5.04 GIVOSIRAN, Solution for injection 189 mg in 1 mL, Givlaari®, MEDISON PHARMA AUSTRALIA PTY LIMITED

1 Purpose of submission

1.1 The Category 1 submission requested a General Schedule Authority Required listing for the initial treatment and an Authority Required (STREAMLINED) listing for the continuing treatment of Acute Hepatic Porphyria (AHP) in adults and adolescents aged 12 years and older.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care (BSC) which was based on review of locally available therapies and consultation with Australian clinical experts involved in the treatment of AHP.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults and adolescents aged 12 years and older with AHP. The proposed PBS listing is for patients with a confirmed diagnosis and recurrent disease, defined as ≥2 porphyria attacks requiring hospitalisation, presentation at an emergency department or medical intervention via a porphyria clinic within the 6 months prior to treatment initiation.
Intervention	Givosiran 2.5 mg/kg body weight once monthly, administered as a subcutaneous injection by a healthcare professional
Comparator	Best supportive care (BSC), which includes: Rescue therapy for acute attacks, including IV hemin (via the Special Access Scheme) Supportive therapy for chronic symptoms such as pain, hypertension, gastrointestinal issues, and sleep or mood disorders (i.e., opioids, OTC analgesics) Preventative therapy, not TGA-registered for AHP (i.e., GnRH analogues for women, prophylactic IV hemin)
Outcomes	Annualised number of acute attacks (defined as porphyria attacks requiring hospitalisation, an urgent healthcare visit or treated with IV hemin at home) Porphyrin precursor concentrations in urine Chronic symptoms: levels of pain, nausea and fatigue Safety Quality of life and other patient-rated outcomes.
Clinical claim	In adults and adolescents with AHP, givosiran is superior to BSC at reducing the frequency and severity of porphyria attacks, and non-inferior in terms of safety.

Source: Table 1.1, p13 of the submission
Abbreviations: AHP, acute hepatic porphyria; BSC, best supportive care; GnRH, gonadotropin-releasing hormone; IV, intravenous; OTC, over the counter; TGA, Therapeutic Goods Administration

2 Background

Registration status

2.1 Givosiran was TGA registered on 16 November 2023 for the treatment of AHP in adults and adolescents aged 12 years and older.

3 Requested listing

3.1 Secretariat suggested changes to the restriction are shown below; suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
GIVOSIRAN					
Givosiran, (189mg per 1ml vial)*, solution for SC injection	$153,585.94 published price $[redacted] effective price	2	2	5	GIVLAARI®, Medison Pharma Australia Pty Ltd

Restriction Summary NEW1 / Treatment of Concept: NEW1A	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ General Schedule
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required – *full assessment (in writing only via post/HPOS upload)*
Prescribing rule	***Administrative Advice:*** *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Special Pricing Arrangements apply.*
	Indication: Chronic treatment of Acute Hepatic Porphyria (AHP)
	Treatment Phase: *Initial* treatment ~~Initiation 1: New patient~~
	Clinical criteria:
	Patient must have ~~C~~confirmed diagnosis of AHP based on clinical features ~~(e.g., acute attacks of abdominal, back, chest, extremities, and/or limb pain)~~
	AND
	Clinical criteria:
	~~Documented urinary or plasma porphobilinogen or delta-aminolevulinic acid value~~ *~~at least~~* ~~≥4× *times greater than* upper limit of normal (ULN) on at least one occasion within the past year~~
	Patient must have a previous result that showed a 4 times greater than upper limit of the normal (ULN) on one of the following tests: (i) urinary porphobilinogen, (ii) plasma porphobilinogen, (iii) or delta-aminolevulinic acid
	AND
	Clinical criteria:
	Patient must have had ~~Active disease, with~~ at least 2 porphyria attacks *within the 6 months prior to (i) commencement of this drug or (ii) prophylactic treatment with gonadotropin-releasing hormone analogues or hemin requiring: (i)* hospitalisation, *(ii)* presentation at an emergency department*, or (iii)* ~~or~~ medical intervention via a porphyria clinic ~~within the 6 months prior to treatment initiation~~
	AND
	Clinical criteria:
	Patient must not have previously undergone a liver transplant.
	Treatment criteria:
	~~Treatment should~~ *Must* be initiated under the supervision of a healthcare professional experienced in the management of porphyria.
	Population criteria:
	Patient must be aged 12 years or older.
	Prescribing Instructions*:* *For the purposes of administering this restriction clinical features to confirm a diagnosis of AHP can include, but are not limited to acute attacks of: abdominal, back, chest, extremities, and/or limb pain.*

	Prescribing Instructions: At the time of the authority application, prescribers should request the appropriate number of vials for a single dose based on the patient's weight, as per *the TGA approved* Product Information
	Prescribing Instructions: *The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include:* *(1) The baseline number of porphyria attacks within a defined 6-month period [dates of the 6-month period must be included]* *(2) pathology measurements that indicate 4 times greater than the ULN of one of the following tests: (i) urinary porphobilinogen, (ii) plasma porphobilinogen, (iii) delta-aminolevulinic acid. Date of pathology report and unique identifying number/code that links the pathology result to the individual patient must be included.* *(3) current weight of the patient*
	Prescribing Instructions: *If the application is submitted through HPOS form upload or mail, it must include:* *(i) details of the proposed prescription; and* *(ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*
	Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)* *Alternatively, applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
Restriction Summary NEW2 / Treatment of Concept: NEW2A	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ General schedule
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED)
Prescribing rule	***Administrative Advice:*** *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Special Pricing Arrangements apply.*
	Indication: Chronic treatment of Acute Hepatic Porphyria (AHP)
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must demonstrate improvement in the frequency or severity of AHP attacks *from baseline* while on treatment with this drug
	AND
	Clinical criteria:
	Must be treated by a healthcare professional experienced in the management of porphyria or in consultation with a healthcare professional experienced in the management of porphyria.

	AND
	Clinical criteria:
	Patient must not have previously undergone a liver transplant.
	Population criteria:
	Patient must be aged 12 years or older.
	***Prescribing Instructions**:* *The number of AHP attacks while on treatment must be documented in the patients' medical records*
	Prescribing Instructions: At the time of the authority application, prescribers should request the appropriate number of vials for a single dose based on the patient's weight, as per *the TGA approved* Product Information

Source: Table 1.9, p32, Table 1.10, p33, Table 1.11, p34, Table 1.12, p34 of the submission.

3.2 The proposed ex-manufacturer price for givosiran was $[redacted] per vial. The maximum quantity and resulting dispensed price for maximum quantity (DPMQ, $[redacted]) was based on two vials of givosiran, however the submission claimed that the average quantity used in ENVISION was 1.2 vials and so most patients will require only one vial. At a recommended dose of 2.5 mg/kg, one vial is needed for a patient body weight of up to 75.6 kg, and two vials for a body weight above 75.6 kg.

