果は、基礎疾患の種類（C3G 又は一次性 IC-MPGN）、年齢グループ（成人又は 12 歳以上の青年期）及び腎移植歴（自然腎で罹患又は腎移植後の疾患再発）に基づく全ての部分集団で一貫していた。また、主な副次評価項目である腎臓複合評価項目（タンパク尿の減少及び eGFR の安定を組み合わせた評価）及びタンパク尿のベースラインから 50%以上の減少について、プラセボ群と比較してペグセタコプラン群で統計学的有意性が認められた。加えて、腎生検での C3c 染色の減少及び eGFR で測定した腎機能の安定の評価項目について、プラセボ群と比較してペグセタコプラン群で名目的な有意差が認められた。また、無作為化投与期間にプラセボの投与を受け、非盲検投与期間にペグセタコプラン投与に切り替えた被験者（切替群）では、26 週間の非盲検投与期間でペグセタコプランを投与した後、タンパク尿の減少（uPCR で測定）及び腎機能の安定（eGFR で測定）で同様の効果を達成した。無作為化投与期間にペグセタコプランの投与を受け、非盲検投与期間に継続投与した被験者（継続群）では、非盲検投与期間を通してタンパク尿の減少及び腎機能の安定に持続的な治療効果が認められた。

長期継続試験である APL2-C3G-314 試験の被験者も同様に、ペグセタコプランの継続投与期間中にタンパク尿の減少及び腎機能の安定が持続した。さらに、APL2-201 試験では、ペグセタコプランを約 4 年間投与した C3G 患者の長期有効性データから、持続的なタンパク尿の減少及び eGFR の安定化が認められた。

本邦では一次性 MPGN が難病に指定されている（指定難病 223）。疾患の原因として「I 型及び III 型では、免疫グロブリン沈着に加えて補体活性化を示す C3 の沈着が見られ免疫複合

体が主要因である。」こと及び「I 型・III 型の中で C3 沈着が優位で免疫グロブリンの沈着を伴わないものを C3 腎炎（C3 glomerulonephritis）と呼称し、従来の II 型（デンスデポジット病：DDD）と C3 腎炎を合わせ C3 腎症と総称され、一次性に含有される。」ことが示されており、本邦で一次性 MPGN として取り扱われている患者集団には、C3G と一次性 IC-MPGN が含まれている。

これらのことから、効能又は効果（案）を「C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎」とした。

1.8.2.3 効能又は効果に関連する注意（案）

〈効能共通〉

5.1 本剤は、補体 C3 及び C3b に結合し、補体経路を阻害するため、髄膜炎菌、肺炎球菌及びインフルエンザ菌をはじめとする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。［1.1、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〉

5.2 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。

〈C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

5.3 本剤は、国内外の最新の診療ガイドラインを参考に、C3 染色や免疫グロブリン染色の結果等に基づき、C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎と確定診断された患者にのみ使用すること。

5.4 「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］

（下線部：追記、変更）

1.8.2.4 設定根拠

効能共通の注意と効能ごとの注意に記載を分けた。〈効能共通〉及び〈発作性夜間ヘモグロビン尿症〉の項は、現行添付文書の注意喚起内容から変更はない。〈C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉の 5.3 項は、本薬の投与対象が C3G 又は一次性 IC-MPGN であることから、適切に適応患者を選択するよう注意喚起するために設定した。5.4 項は、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、設定した。

1.8.3 用法及び用量（案）及びその設定根拠

1.8.3.1 用法及び用量（案）

用法及び用量（案）は、以下のとおり設定した。

〈発作性夜間ヘモグロビン尿症〉

通常、成人には、ペグセタコプランとして 1 回 1080mg を週 2 回皮下投与する。なお、十分な効果が得られない場合には、1 回 1080mg を 3 日に 1 回の間隔で皮下投与することができる。

〈C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉

通常、18 歳以上の患者にはペグセタコプランとして 1 回 1080mg を週 2 回皮下投与する。

通常、12 歳以上 18 歳未満の患者にはペグセタコプランとして体重に基づいて下表に示す投与量を週 2 回皮下投与する。

投与量換算表

体重	初回投与量	2 回目投与量	3 回目以降投与量
50kg 以上	1080mg	1080mg	1080mg
35kg 以上 50kg 未満	648mg	810mg	810mg
30kg 以上 35kg 未満	540mg	540mg	648mg

（下線部：追記）

1.8.3.2 設定根拠

C3G 及び一次性 IC-MPGN の成人に対する投与レジメンである 1080 mg を週 2 回皮下投与は、意味のある PD 反応が生じるのに十分なペグセタコプランの全身曝露が得られ、概ね安全で良好な忍容性を示すよう意図された。