3.3 While the specified criteria for an acute attack (defined as requiring hospitalisation, presentation at an emergency department or medical intervention via a porphyria clinic) in the requested restriction was reasonably consistent with the definition of an attack in ENVISION, attacks which did not result in medical intervention (which may be related to accessibility to treatment rather than severity) would not be considered in the eligible criteria and this may present an equity issue. The Sub-Committees noted that clinicians treating patients through porphyria clinics would try to avoid hospitalisations during attacks, and commented that the inclusion of "medical intervention via a porphyria clinic" in the proposed restriction was appropriate in including attacks that could be managed without hospitalisation.

3.4 Further, the definition of acute attack based on Stein 2023 (which was referenced by Australian clinicians from a focus group conducted by the sponsor, see Figure 1) was more prescriptive in terms of symptoms of the acute attack being specifically described, and also required significantly elevated porphobilinogen (PBG)/creatinine ratio. As such, it was unclear whether the definition of acute attack in the requested restriction was sufficient. The required number of attacks (at least two attacks within the six months prior to treatment initiation) was consistent with the inclusion criteria in ENVISION.

Figure 1: Definition of acute porphyria attack in the Delphi consensus led by the European porphyria network

Acute porphyria attack	*An acute porphyria attack* is an episode that includes: 2 or more of the following manifestations typically persisting for more than 24 h in the absence of other likely explanations. AND significantly increased urinary PBG/creatinine ratio.[b] • Intense pain, severe enough to require hospital admission, is a feature of nearly all attacks. Pain is most common in the abdomen but may affect other areas such as the back, legs, arms, or chest • Nausea, vomiting, and/or constipation • Systemic arterial hypertension and/or tachycardia • Hyponatraemia • Peripheral neuropathy (e.g., muscle weakness, paralysis or reduced tendon reflexes) • Urinary retention or incontinence • Central nervous system involvement (e.g., seizures, confusion, reduced consciousness, psychosis, or posterior reversible encephalopathy syndrome on MRI scan) *2a. A severe acute porphyria attack* is associated with 1 or more of the following features: significant hyponatraemia, peripheral neuropathy, urinary retention or incontinence, central nervous system involvement, arrhythmias. Note that attack severity may evolve, and any attack may rapidly become severe.

Source: Figure 1, Summary of Clinician Input including Focus group meeting, taken from Stein 2023

[b] Considerations in the interpretation of Urine PBG/creatinine ratio: (1) The quality of the PBG analysis should be within specifications set by Epnet EQAS(or another EQA organisation). (2) PBG/creatinine ratio is typically increased to more than 10 times the upper limit of normal during attacks. However, if the upper limit of normal is ≤1 µmol/mmol creatinine (e.g., when measured by mass spectrometry), a result above

10 µmol/mmol creatinine is expected during attacks. (3) If the patient's PBG when asymptomatic is higher than 10 times the upper limit of normal or more than 10 µmol/mmol creatinine if measured by mass spectrometry, a significant further increase above baseline is expected during attacks. (4) In AIP, PBG/creatinine typically remains elevated for many years after or between attacks. (5) In VP and HCP, PBG/creatinine may fall to normal once the attack has resolved. (6) APBG/creatinine ratio of 4 times the upper limit of normal is equivalent to 4 µmol/mmol creatinine if measured by mass spectrometry.

3.5 The submission requested an alternative initiation restriction for a small population of patients who have a documented history of acute porphyria attacks within six months prior to the initiation of off-label prophylactic treatment with gonadotropin-releasing hormone (GnRH) analogues or hemin. The submission claimed that this criterion was proposed by Australian clinical experts who expressed concern that patients with refractory, persistent disease who have started off-label prophylaxis (e.g., GnRH analogues or hemin) in the absence of other non-surgical preventive options would need to cease their prophylaxis and wait for two life-threatening attacks to qualify for givosiran treatment. The Sub-Committees agreed with the submission that it was appropriate for the restrictions to allow patients on prophylactic treatment, with a documented history of acute porphyria attacks (as per the initiation criteria), to receive treatment with givosiran without the need to demonstrate additional attacks and noted that the Secretariat revised restrictions addressed this concern.

3.6 The submission requested a grandfathering restriction which will apply to eight patients currently receiving treatment through the Expanded Access Program (EAP). It was noted that grandfathered patients must also have had a documented history of at least two porphyria attacks prior to initiation of givosiran. Providing they meet the criteria for diagnosis of AHP, these patients would be eligible for treatment under the initial treatment restriction with Secretarial revisions.

3.7 The submission's clinical criteria for diagnosis were broader than the enrolment criteria in ENVISION, as the requested restriction does not include the requirement of genetic testing which was conducted for the ENVISION trial (though patients without an identified AHP-related genetic variant were eligible for the study on the basis of

clinical features accompanied by supportive biochemical criteria. The Commentary considered this would mean that there is potential for misdiagnosis. The Sub-Committees noted that the submission claimed that an identified variant is not essential for diagnosis since it is known that mutations cannot be found in a small proportion of patients (<5%) with the disease. The Sub-committees considered that diagnosis based on clinical features and diagnostic biochemical criteria (as proposed in the restrictions) was appropriate.

3.8 The proposed continuation criteria require patients to "demonstrate improvement in the frequency or severity of AHP attacks while on treatment". However, it was unclear from the submission how this clinical benefit would be objectively measured in practice as there was no requirement for clinicians or patients to establish a background rate or severity of attack (or what instrument would be used to measure the severity of attack) prior to treatment. The Sub-Committees noted that assessment of response relied on clinical judgement, but considered that this was reasonable. The Sub-Committees noted that it is likely that patients would trial discontinuation of treatment as some stage, especially for women who have reached menopause.

3.9 The criteria in the submission's requested restriction do not require the discontinuation of prophylactic hemin, whereas all patients must have discontinued prophylactic hemin prior to treatment in ENVISION. The submission indicated that givosiran would be used in addition to best supportive care (including hemin), however the Sub-committees noted that patients are unlikely to continue prophylactic treatment with hemin as it is associated with substantial safety concerns (see also paragraph 5.6).

3.10 The requested restriction specified that patients who have previously undergone a liver transplant were not eligible for givosiran treatment. However, patients who have previously had oophorectomy or hysterectomy remain eligible. Patients who had previously undergone a liver transplant were not specifically excluded from the submission's financial estimates, but this may have been accounted for in other ways (i.e. the proportion of patients presenting with an attack).

3.11 The Sub-Committees noted that the submission proposed limiting treatment to patients 12 years or older. The trial did not enrol any patients 12-18 years, though they were not excluded. The Sub-Committees noted that AHP does not typically present until early adulthood.

3.12 The Sub-Committees noted that the submission proposed limiting initiation of treatment to patients under the supervision of a healthcare professional experienced in the management of porphyria. The Sub-Committees considered it was reasonable not to further specify the specialist groups who can prescribe givosiran.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Porphyria comprises a family of rare genetic diseases, resulting from a partial deficiency in the activity of one of the eight enzymes responsible for haem synthesis. Porphyria is typically classified as erythropoietic or hepatic, depending on whether the major site of accumulation of haem precursor is erythroid related (e.g., bone marrow) or hepatic (liver), and as neurologic or cutaneous depending on the cardinal clinical manifestations. The four types of AHP are acute intermittent porphyria (AIP, the most common type), variegate porphyria (VP), hereditary coproporphyria (HCP) and the ultra-rare ALA dehydratase deficiency porphyria (ADP), each resulting from a different enzyme deficiency.

4.2 Although each AHP subtype arises from variants of unique genes, they all result in depletion of the hepatic free haem pool and induction of delta-aminolevulinic acid synthase 1 (ALAS1), the first and rate-limiting enzyme in the eight-step pathway of haem biosynthesis in the liver. In patients with AHP, whose haem biosynthesis is dysfunctional, the upregulation of ALAS1 can lead to increased levels of haem precursors.

4.3 All four subtypes of AHP are characterised by acute neurovisceral symptoms that are clinically indistinguishable (Balwani 2017) though patients with HCP and VP may additionally experience cutaneous phototoxicity and skin lesions due to a build-up of porphyrins in the skin of dermal blood vessels (Balwani 2017).

4.4 The prevalence of AHP in Australia is unknown, but based on European data reported by Elder 2013, it is estimated at 10.06 per million (1.06 per 100,000). Elder 2013 reported AIP and VP prevalence at 5.9 and 3.2 per million, respectively.

4.5 The submission claimed five Australian clinical experts who attended a sponsor-run focus group explained that AIP is the most common AHP subtype they manage in their respective clinics (60%–80% of cases). In addition, Australian clinical experts noted the VP and HCP subtype may be more common in Australia than internationally; however, AIP is still the dominant subtype in Australia in terms of prevalence and severity and associated with the majority of acute attacks.

4.6 The distribution of AHP subtypes in Australia from the focus group meeting could not be verified based on the summary provided. The summary did note that AIP is the dominant subtype in Australia and accounts for ~80% of acute attacks.

4.7 The submission noted that individuals experiencing AHP for the first time usually present between the ages of 18 and 35 years, with a typical onset after puberty, trauma, or pregnancy. According to Orphanet[1], a comprehensive online resource on rare diseases, approximately 80% of individuals with AHP are women, typically aged between 20 and 45 years. Additionally, an expert review by Wang 2023, stated that

[1] https://www.orpha.net/en/disease/detail/95157 accessed 12 May 2025

attacks are rare before the onset of menses or after menopause. Clinical experts from the Canadian Agency for Drugs and Technologies in Health (CADTH) also stated that the disease is expected to improve at the time of menopause for all female patients with AHP (i.e., severity and frequency of attacks is expected to decrease) (p155, CADTH 2021[2]). In the economic evaluation, the age of menopause onset and assumptions around symptoms post menopause are important factors.

4.8 During acute attacks, patients may clinically present with intense, usually diffuse, and increasingly persistent abdominal pain and muscle weakness followed by nausea and vomiting, constipation or diarrhoea, hypertension, tachycardia, pain in the limbs, head, neck or chest, fever, and neurological symptoms, including confusion, hallucinations, convulsions, and seizures (Szlendak 2016).

4.9 In EXPLORE, a prospective, multinational, natural history study of patients with AHP with recurrent attacks (n=112, mean age: 39.3 years) (Gouya 2019), chronic symptoms were reported by 65% (73/112) of patients. Of these patients, the submission noted that 71% (52/73) reported daily symptoms, the most common chronic symptoms were pain, nausea, tiredness, and anxiety. Several long-term complications such as chronic kidney disease (CKD), hepatocellular carcinoma (HCC), hypertension, and psychiatric issues, are associated with AHP, potentially reducing life expectancy.

4.10 However, there is no clear evidence that AHP reduces life expectancy. Baravelli 2020, a study in Norway which examined 333 individuals with a confirmed AHP diagnosis between 1992 and 2017, found that AHP was associated with an 84.4 times higher risk of mortality due to HCC, but no overall increased risk of premature death compared to the general population. Baravelli 2020 was relied upon by the submission in the economic evaluation to inform mortality of patients.

4.11 Diagnosis of AHP in Australia follows the Australian Porphyria Association guidelines, which recommend biochemical testing (urine PBG ± ALA) as the first-line approach, ideally conducted during an acute attack. Elevated levels of PBG and aminolevulinic acid (ALA) are diagnostic markers, though some patients (especially those with AIP) may show elevated levels even outside of attacks. The submission stated that genetic testing is not used for initial diagnosis or treatment decisions but plays a role in familial screening after biochemical confirmation. However, Anderson 2019, identified by the submission in its literature review, suggests genetic confirmation is now standard of care, particularly when biochemical markers are inconclusive.

4.12 Givosiran is a double-stranded small interfering ribonucleic acid (siRNA) that causes degradation of ALAS1 messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. ALAS1 is the first and rate-limiting step of haem synthesis in the liver. Its expression is induced in AHP due to a loss-of-function gene mutation in a downstream haem synthesis enzyme. Givosiran acts to reduce elevated levels of liver ALAS1 mRNA.

[2] CADTH 2021. CADTH Reimbursement Review Givosiran (Givlaari) Canadian Journal of Health Technologies Vol 1(11). https://www.cda-amc.ca/sites/default/files/DRR/2021/SR0679-Givlaari%20combined-meta.pdf

This leads to reduced circulating levels of neurotoxic haem intermediates ALA and PBG, the key causal factors of attacks and other disease manifestations of AHP. Givosiran is intended for use as a long-term therapy.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated BSC as the main comparator, as givosiran is the only disease-modifying therapy that targets the underlying AHP disease process, preventing attacks and addressing chronic pain (Balwani 2020). The Sub-Committees agreed with the Commentary that the nominated comparator was generally reasonable.

5.2 In Australia, BSC for AHP comprises of rescue therapy, supportive therapy and preventative therapy. It was assumed that the type of supportive therapy and preventative therapy required will be dependent on the symptoms and needs of the patient, and may differ between patients.

5.3 Intravenous hemin is currently considered the most effective rescue therapy for acute attacks although there is an absence of high-quality clinical trial evidence (Anderson 2019). Hemin is available as either haem arginate or lyophilised hematin. However, neither haem arginate nor lyophilised hematin are TGA-registered, but the submission claimed that focus Group attendees have advised that they can be ordered via the Special Access Scheme as rescue therapy for AHP patients. Australian clinicians also noted that there are barriers to accessing hemin, and it may take multiple days for patients to receive hemin if they live in rural areas. The Sub-Committees noted that hemin is usually available via larger hospitals, but access in smaller centres can be more difficult and delays are common, with patients with an acute attack often requiring opioid treatment while waiting for treatment. The Sub-Committees noted that patients need, on average, around 5 days of hemin treatment as rescue therapy for an acute attack.