また、C3G 及び一次性 IC-MPGN の主要な臨床試験での青年期（12～17 歳）の被験者に対する投与レジメンは、成人被験者に対してペグセタコプラン 1080 mg を週 2 回皮下投与したときと同様の曝露量を得ることを目的として設定した。青年期被験者の皮下投与レジメンを選択するために使用したモデル解析の結果を以下に要約する。

- 体重 50 kg 以上の青年期被験者に対する 1080 mg を週 2 回の投与レジメンは、成人被験者に同用量を投与するときと同様の曝露量を得ると想定された。
- 体重 35 kg 以上 50 kg 未満の青年期被験者に対する初回用量 648 mg 及びその後 810 mg を週 2 回の投与レジメンは、Week 1、Week 2 及び Week 16（定常状態）に、成人被験者に 1080 mg を週 2 回投与するときと同様の曝露量を得ると想定された。

- 体重 30 kg 以上 35 kg 未満の青年期被験者に対する初回及び 2 回目に 540 mg、並びにその後 648 mg を週 2 回の投与レジメンは、Week 1、Week 2 及び Week 16（定常状態）に、成人被験者に 1080 mg を週 2 回投与するときと同様の曝露量を得ると想定された。

上述の投与レジメンで実施した APL2-C3G-310 試験（日本人被験者 3 例を含む）において、C3G 及び一次性 IC-MPGN に対する有効性及び許容可能な安全性プロファイルが示された。

日本人と外国人の間で C3G 又は一次性 IC-MPGN の疾患特性に違いがなく、C3G 及び一次性 IC-MPGN に対する現在の治療法が本邦と他国で類似しており、外因性要因に違いはない。加えて、ペグセタコプランの初回承認申請時に提出した発作性夜間ヘモグロビン尿症患者を対象とした臨床試験の結果では、日本人と外国人の間で PK パラメータに意味のある差は認められず、内因性要因に違いはなかった。さらに、APL2-C3G-310 試験の日本人被験者の有効性の結果は、全体集団の有効性の結果に基づく想定範囲内であり、日本人及び外国人の C3G 又は一次性 IC-MPGN を有する患者の間でバイオマーカーの結果も同様であった。APL2-C3G-310 試験に参加した日本人被験者は少なく、一次性 IC-MPGN を有する被験者は組入れられなかったため、一概に結論づけることは難しいものの、これらの所見に基づき、日本人患者でも外国人患者と同様の用量で、同様の有効性を達成することが期待され、日本人患者に対する用量調整は不要と考えられる。

これらに基づき、当該用法及び用量（案）を設定した。

1.8.3.3 用法及び用量に関連する注意（案）

〈効能共通〉

7.1 投与を忘れた場合は、気づいた時点で速やかに本剤を投与し、その後はあらかじめ定めた投与日に投与すること。

〈発作性夜間ヘモグロビン尿症〉

7.2 補体（C5）阻害剤から本剤に切り替える際は、補体（C5）阻害剤中止による溶血を抑えるため、本剤投与開始後 4 週間は補体（C5）阻害剤を併用すること。

（下線部：追記、変更）

1.8.3.4 設定根拠

効能共通の注意と効能ごとの注意に記載を分けた。現行添付文書の注意喚起内容から変更はない。

1.8.4 使用上の注意（案）及びその設定根拠

使用上の注意	設定根拠
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。［5.1、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投与すること。 1.1.4 髄膜炎菌等の感染症のリスクについて患者に説明し、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。	現行の添付文書の記載内容から変更はない。
1.2 適応疾患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。	C3 腎症及び一次性免疫複合体型膜性増殖性糸球体腎炎は、腎疾患領域の希少疾病であり、治療にあたっては腎疾患の治療に十分な経験を持つ医師のもとで使用することが望ましいこと、発作性夜間ヘモグロビン尿症を含むすべての効能に共通の注意喚起であることから、「適応疾患に」として設定した。