5.4 Carbohydrate loading is another rescue therapy option for patients experiencing an acute attack; however, since reliable data on its effectiveness are lacking, it is typically limited to mild attacks or as a stop-gap measure until hemin can be administered. The submission claimed Australian clinical experts confirmed that, in local practice, glucose loading may be used as an initial treatment for an acute attack (e.g., in the case of a delay to hemin access); however, the response may not be adequate, in which case hemin is subsequently administered.

5.5 Supportive therapy primarily encompasses symptomatic therapy for managing symptoms such as pain, hypertension, tachycardia, nausea, vomiting, and seizures. Opioid-based pain management is often used to address severe abdominal pain in AHP. Mild pain can be treated with paracetamol and anti-inflammatory drugs. The submission notes that Australian clinical experts confirmed the use of neuropathic pain agents for treating pain in AHP. Additionally, the potential for opioid addiction

was raised as a potentially serious complication. The extent of opioid addiction in the management of AHP was not explored in the submission, but was included in the economic model presented in the submission (see Paragraph 6.64).

5.6 Preventative therapy includes hormonal modulation (e.g., GnRH analogues, intrauterine devices (IUDs)) and lifestyle changes to avoid known triggers. The submission noted that although intravenous hemin is indicated as rescue therapy for acute attacks, there remain insufficient data available for prophylaxis with hemin. The UK product monograph explicitly cautions against use of haem arginate as a preventative option since available data are too limited and long-term administration of regular infusions carries the risk of iron overload. Nonetheless, during the evaluation of givosiran by the National Institute for Health and Care Excellence (NICE), the committee concluded that prophylactic haem arginate should be used as the comparator in the economic model, based on its use in the National Health Service (NHS) clinical practice for patients with recurrent porphyria attacks. The submission stated that clinical experts from Australia explained that hemin prophylaxis is not a treatment of choice and that it is only administered infrequently due to the lack of other options. The submission emphasised the uncertain clinical benefits and established harms of prophylactic haem arginate including tachyphylaxis, dependency, and problems maintaining venous access because hemin is damaging to the vasculature. The costs of managing adverse events (AEs) associated with hemin were included in the economic evaluation. The Sub-Committees noted that hemin is used as prophylaxis in some cases, but agreed with the submission that it is not routinely used given its substantial safety concerns.

5.7 The nominated comparator of BSC was well described in the submission and appropriate. It was acknowledged by the submission that rescue therapy (hemin) and other supportive therapies would not be replaced by givosiran. As such, the comparison is more accurately described as givosiran + BSC compared to BSC alone. In the submission's economic model, the use of BSC therapies was assumed to be reduced due to less frequent AHP attacks in patients treated with givosiran. However, no substitution-related cost offsets were considered in the submission's financial estimates.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician noted that diagnosis includes clinical symptoms and biochemical measures, and genetic testing is not required for treatment as multiple genes are involved in AHP and not all are known. The clinician noted AHP is a complex and heterogeneous set of diseases, resulting in a range of impacts on patients, from asymptomatic disease to very severe disease requiring a high level of healthcare resources and resulting in very poor QoL. The

clinician noted some patients have infrequent but severe attacks whereas others experience much more frequent attacks and need long term control. The clinician noted that there are limited options for preventing attacks and treatment largely involves addressing symptoms. In some cases, patients require extended hospitalisation, which is associated with a high cost, especially where patients with seizures or respiratory paralysis require treatment in the ICU and where long-term neurological damage requires lengthy rehabilitation. The clinician noted that many attacks are hormonally triggered and treatments directed to this can include significant procedures (oophorectomy, hysterectomy). Although many patients see an improvement after menopause, not all patients have resolution of attacks, and although not all patients will need to continue treatment, the clinician noted there is a need for ongoing access to givosiran for those who require it. The clinician noted experience with givosiran working well for patients and was supportive of the submission. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (27), health care professionals (5) and organisations (1) via the Consumer Comments facility on the PBS website. Comments from health care professionals noted that patients experience multiple continuous or sporadic symptoms including pain, abdominal symptoms and cognitive changes. Health care professionals with experience treating AHP noted that there is a lack of treatment options for AHP patients. Comments noted treatment with haem arginate is mainly used in response to attacks, though prophylactic infusion is also used to manage recurrent attacks. However, treatment with haem arginate requires inpatient or day-clinic admissions and carries substantial risks (iron overload, vascular occlusion, risk of sepsis, rebound flares and tachyphylaxis). The comments noted that other treatments and procedures to reduce symptoms also carry other major risks and are not suitable for all patients. Input described givosiran as well-tolerated and life-changing due to its effectiveness resulting in significantly reduced or eliminated porphyria attacks, reduced hospital admissions and long-term complications such as renal failure, hypertension and hepatoma. The emotional impacts of managing a condition with unpredictable attacks were also described, with individuals' commonly experiencing anxiety and depression. Input emphasised the major impact givosiran can have on individuals' quality of life, through effective management of symptoms. Input highlighted the potential for givosiran to provide a more equitable treatment option, as its subcutaneous administration could potentially be delivered in community or home settings.

6.3 Patients described current treatments for AHP as ineffective, invasive, difficult to access and associated with serious side effects. Individuals who have received givosiran highlighted the substantial reductions in attack severity and hospitalisations and noted the major difference in quality of life, allowing patients to regain a normal life, restoring independence and the ability to participate in work and study.

Individuals who would like to access treatment also noted the burden of disease in terms of financial implications of disease management, loss of productivity and income, and noted that the cost of givosiran is financially prohibitive. Input from other interested individuals also noted the significant burden on carers and families of people with AHP.

6.4 The PBAC noted the advice received from Porphyria Association Inc (Australia) outlining the impact of AHP on individual quality of life, and the burden of AHP on the Australian health system due to frequent and prolonged hospital admissions. The comments also provided the perspective of patients who have accessed givosiran through clinical trials or compassionate access schemes and described the community desire for access to givosiran.

6.5 The PBAC noted the comments and patient experiences were supportive of the evidence provided in the submission. The PBAC valued the comments provided as the input allowed insight into the patient and health care provider perspective for a rare disease.

Clinical studies/trials

6.6 The submission was based on:

- ENVISION: a randomised, double-blind (DB), head-to-head, phase 3 trial of givosiran 2.5 mg/kg body weight (n=48) or placebo (n=46) once monthly (QM) for 6 months in adults and adolescents (≥12 years old) with a documented diagnosis of AHP and at least two porphyria attacks in the last 6 months (Balwani 2020).
- ENVISION open-label extension (OLE): following the 6-month DB period in ENVISION, all eligible patients had the option to enter a 30-month OLE (93 of 94 (99%) patients randomised in ENVISION continued to ENVISION OLE), in which they received givosiran 2.5 (n=56) or 1.25 (n=37) mg/kg QM[3] (Kuter 2023).