使用上の注意	設定根拠
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。］［11.1.2 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。］［11.1.1 参照］ 2.3 本剤の成分に対し過敏症の既往歴のある患者［11.1.3 参照］	現行の添付文書の記載内容から変更はない。
8. 重要な基本的注意 〈効能共通〉 8.1 本剤の投与開始にあたっては、医療施設において、必ず医師によるか、医師の直接の監督の下で投与を行うこと。自己投与の適用については、医師がその妥当性を慎重に検討し、投与方法等について十分な教育訓練を実施した後、本剤投与による危険性と対処法について患者又はその保護者が理解し、患者又はその保護者が確実に投与できることを確認した上で、医師の管理指導の下で実施すること。自己投与の適用後、感染症等の本剤による副作用が疑われる場合や自己投与の継続が困難な状況となる可能性がある場合には、直ちに自己投与を中止させ、医師の管理下で慎重に観察するなど適切な処置を行うこと。また、本剤投与後に副作用の発現が疑われる場合は、医療施設へ連絡するよう患者又はその保護者に指導を行うこと。使用済みの注射器等を再使用しないように患者又はその保護者に注意を促し、すべての器具の安全な廃棄方法に関する指導を行うと同時に、使用済みの注射器等を廃棄する容器を提供すること。 〈発作性夜間ヘモグロビン尿症〉 8.2 本剤を中止した場合に重篤な溶血があらわれるおそれがある。本剤の投与を中止した患者に対しては、最低 8 週間、溶血及びそれに付随する臨床症状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。	本剤は自己投与が可能な薬剤であり、小児では保護者による投与が想定されるため、自己投与の適用にあたっての一般的な注意として本剤の CCDS の記載に基づき追記した。 現行の添付文書の記載内容から変更はない。

使用上の注意	設定根拠
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。 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）による感染症に罹患しやすくなるおそれがある。	現行の添付文書の記載内容から変更はない。 現行の添付文書の記載内容から変更はない。
9.4 生殖能を有する者 妊娠可能な女性には、本剤投与中及び投与終了後一定期間は適切な避妊を行うよう指導すること。［9.5 参照］	現行の添付文書の記載内容から変更はない。
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。妊娠カニクイザルに本剤 28mg/kg/日（ヒトの定常状態における C_{max} の 2.5 倍）を皮下投与したとき、流産及び死産が増加した。サルで胎児への移行が認められている。［9.4 参照］	現行の添付文書の記載内容から変更はない。
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。サルで乳汁移行が認められている。	現行の添付文書の記載内容から変更はない。
9.7 小児等 〈発作性夜間ヘモグロビン尿症〉 小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。 〈C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎〉 12 歳未満の小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。	現行の添付文書の記載内容から変更はない。 C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者を対象とした国際共同第Ⅲ相試験（APL2-C3G-310 試験）において、12 歳未満の小児に関す

<table>
<tr><th>使用上の注意</th><th>設定根拠</th></tr>
<tr><td></td><td>る利用可能な成績は得られていないことから設定した。</td></tr>
<tr><td>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。</td><td></td></tr>
<tr><td>11.1 重大な副作用
11.1.1 感染症（頻度不明）
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る。［1.1、2.2、5.1 参照］</td><td>現行の添付文書の記載内容から変更はない。</td></tr>
<tr><td>11.1.2 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、5.1 参照］</td><td>現行の添付文書の記載内容から変更はない。</td></tr>
<tr><td>11.1.3 過敏症（2.5%）
アナフィラキシー等の重度の過敏症があらわれることがある。［2.3 参照］</td><td>現行の添付文書の記載内容から変更はない。</td></tr>
<tr><td>11.2 その他の副作用
<table><tr><th>器官別大分類</th><th>5-10%</th><th>5%未満</th></tr><tr><td>胃腸障害</td><td></td><td>下痢</td></tr><tr><td>一般・全身障害および投与部位の状態</td><td>注射部位紅斑、注射部位そう痒感、注入部位反応</td><td>注射部位硬結、注射部位腫脹、注射部位疼痛、注射部位内出血、注射部位反応、発熱</td></tr><tr><td>免疫系障害</td><td></td><td>過敏症注)</td></tr><tr><td>感染症および寄生虫症</td><td></td><td>上咽頭炎、インフルエンザ</td></tr><tr><td>腎および尿路障害</td><td></td><td>急性腎障害</td></tr></table>注）紅斑、蕁麻疹、そう痒症</td><td>発作性夜間ヘモグロビン尿症患者を対象とした国際共同第Ⅲ相試験（APL2-302 試験）及び C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者を対象とした国際共同第Ⅲ相試験（APL2-C3G-310 試験）で発現した副作用及び CCDS に基づいて設定した。</td></tr>
<tr><td>12. 臨床検査結果に及ぼす影響
凝固検査パネルにシリカ試薬を使用すると、本剤との間に干渉作用が生じ、見かけ上、活性化部分トロンボプラスチン時間（aPTT）が延長するおそ</td><td>現行の添付文書の記載内容から変更はない。</td></tr>
</table>

使用上の注意	設定根拠
れがある。凝固検査パネルにはシリカ試薬を使用しないこと。	
14. 適用上の注意 14.1 薬剤調製時の注意 14.1.1 投与前に、微粒子、変色がないか目視にて確認し、異常が認められた場合は使用しないこと。	現行の添付文書の記載内容から変更はない。
14.2 薬剤投与時の注意 14.2.1 注入部位は、腹部、大腿部、臀部、上腕部とし、順次変更すること。皮膚が敏感な部位、皮膚に異常のある部位（傷、発赤、硬結等）には注射しないこと。	現行の添付文書の記載内容から変更はない。
14.2.2 注入部位が 2 ヵ所の場合は、注入部位の間隔を 8cm 以上あけること。	現行の添付文書の記載内容から変更はない。
14.2.3 シリンジポンプを用いて、約 15～30 分（注入部位が 2 ヵ所の場合）又は約 30～60 分（注入部位が 1 ヵ所の場合）かけて注入すること。シリンジに本剤を充填後、直ちに注入を開始すること。薬剤の調製開始後 2 時間以内に投与を完了すること。	現行の添付文書の記載内容から変更はない。
14.3 薬剤交付時の注意 14.3.1 患者が家庭で保存する場合においては、冷蔵庫内（2～8℃）で保存し、使用期限を超えない範囲で使用するよう指導すること。	現行の添付文書の記載内容から変更はない。
15. その他の注意 15.1 臨床使用に基づく情報 発作性夜間ヘモグロビン尿症患者を対象とした国際共同第Ⅲ相試験及び、C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者を対象とした国際共同第Ⅲ相試験において、本剤に対する抗体の産生が報告されている。［17.3.1 参照］	C3 腎症又は一次性免疫複合体型膜性増殖性糸球体腎炎患者を対象とした国際共同第Ⅲ相試験（APL2-C3G-310 試験）の結果に基づき追記した。
15.2 非臨床試験に基づく情報 ウサギ及びカニクイザルを用いた反復投与毒性試験において、本剤の臨床最大用量投与時の 0.06 倍及び 1.27 倍の曝露量で、全身の器官・組織のマク	現行の添付文書の記載内容から変更はない。

使用上の注意	設定根拠
ロファージの空胞化、脳脈絡叢及び滑膜の上皮細胞の空胞化、並びに腎臓の尿細管変性が認められた。これらの空胞化形成は、長鎖ポリエチレングリコール（PEG）の蓄積に関連した変化と考えられ、回復性があり機能障害は認められなかった。また、腎臓の尿細管変性について、腎機能障害の徴候は認められず、臨床的意義及び機能的影響は不明である。	