6.7 The submission also presented supplementary evidence in Appendix A to the submission from Study 001 (NCT02452372; Sardh 2019), a phase 1 randomised, placebo-controlled trial, which had three parts (Parts A, B and C). Patients enrolled in Parts A and B were not consistent with the proposed PBS population and these parts of Study 001 are not discussed further. Part C investigated givosiran (2.5 (n=3) or 5.0 (n=3) mg/kg QM; total of four injections), givosiran (2.5 (n=3) or 5.0 (n=4) mg/kg once quarterly; total of two injections) or placebo (n=4) during a 12-week period, starting on day 0 in patients with recurrent attacks (defined as ≥2 attacks within 6 months before the run-in period or receiving scheduled hemin prophylaxis at the start of the run-in period) and were required to have had at least one attack before

[3] Patients entering the OLE period under the original protocol, protocol Amendment 1, or protocol Amendment 2 received givosiran 2.5 mg/kg QM; those entering under protocol Amendment 3 or protocol Amendment 4 patients received givosiran 1.25 mg/kg QM. Upon implementation of protocol Amendment 5, all patients receiving givosiran 1.25 mg/kg QM had their dose increased to givosiran 2.5 mg/kg QM.

randomisation. Also presented was Study 002 (NCT02949830; Sardh 2024): phase 1/2 OLE of Study 001 Part C of givosiran 2.5 mg/kg once per month[4] with treatment up to 48 months in patients with AIP and recurrent attacks who completed Part C of Study 001 (16 of 17 (94%) patients randomised in Study 001 Part C continued to Study 002).

6.8 Details of the trials/studies presented in the submission are provided in Table 2. Only the main publications are presented; each are also associated with a number of conference abstracts.

[4] At entry into the Phase 1/2 OLE study, patients received givosiran at 2.5 mg/kg QM or 5.0 mg/kg QM or every 3 months. After a review of the emerging safety, efficacy, and pharmacokinetic and pharmacodynamic modelling data from the Phase 1 study, all patients transitioned to 2.5 mg/kg QM starting in August 2017, and remained on this dose for the duration of the Phase 1/2 OLE study.

Table 2: Trials/studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ENVISION ALN-AS1-003 NCT03338816	Alnylam Pharmaceuticals. Data on File. ENVISION (ALN-AS1-003) Clinical Study Report (CSR)	2 June 2020
	Alnylam Pharmaceuticals. Clinical study report 3 Final analysis for ALN-AS1-003 (givosiran)	23 November 2021
	Alnylam Pharmaceuticals. Clinical study protocol ALN-AS1-003 (ENVISION): Amendment 3	21 September 2021
	Alnylam Pharmaceuticals. Statistical analysis plan ENVISION: A Phase 3 Randomized, Double-blind, Placebo-Controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias.	2018
	Alnylam Pharmaceuticals. Clinical Study Report ALN-AS1-003 (ENVISION): Primary Analysis	16 May 2019
	Balwani, M., Sardh, E., Ventura, P., Peiró, P. A., Rees, D. C., Stölzel, U., et al, Gouya, L. (2020). Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria	The New England Journal of Medicine, 382(24), 2289-2301.
	Lee, M. J., Kuo, H. C., Chou, L. N., Sweetser, M. T., & Wang, J. D. (2024). A randomized, placebo-controlled study of givosiran in patients with acute hepatic porphyrias (ENVISION): final (36-month) analysis of the Taiwan Cohort.	Journal of the Formosan Medical Association / Taiwan yi zhi, 123(6), 679-686.
ENVISION OLE ALN-AS1-003 NCT03338816	Alnylam Pharmaceuticals. Clinical study report 2 interim analysis for ALN-AS1-003 (ENVISION)	2 June 2020
	Kuter, D. J., Bonkovsky, H. L., Monroy, S., Ross, G., Guillén-Navarro, E., Cappellini, M. D., et al, Thapar, M. (2023). Efficacy and safety of givosiran for acute hepatic porphyria: Final results of the randomized phase III ENVISION trial.	Journal of Hepatology, 79(5), 1150-1158.
Study 001 ALN-AS1-001 NCT02452372	Alnylam Pharmaceuticals. Clinical study report ALN-AS1-001 Givosiran	2018
	Sardh, E., Harper, P., Balwani, M., Stein, P., Rees, D., Montgomery Bissell, D., et al, Anderson, K. E. (2019). Phase 1 trial of an RNA interference therapy for acute intermittent porphyria	New England Journal of Medicine, 380(6), 549-558.
Study 002 ALN-AS1-002 NCT02949830	Alnylam Pharmaceuticals. Clinical Study Report ALN-AS1-002 (Study 002): Report 3	18 March 2022). 2022:1-115.
	Alnylam Pharmaceuticals. Data on File. Study 002 (ALN-AS1-002) Clinical Study Report (CSR).	16 March 2020
	Sardh, E., Balwani, M., Rees, D.C. et al. Long-term follow-up of givosiran treatment in patients with acute intermittent porphyria from a phase 1/2, 48-month open-label extension study	Orphanet Journal Rare Diseases 19, 365 (2024).

Source: Table 2.3, pp42-46 of the submission

6.9 The key features of the direct randomised trials and studies are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Givosiran versus BSC						
ENVISION	94	R, DB; 6 mths	Low	AHP (95% AIP)	AAR in AIP (1°) AAR in AHP Urinary ALA and PBG; daily hemin use; pain, nausea fatigue assessments; HRQoL	Used
Study 001 Part C	17	R, DB; 3 mths	Low	AIP	AEs (1°) PD; urinary ALA and PBG; daily hemin use ARR (exploratory)	Not used
Open-label extension studies						
ENVISION OLE	93	OL, 30 mths	Sound[a]	AHP (96% AIP)	AAR Urinary ALA and PBG; daily hemin use; HRQoL	Used
Study 002	16	OL; up to 48 mths	Sound[a]	AIP	AEs (1°) AAR PD; urinary ALA and PBG; daily hemin use	Not used

Source: compiled during the evaluation.
1°=primary outcome; AAR=acute attack rate; AEs=adverse events; AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; ALA=aminolevulinic acid; PBG=porphobilinogen; DB=double blind; HRQoL=health related quality of life; mths=months; OL=open label; PD=pharmacodynamic; PK=pharmacokinetic; R=randomised.
a assessed as "Methodologically sound" using the Critical Appraisal Skills Programme (CASP) tool

Comparative effectiveness

6.10 The porphyria attack composite endpoint—defined as attacks requiring hospitalisation, urgent healthcare visits, or intravenous hemin administration at home—was the primary endpoint for AIP patients (full analysis set; FAS_{AIP}) and a secondary endpoint for all AHP patients (FAS). Annualised rate of porphyria attack composite endpoint during the 6-month DB period in FAS_{AIP} and FAS are presented Table 4.