（下線部：追記、変更）

エムパベリ®皮下注 1080 mg

＜ペグセタコプラン＞

（C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎）

第 1 部（モジュール 1）
申請書等行政情報及び添付文書に関する情報

1.9　一般的名称に係る文書

Swedish Orphan Biovitrum Japan 株式会社

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目次

1.9　一般的名称に係る文書.....3
1.9.1　医薬品の一般的名称に関する資料.....3
1.9.2　医薬品の国際一般名称に関する資料.....3

1.9 一般的名称に係る文書

1.9.1 医薬品の一般的名称に関する資料

令和 4 年 4 月 18 日付薬生薬審発 0418 第 1 号により通知された。

［1.9.1_医薬品の一般的名称に関する資料］参照。

1.9.2 医薬品の国際一般名称に関する資料

［1.9.2_医薬品の国際一般名称に関する資料］参照。

エムパベリ®皮下注 1080 mg

＜ペグセタコプラン＞

（C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎）

第 1 部（モジュール 1）
申請書等行政情報及び添付文書に関する情報

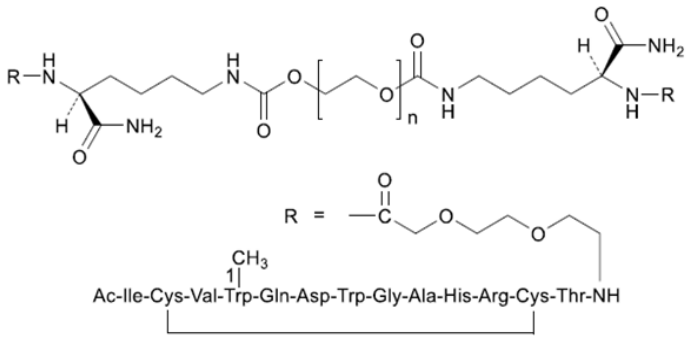
1.10　毒薬・劇薬等の指定審査資料のまとめ

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1.10 毒薬・劇薬等の指定審査資料のまとめ

＜現行＞

化学名・別名	ペグセタコプランはPEG化ペプチド（分子量：約43,500）であり，補体C3に結合する2本の同一の合成ペプチドが，C末端リシンアミドのε-アミノ基を介してポリエチレングリコール（分子量：約39,600）の両端にそれぞれ結合している．ペプチド部分は15個のアミノ酸残基からなる．化学名は以下の通りである． *O,O'*-ビス[(S^2,S^{12}-シクロ{*N*-アセチル-L-イソロイシル-L-システイニル-L-バリル-1-メチル-L-トリプトフィル-L-グルタミニル-L-α-アスパルチル-L-トリプトフィルグリシル-L-アラニル-L-ヒスチジル-L-アルギニル-L-システイニル-L-スレオニル-2-[2-(2-アミノエトキシ)エトキシ]アセチル-L-リシンアミド})-$N^{6\ 15}$-カルボニル]ポリエチレングリコール （別名：ペグセタコプラン）
構造式	 nは約800~1100である.
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、ペグセタコプランとして 1 回 1080 mg を週 2 回皮下投与する。なお、十分な効果が得られない場合には、1 回 1080 mg を 3 日に 1 回の間隔で皮下投与することができる。
劇薬等の指定	劇薬（原体、製剤）
市販名及び有効成分・分量	原体：ペグセタコプラン 製剤：エムパベリ皮下注 1080mg （1 バイアル中にペグセタコプラン 1080 mg を含む）

毒性

急性：

動物種	投与経路	投与量（mg/kg）	最大非致死量（mg/kg）
ウサギ[#1]	皮下	7、28、140	雌雄：140
サル[#2]	皮下	7、28、140	雌雄：140
サル[#3]	皮下	28、140	雄：140

#1 単回投与毒性試験は実施していない。ウサギを用いた 28 日間毒性試験（13CATX-003）の初回投与後の情報。
#2 単回投与毒性試験は実施していない。サルを用いた 28 日間毒性試験（13CATX-004）の初回投与後の情報。
#3 単回投与毒性試験は実施していない。サルを用いた安全性薬理試験（13CATX-005）の本剤投与後の情報。

亜急性：

動物種	投与経路	投与量（mg/kg/日）	投与スケジュール	無毒性量（mg/kg/日）	主な所見
ウサギ	皮下	7、28、140	1 日 1 回 28 日間	28	腎尿細管変性（140 mg/kg/日）
サル	皮下	7、28、140	1 日 1 回 28 日間	7	腎尿細管変性（28 mg/kg/日及び 140 mg/kg/日）

慢性：

動物種	投与経路	投与量（mg/kg/日）	投与スケジュール	無毒性量（mg/kg/日）	主な所見
ウサギ	皮下	1、7、28	1 日 1 回 6 ヵ月間	1 未満	腎尿細管変性（全投与量）
サル	皮下	1、7、28	1 日 1 回 9 ヵ月間	7	腎尿細管変性（28 mg/kg/日）

副作用

国際共同第 3 相臨床試験（APL2-302 試験）において、本剤投与を受けた 80 例中 39 例（48.8%）に副作用が認められた。

副作用の種類	例数
注射部位紅斑	12
注射部位硬結	5
注射部位そう痒感	5
注射部位反応	5
注射部位腫脹	5

会社

Swedish Orphan Biovitrum Japan 株式会社　製剤：輸入

＜追加・変更＞（下線部）

<table>
<tr><td>化学名・別名</td><td></td></tr>
<tr><td>構造式</td><td></td></tr>
<tr><td>効能・効果</td><td>○発作性夜間ヘモグロビン尿症
○C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎</td></tr>
<tr><td>用法・用量</td><td>＜発作性夜間ヘモグロビン尿症＞
通常、成人には、ペグセタコプランとして 1 回 1080 mg を週 2 回皮下投与する。なお、十分な効果が得られない場合には、1 回 1080 mg を 3 日に 1 回の間隔で皮下投与することができる。
＜C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎＞
通常、18 歳以上の患者にはペグセタコプランとして 1 回 1080 mg を週 2 回皮下投与する。
通常、12 歳以上 18 歳未満の患者にはペグセタコプランとして体重に基づいて下表に示す投与量を週 2 回皮下投与する。
投与量換算表
<table>
<tr><th>体重</th><th>初回投与量</th><th>2回目投与量</th><th>3回目以降投与量</th></tr>
<tr><td>50 kg以上</td><td>1080 mg</td><td>1080 mg</td><td>1080 mg</td></tr>
<tr><td>35 kg以上50 kg未満</td><td>648 mg</td><td>810 mg</td><td>810 mg</td></tr>
<tr><td>30 kg以上35 kg未満</td><td>540 mg</td><td>540 mg</td><td>648 mg</td></tr>
</table>
</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td></td></tr>
<tr><td>毒性</td><td></td></tr>
<tr><td>副作用</td><td>＜発作性夜間ヘモグロビン尿症＞
国際共同第 3 相臨床試験（APL2-302 試験）において、本剤投与を受けた 80 例中 39 例（48.8%）に副作用が認められた。
<table>
<tr><th>副作用の種類</th><th>例数</th></tr>
<tr><td>注射部位紅斑</td><td>12</td></tr>
<tr><td>注射部位硬結</td><td>5</td></tr>
<tr><td>注射部位そう痒感</td><td>5</td></tr>
<tr><td>注射部位反応</td><td>5</td></tr>
<tr><td>注射部位腫脹</td><td>5</td></tr>
</table>
＜C3 腎症、一次性免疫複合体型膜性増殖性糸球体腎炎＞
国際共同第 3 相臨床試験（APL2-C3G-310 試験）において、本剤投与を受けた 120 例中 49 例（40.8%）に副作用が認められた。
<table>
<tr><th>副作用の種類</th><th>例数</th></tr>
<tr><td>注射部位そう痒感</td><td>5</td></tr>
<tr><td>そう痒症</td><td>5</td></tr>
<tr><td>注入部位そう痒感</td><td>4</td></tr>
<tr><td>注入部位腫脹</td><td>4</td></tr>
<tr><td>注射部位腫脹</td><td>4</td></tr>
<tr><td>発熱</td><td>4</td></tr>
<tr><td>頭痛</td><td>4</td></tr>
</table>
</td></tr>
<tr><td>会社</td><td></td></tr>
</table>

第3 部（モジュール3）：品質に関する文書

該当なし

第4 部（モジュール4）：非臨床試験報告書

該当なし

第5 部（モジュール5）：臨床試験報告書

資料番号	試験番号	表題	国内/海外	社内資料/公表論文	評価資料/参考資料	申請電子データの有無
5.2 全臨床試験一覧表						
5.2	－	臨床試験一覧表	－	社内資料	－	無
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						
5.3.1.4.1-1	BIO.VR.0210-1989.06	Validation of an LC-MS/MS Assay for Determination of APL-2 in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.1-2	BIO.VR.0210-2629.02	Cross-Validation of LC-MS/MS Assays for the Determination of APL-2 in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.1-3	AV21-190 Amendment 1	Amendment 1 to HPLC/MS/MS Assay Validation for the Determination of APL-2 from Human Serum High Range	海外	社内資料	参考資料	無
5.3.1.4.1-4	AV21-190 Addendum 1	Addendum 1 to HPLC/MS/MS Assay Validation for the Determination of APL-2 from Human Serum High Range	海外	社内資料	参考資料	無

第5 部（モジュール5）：臨床試験報告書

資料番号	試験番号	表題	国内/海外	社内資料/公表論文	評価資料/参考資料	申請電子データの有無
5.3.1.4.1-5	AV21-190 Addendum 2	Interference and Stability in the Presence of C3G and IC-MPGN Disease State Serum Addendum 2 to HPLC/MS/MS Assay Validation for the Determination of APL2 from Human Serum High Range	海外	社内資料	参考資料	無
5.3.1.4.2-1	BAL-23-143-160-REP	Validation of a Direct Binding Assay for the Detection of Antibodies Against Pegcetacoplan Peptide in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.2-2	BAL-23-143-160.01-REP	Validation of a Direct Binding Assay for the Detection of Antibodies Against Pegcetacoplan Peptide in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.3-1	BAL-17-143-050.02-REP	Validation of a Direct Binding ELISA for the Detection of Antibodies Against PEG in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.3-2	BAL-17-143-050.03-REP	Validation of a Direct Binding ELISA for the Detection of Antibodies Against PEG in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.3-3	BAL-17-143-050.04-REP	Validation of a Direct Binding ELISA for the Detection of Antibodies Against PEG in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.3-4	BAL-17-143-050.05-REP	Validation of a Direct Binding ELISA for the Detection of Antibodies Against PEG in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.3-5	181686VRDW-APWM	Validation of a Bead-Based Sandwich ELISA for the Detection of anti-PEG Antibodies in Human Serum	海外	社内資料	参考資料	無
5.3.1.4.4	BAL-23-143-161-REP	Validation of a Competitive Ligand Binding Electrochemiluminescent Immunoassay in Human Serum for the Detection of Neutralizing Anti-Pegcetacoplan Antibodies	海外	社内資料	参考資料	無
5.3.1.4.5-1	24NJH-PDMVR-002	NJH AHSO Microplate Hemolytic Assay Validation Summary	海外	社内資料	参考資料	無