Table 4: Annualised rate of porphyria attack composite endpoint during the 6-month DB period – FAS_{AIP} and FAS (all AHP patients)

Statistics	FAS_{AIP}		FAS	
	Givosiran (N=46)	**Placebo (N=43)**	**Givosiran (N=48)**	**Placebo (N=46)**
Total number of attacks	83	284	90	297
Total follow-up time (years)	21.5	19.4	22.4	21.2
Number of patients with 0 attacks, n (%)	23 (50.0)	7 (16.3)	24 (50.0)	8 (17.4)
Median AAR (Q1,Q3)	1.0 (0.0, 6.2)	10.7 (2.2, 26.1)	1.0 (0.0,6.4)	10.7 (2.2,25.9)
Mean AAR (95% CI)	3.2 (2.3, 4.6)	12.5 (9.4, 16.8)	3.4 (2.4, 4.7)	12.3 (9.2, 16.3)
Rate ratio (95% CI) givosiran vs placebo	**0.26 (0.16, 0.41)**		**0.27 (0.17, 0.43)**	
p-value	<0.001		<0.001	

Source: Table 14 and Table 18 of ENVISION CSR ('ALN-AS1-003 Report Body CSR1').
AAR=annualised attack rate; AHP=acute hepatic porphyria; CI=confidence interval; DB=double-blind; FAS=full analysis set; FAS_{AIP},=AIP patients in full analysis set.

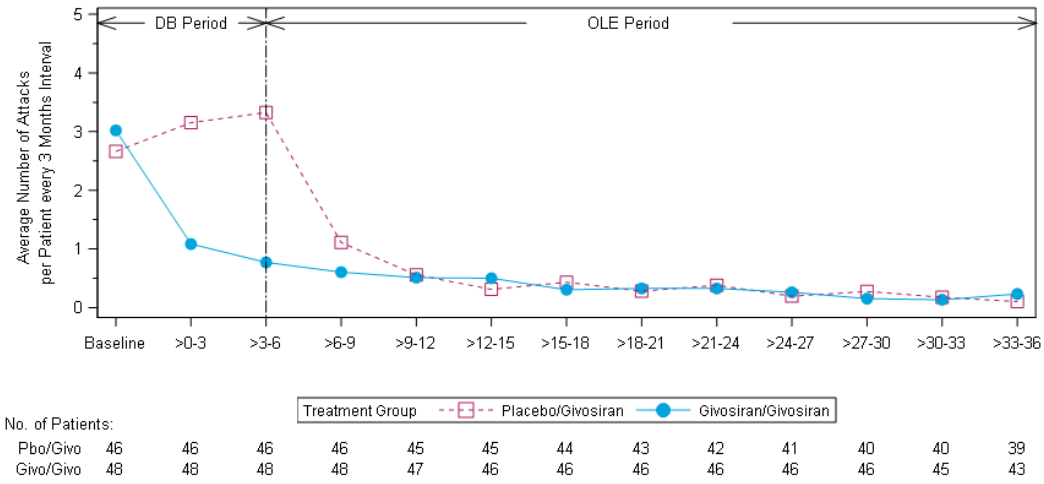
6.11 At 6 months, the median (interquartile range [IQR]) AAR was 1.0 (0.0 to 6.2) in the AIP givosiran group and 10.7 (2.2 to 26.1) in the placebo group, a relative difference of 90%. Givosiran demonstrated a statistically significant reduction of 74% in the mean

AAR of the porphyria attack composite endpoint compared to placebo in AIP patients (rate ratio=0.26, p<0.0001). Consistent findings were observed across both AIP and the broader AHP populations; this is expected as 89/94 (95%) patients in ENVISION had the AIP subtype.

6.12 The Study 001 Part C similarly showed that monthly treatment with givosiran was associated with a 79% reduction in mean AAR compared to placebo.

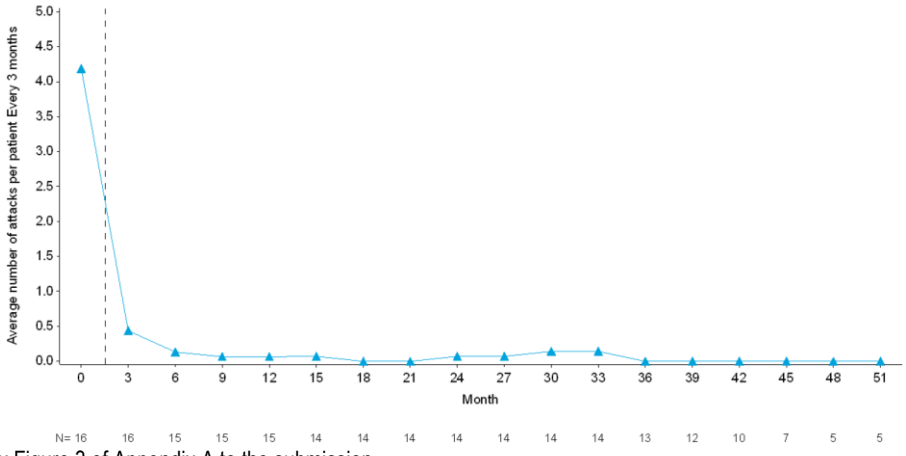
6.13 The ENVISION OLE and Study 002 showed that long-term monthly treatment with givosiran was associated with sustained AAR reduction, see Figure 2 and Figure 3.

Figure 2: Composite porphyria attack rate in patients with AHP in the ENVISION OLE



Source: Figure 2.11 of the submission.
AHP=acute hepatic porphyria; DB=double-blind; Givo=givosiran; OLE=open-label extension; Pbo=placebo

Figure 3: Mean number of composite attacks per patient per every 3-month interval for patients on 2.5 mg/kg QM in Study 002 (Safety Analysis Set)



Source: Appendix Figure 3 of Appendix A to the submission
QM=once monthly

6.14 Sensitivity analyses around the definition of an 'acute attack' in the AIP population using negative binomial regression was performed in ENVISION to assess the robustness of the AAR results. These were as follows:

- Counting All Discrete Attacks: testing the impact of under-counting. For attacks meeting the primary definition, all discrete attacks were counted even if they overlap during a day.
- Counting Attacks Using a 2-Day Window: testing the impact of over-counting. For attacks meeting the primary definition, extend the attack counting window from 1-day to a 2-day window, i.e. attacks that occur on the same calendar day, or are separated by one calendar day were counted as one attack.
- All Investigator-Confirmed Attacks: attacks meeting the primary definition PLUS treatment at home not requiring hemin use.
- All Porphyria Attacks, Counting Potential Attacks: attacks meeting the definition of 'All-Investigator-Confirmed Attacks' PLUS attacks not confirmed by Investigator but deemed as potential attacks.
- Per protocol (PP) analysis (where 1 patient in the placebo arm was excluded).

6.15 The definition of 'acute attack' had implications on the estimated incremental treatment effect of givosiran versus BSC, with rate ratios (95% CI) ranging from of 0.25 (0.16, 0.40) [PP] to 0.43 (0.29, 0.65) [All porphyria attacks, counting potential attacks].

6.16 A summary of other outcomes from the ENVISION trial are presented in Table 5. The results indicated that treatment with givosiran, compared with placebo, resulted in (i) reductions in urinary ALA and PBG levels—key biomarkers associated with AHP and (ii) significantly fewer annualised days of hemin use. Similar results were reported in Study 001 Part C, and both ENVISION OLE and Study 002 showed sustained benefits in these outcomes over time.