第5 部（モジュール5）：臨床試験報告書

資料番号	試験番号	表題	国内/海外	社内資料/公表論文	評価資料/参考資料	申請電子データの有無
5.3.1.4.5-2	EXVAL.003.02	Validation Report EXVAL.Report.003.02 AH50 HEMOLYTIC ASSAY	海外	社内資料	参考資料	無
5.3.1.4.5-3	24NJH-PDMVR-007	NJH Complement C1q Level Assay Validation Summary	海外	社内資料	参考資料	無
5.3.1.4.5-4	24NJH-PDMVR-012	NJH Complement C3 Assay Validation Summary	海外	社内資料	参考資料	無
5.3.1.4.5-5	14MRL-PDMVR-001	Complement C3 in Plasma by Nephelometry on Siemens BNII	海外	社内資料	参考資料	無
5.3.1.4.5-6	17MRL-PDMVR-001	Complement C3 in Serum and Plasma by Nephelometry on Siemens BNII	海外	社内資料	参考資料	無
5.3.1.4.5-7	24ECL-PDMVR-005	Method Performance Sheet_[redacted]_Complement C3c and C4_Roche Cobas	海外	社内資料	参考資料	無
5.3.1.4.5-8	24NJH-PDMVR-008	NJH Complement C3a Assay Validation Summary	海外	社内資料	参考資料	無
5.3.1.4.5-9	EXVAL.REPORT.004.01	Validation Report EXVAL.Report.004.01 Validation of Assay Quidel C3a ELISA	海外	社内資料	参考資料	無
5.3.1.4.5-10	23ARL-PDMVR-001	IHCDSOP 186 C3c PIF SOP Validation IQCP and PT	海外	社内資料	参考資料	無
5.3.1.4.5-11	EXVAL.REPORT.024.01	Validation Report EXVAL.Report.024.01 Validation of Assay Quidel IC3b ELISA	海外	社内資料	参考資料	無
5.3.1.4.5-12	24NJH-PDMVR-003	NJH Complement C3-Nephritic Factor Assay Validation Summary	海外	社内資料	参考資料	無
5.3.1.4.5-13	24NJH-PDMVR-010	NJH Complement C4 Assay Validation Summary	海外	社内資料	参考資料	無

第5 部（モジュール5）：臨床試験報告書

資料番号	試験番号	表題	国内/海外	社内資料/公表論文	評価資料/参考資料	申請電子データの有無
5.3.1.4.5-14	24NJH-PDMVR-006	NJH Complement CSa Assay Validation Summary	海外	社内資料	参考資料	無
5.3.1.4.5-15	EXVAL.REPORT.007.01	Validation Report EXVAL.Report.007.01 Validation of Assay for C5a Measurement by Quidel ELISAQuidel C5a ELISA	海外	社内資料	参考資料	無
5.3.1.4.5-16	24NJH-PDMVR-001	NJH CH50 Microplate Hemolytic Assay Validation Summary	海外	社内資料	参考資料	無
5.3.1.4.5-17	EXVAL.002.04	Validation Report EXVAL.002.04 Hemolytic Assay, CH50 Total Classical Pathway Function	海外	社内資料	参考資料	無
5.3.1.4.5-18	IM-VER-016.001	18NJH-PDMVR-001 Validation Report	海外	社内資料	参考資料	無
5.3.1.4.5-19	24NJH-PDMVR-011	Phospholipase A2 Receptor (PLA2R) Antibody, IgG with Reflex to Titer	海外	社内資料	参考資料	無
5.3.1.4.5-20	24NJH-PDMVR-005	NJH Complement sCSb-9 Assay Validation Summary	海外	社内資料	参考資料	無
5.3.1.4.5-21	EXVAL.REPORT.005.2.04	Validation Report EXVAL.005.2.04 Quidel SC5b-9 ELISA	海外	社内資料	参考資料	無
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						
5.3.2.1 血漿蛋白結合試験報告書：該当なし						
5.3.2.2 肝代謝及び薬物相互作用試験報告書：該当なし						
5.3.2.3 他のヒト生体試料を用いた試験報告書：該当なし						
5.3.3 臨床薬物動態（PK）試験報告書						

第5 部（モジュール5）：臨床試験報告書

資料番号	試験番号	表題	国内/海外	社内資料/公表論文	評価資料/参考資料	申請電子データの有無
5.3.3.1 健康被験者における PK 及び初期忍容性試験報告書：該当なし						
5.3.3.2 患者における PK 及び初期忍容性試験報告書：該当なし						
5.3.3.3 内因性要因を検討した PK 試験報告書：該当なし						
5.3.3.4 外因性要因を検討した PK 試験報告書：該当なし						
5.3.3.5 ポピュレーション PK 試験報告書						
5.3.3.5.1	APL-EX25-CP-020	Modeling Analysis Report Updated Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Modeling of Pegcetacoplan (APL-2) in Patients with C3 Glomerulopathy or Primary Immune-Complex Membranoproliferative Glomerulonephritis	国内/海外	社内資料	評価資料	有
5.3.3.5.2	APL-EX20-CP-001	POPULATION MODELING ANALYSIS REPORT POPULATION PHARMACOKINETIC AND EXPOSURERESPONSE MODELING TO SUPPORT CLINICAL DEVELOPMENT OF PEGCETACOPLAN (APL-2) IN PEDIATRIC PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA	国内/海外	社内資料	参考資料	無
5.3.4 臨床薬力学（PD）試験報告書						
5.3.4.1 健康被験者における PD 試験及び PK/PD 試験報告書：該当なし						
5.3.4.2 患者における PD 試験及び PK/PD 試験報告書：該当なし						

第5 部（モジュール5）：臨床試験報告書

資料番号	試験番号	表題	国内/海外	社内資料/公表論文	評価資料/参考資料	申請電子データの有無
5.3.5 有効性及び安全性試験報告書						
5.3.5.1 申請する適応症に関する比較対照試験報告書						
5.3.5.1.1-1	APL2-C3G-204 12W	An Open-Label, Randomized, Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Pegcetcoplan in the Treatment of Post-Transplant Recurrence of C3G or IC-MPGN	海外	社内資料	評価資料	有
5.3.5.1.1-2	APL2-C3G-204 52W	An Open-Label, Randomized, Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Pegcetcoplan in the Treatment of Post-Transplant Recurrence of C3G or IC-MPGN	海外	社内資料	評価資料	有
5.3.5.1.2-1	APL2-C3G-310 26W	A Phase 3, Randomized, Placebo-Controlled, Double-Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients With C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis	国内/海外	社内資料	評価資料	有
5.3.5.1.2-2	APL2-C3G-310 52W	A Phase 3, Randomized, Placebo-Controlled, Double-Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients With C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis	国内/海外	社内資料	評価資料	有
5.3.5.2 非対照試験報告書						
5.3.5.2.1-1	APL2-201 Interim	A Phase 2 Study to Evaluate the Safety and Biologic Activity of APL-2 in Patients With IgA Nephropathy, Lupus Nephritis, Primary Membranous Nephropathy, or C3 Glomerulopathy (C3 Glomerulonephritis and Dense Deposit Disease)	海外	社内資料	参考資料	無

第5 部（モジュール5）：臨床試験報告書

資料番号	試験番号	表題	国内/海外	社内資料/公表論文	評価資料/参考資料	申請電子データの有無
5.3.5.2.1-2	APL2-201 Final	A Phase 2 Study to Evaluate the Safety and Biologic Activity of APL-2 in Patients With IgA Nephropathy, Lupus Nephritis, Primary Membranous Nephropathy, or C3 Glomerulopathy (C3 Glomerulonephritis and Dense Deposit Disease)	海外	社内資料	参考資料	無
5.3.5.2.2	APL2-C3G-314 Interim	An Open-Label, Nonrandomized, Multicenter Extension Study to Evaluate the Long-term Safety and Efficacy of Pegcetacoplan in Participants with C3 Glomerulopathy or Immune-Complex Membranoproliferative Glomerulonephritis	国内/海外	社内資料	参考資料	有
5.3.5.3 複数の試験成績を併せて解析した報告書：該当なし						
5.3.5.4 その他の臨床試験報告書：該当なし						
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 for Active substance: pegcetacoplan PSUR [redacted], 20[redacted] - [redacted], 20[redacted]	－	社内資料	参考資料	－
5.3.6.2	－	Periodic safety update report for Active substance: pegcetacoplan PSUR [redacted], 20[redacted] - [redacted], 20[redacted]	－	社内資料	参考資料	－
5.3.7 患者データ一覧表及び症例記録						
5.3.7.2	－	副作用一覧表	－	社内資料	－	－
5.3.7.3	－	重篤な有害事象一覧表	－	社内資料	－	－

第5 部（モジュール5）：臨床試験報告書

資料番号	試験番号	表題	国内/海外	社内資料/公表論文	評価資料/参考資料	申請電子データの有無
5.3.7.4	－	臨床検査値一覧表	－	社内資料	－	－

第5 部（モジュール5）：臨床試験報告書

5.4 参考文献

資料番号	表題/著者/掲載誌
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