6.17 ENVISION reported significantly lower daily worst pain score (there were no significant between-group differences in the daily worst scores for fatigue or nausea) and a potential benefit in reducing opioid dependency, however the clinical significance of this reduction in opioid use remains uncertain.

6.18 With respect to the health-related quality of life (HRQoL) measures, given that the secondary outcomes were analysed in a hierarchical order, statistical significance was not tested for 12-Item Short Form Health Survey (SF-12) as the earlier endpoint in the prespecified hierarchy (i.e., daily worst scores for fatigue) did not reach statistical significance. Despite this, the submission claimed that change from baseline in the physical component summary (PCS) that was 3.9±1.7 points higher (indicating improvement) in the givosiran versus placebo group was clinically meaningful based on published literature relating to conditions like rheumatoid arthritis, arthroplasty, lumbar stenosis surgery. While these conditions may present with overlapping symptoms such as pain and fatigue, they differ substantially in pathophysiology, chronicity, and disease course. Therefore, the clinical relevance of the observed

change in SF-12 PCS in AIP remains uncertain. These improvements were maintained throughout ENVISION OLE.

Table 5: Summary of outcomes from the Phase 3 ENVISION study

Outcome name (unit)	Effect Size		Statistical test	
	Value	95%CI	Type	p-value
LS mean urinary ALA in AIP at 3 months (mmol/mol Cr)	-18	(-22.3, -14.2)	t-test	<0.001
LS mean urinary ALA in AIP at 6 months (mmol/mol Cr)	-19	(-26.0, -12.2)	t-test	<0.001
LS mean urinary PBG in AIP at 6 months (mmol/mol Cr)	-36	(-49.7, -22.7)	t-test	<0.001
Mean annualised days on hemin usage in AIP	0.23	(0.11, 0.45)	t-test	<0.001
Daily worst pain (BPI-SF-NRS, range 0–10 points) AUC change from baseline[a]	-12.680	(-25.526, 0.166)	ANCOVA Wilcoxon	0.046
Daily worst nausea (NRS, range: 0–10 points) AUC change from baseline[b]	-6.940	(-19.837, 5.957)	ANCOVA	0.2876
Daily worst fatigue (BFI-SF NRS, range 0-10) AUC change from baseline[b]	5.492	(-4.000, 14.984)	ANCOVA	0.2532
Mean proportion of days with opioid use over 6 months	Givosiran: 23% Placebo: 38%	NR	NR	NR
PCS of SF-12 (range 0–100) in AIP, mean change from baseline[c]	3.9	(0.6, 7.3)	t-test	0.0216
EQ-5D-5L VAS (range 0–100), mean change from baseline[c]	Givosiran: 5.2 Placebo: -1.3	NR	NR	NR
PGIC at 6 months[d]	Givosiran: 59.4% Placebo: 18.4%	NR	NR	NR
PPEQ at 6 months (Givosiran vs Placebo, % patients)[e]				
1. Travelling >1 day for work or pleasure	35.1 vs 13.2	NR	NR	NR
2. Participating in social activities	35.1 vs 7.9	NR	NR	NR
3. Planning future events	35.1 vs 10.5	NR	NR	NR
4. Doing household chores	35.1 vs 5.3	NR	NR	NR
5. Exercising moderately	32.4 vs 5.3	NR	NR	NR
6. Convenience of current porphyria treatment	72.2 vs 8.1	NR	NR	NR
7. Overall satisfaction with porphyria treatment	72.2 vs 13.5	NR	NR	NR
8. Study drug helping more normal life	66.7 vs 10.8	NR	NR	NR
Days of school/work missed at 6 months (Givosiran vs Placebo, mean)	2.4 vs 6.9	NR	NR	NR

Source: Table 2.10 of the submission.

a Pain data not normally distributed; ANCOVA method not valid. Post-hoc analysis using non-parametric stratified Wilcoxon method.

b A higher score indicates worse manifestation.

c A higher score indicates better physical health and functioning.

d Proportion of patients reporting "much improved" or "very much improved". None of the placebo patients reported that their condition was "very much improved".

e Percentage of patients with response "Much Better" for Q1–7 or with response "Always" or "Most of the time" for Q8 at Month 6.

AAR=annualised attack rate; AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; ALA=aminolevulinic acid; ANCOVA=analysis of covariance; AUC=area under the curve; BFI-SF=Brief Fatigue Inventory-Short Form; BPI-SF=Brief Pain Inventory-Short Form; CI=confidence interval; Cr=creatinine; EQ-5D-5L=EuroQol 5-Dimension 5-Level Questionnaire; ITT=intent to treat; LS=least square; mmol=millimole; MMRM=mixed-effects model repeated measures; mol=mole; NR=not reported; NRS=numeric rating scale; NT; not tested PBG=porphobilinogen; PCS=Physical Component Summary; PGIC=Patient Global Impression of Change Questionnaire; PPEQ=Porphyria Patient Experience Questionnaire; RR=rate ratio; SF-12=12-Item Short Form Health Survey; VAS=visual analogue scale.

6.19 The submission also reported the Patient Global Impression of Change (PGIC) and Porphyria Patient Experience Questionnaire (PPEQ) from the ENVISION trial. On the PGIC at 6 months in patients with AHP, the percentage that rated overall health status as either 'much improved' or 'very much improved' was 59% in the givosiran group and 18% in the placebo group. On the PPEQ in patients with AHP, the percentage who had improvements from baseline in their ability to function and perform activities of

daily living and in treatment satisfaction was larger in the givosiran group than in the placebo group (Balwani 2020). However, both the PGIC and PPEQ are tools that were developed specifically for this study and are not validated in the context of AHP. This limits the generalisability and robustness of the findings. Without external validation or corroborative evidence, it remains uncertain whether these patient-reported outcomes accurately reflect the true impact of givosiran on patients' daily lives and overall wellbeing.

Comparative harms

6.20 An overview of the safety results from ENVISION are provided in Table 6. Overall, a higher proportion of patients in the givosiran group experienced any AE (43/48, 90%) compared to the placebo group (37/46, 80%). Severe AEs (17% vs 11%) and serious adverse events (SAEs) (21% vs 9%) were also more frequent with givosiran. One patient in the givosiran group discontinued treatment due to an AE, while no discontinuations occurred in the placebo group. No deaths were reported in either group. No statistically significant differences were observed between treatment groups.

Table 6: Summary of key adverse events in the trials

AE, n (%)	Givosiran (N=48)	Placebo (N=46)	RD, % (95% CI)
Any AE	43 (90%)	37 (80%)	9.1 (-5.2, 23.5)
Any severe AE	8 (17%)	5 (11%)	5.8 (-8.1, 19.7)
Any SAE	10 (21%)	4 (9%)	12.1 (-1.9, 26.2)
Any AE leading to treatment discontinuation	1 (2%)	0 (0%)	2.1 (-2.0, 6.1)
Death	0 (0%)	0 (0%)	NA

Source: Table 2.12 of the submission.
AE=adverse event; NA=not applicable; SAE=serious adverse event

6.21 Table 7 presents the common adverse events in the ENVISION study. The most commonly occurring AEs reported in givosiran-treated patients were injection-site reactions, nausea, CKD, decreased estimated glomerular filtration rate (eGFR), rash, increased ALT, and fatigue. Statistically significantly higher incidences of injection-site reaction, nausea and CKD were observed among those randomised to givosiran compared with placebo. The submission stated that the injection-site reactions were mild to moderate in severity, and none led to treatment discontinuation, however, the potential for unblinding due to these reactions could introduce bias, particularly in subjective outcome reporting (e.g., patient-reported outcomes). AEs with higher frequency in the placebo group were pyrexia, hypoesthesia, dyspepsia, vomiting, urinary tract infection, and back pain; with the incidence of pyrexia, hypoesthesia and dyspepsia occurring statistically significant more among those randomised to placebo. The renal and hepatic signals observed with givosiran need to be carefully considered, as they raise potential long-term safety concerns. Given that the study duration was only six months, it does not provide sufficient insight into long-term risks—particularly in populations with pre-existing renal or hepatic conditions.

Table 7: Common adverse events in ENVISION

AE, n (%)	Givosiran (N=48)	Placebo (N=46)	RD, % (95% CI)
AEs with higher frequency (≥5 % difference) in the givosiran group			
Injection-site reaction	12 (25%)	0 (0%)	**25.0 (12.8, 37.3)**
Nausea	13 (27%)	5 (11%)	**16.2 (0.8, 31.7)**
Chronic kidney disease	5 (10%)	0 (0%)	**10.4 (1.8, 19.1)**
Decreased eGFR	3 (6%)	0 (0%)	6.3 (-0.6, 13.1)
Rash	3 (6%)	0 (0%)	6.3 (-0.6, 13.1)
Increased alanine aminotransferase	4 (8%)	1 (2%)	6.2 (-2.7, 15.0)
Fatigue	5 (10%)	2 (4%)	6.1 (-4.4, 16.5)
AEs with higher frequency (≥5 % difference) in the placebo group			
Pyrexia	1 (2)	6 (13%)	**-11.0 (-21.5, -0.4)**
Hypoesthesia	0 (0%)	4 (9%)	**-8.7 (-16.8, -0.6)**
Dyspepsia	0 (0%)	4 (9%)	**-8.7 (-16.8, -0.6)**
Vomiting	2 (4%)	5 (11%)	-6.7 (-17.3, 3.9)
Urinary tract infection	3 (6%)	6 (13%)	-6.8 (-18.7, 5.1)
Back pain	1 (2%)	4 (9%)	-6.6 (-15.7, 2.5)

Source: Table 2.13 of the submission.
AE=adverse event; eGFR=estimated glomerular filtration rate
Bold font indicates statistically significant differences

6.22 Placebo-treated patients who crossed over to givosiran during ENVISION OLE had a similar safety profile to patients randomised to givosiran treatment during the DB period. In the OLE, 3% of patients had treatment-emergent antidrug antibodies (ADA) of low titre and positive only at a single timepoint. The presence of ADAs did not affect the efficacy or safety of givosiran. Lastly, there was one death in the OLE attributed to aortic dissection and considered not related to the study drug.

6.23 In Study 001, the safety of givosiran was compared to that of placebo (n=33 vs n=10 patients, respectively). Most patients (30/33 [91%]) in the givosiran group and 100% of patients in the placebo group experienced at least one AE. The most common AEs were nasopharyngitis (nine patients in the givosiran group vs two patients in the placebo group), abdominal pain (eight vs one), nausea (six vs three), and diarrhoea (four vs two).

6.24 In Study 001, six patients (18%) in the givosiran group had SAEs, which were abdominal pain (two events), spontaneous abortion, influenza A infection, functional gastrointestinal (GI) disorder (opioid bowel dysfunction), staphylococcal bacteraemia, auditory hallucination, and haemorrhagic pancreatitis (one event each). None were related to the study drug. There were no SAEs in the placebo group. The patient who experienced haemorrhagic pancreatitis ultimately died; however, the death was assessed as unlikely related to study drug. Severe AEs were reported in both treatment groups, but most AEs were mild to moderate in severity. The proportion of patients in Study 001 Part C who experienced a severe AE was similar between the givosiran and placebo groups.

6.25 For Study 002, the interim data cut-off was 16 October 2019, in which at least one AE was reported by 100% (16/16) of patients; most AEs were mild or moderate in severity. AEs occurring in more than three patients were abdominal pain, fatigue, nausea, injection-site erythema, headache, myalgia, nasopharyngitis, diarrhoea,

injection-site pruritus, and international normalised ratio (INR) increased. Injection-site reactions were reported by seven patients; all reactions were mild to moderate. Ten SAEs were reported in six patients, nine of which were deemed by investigators unlikely to be related to study treatment. One patient had an SAE of anaphylactic reaction that was considered related to the study drug. The event resolved and the patient discontinued the study drug. Three of the SAEs (pyrexia [two events] and deep vein thrombosis) were thought by investigators to be potentially related to catheterisation. There were no deaths.

6.26 The Sub-Committees noted that the Australian PI includes cautions regarding use in patients with pre-existing renal and hepatic conditions and the need to monitor LFT and GFR.

Benefits/harms

6.27 On the basis of direct evidence presented by the submission, the comparison of givosiran and BSC over 6 months resulted in:

- Approximately a 74% reduction in the average number of porphyria attacks requiring hospitalisation, urgent healthcare visits, or intravenous hemin administration at home per year; for example, an average of 10 attacks per year reduced to an average of 2.6 attacks per year (Table 4).
- Mean urinary ALA and PBG reductions of approximately 19 and 36 mmol/mol creatinine, respectively (Table 5). ALA and PBG are key biomarkers associated with AHP.
- Approximately a 77% reduction in the average number of days of hemin usage per year; for example, an average of 10 days per year reduced to an average of 2.3 days per year (Table 5).

6.28 On the basis of direct evidence presented by the submission, for every 100 patients treated with givosiran in comparison with BSC for 6 months

- Approximately 25 additional patients would experience injection site reactions; an additional 16 patients would experience nausea and an additional 10 patients would experience chronic kidney disease (Table 7).

Clinical claim

6.29 The submission described givosiran as superior in terms of effectiveness compared with BSC and non-inferior in terms of safety compared to BSC.

6.30 The Sub-Committees agreed with the Commentary that the therapeutic conclusion regarding effectiveness is adequately supported by the evidence presented in the submission. However, there is some uncertainty regarding the generalisability and/or magnitude of the benefit as observed in the trials compared with the Australian population because:

- There is limited representation of other AHP subtypes apart from AIP. While the submission claimed that 'all AHP subtypes have ALAS1 induction central to their

pathophysiology and respond similarly to acute attack treatments', no evidence was provided to support this claim. The Sub-Committees considered that it is likely that the clinical claim of superior effectiveness is reasonable for all subtypes of AHP based on biological similarities and the mechanism of action of givosiran.

- Patients in both trials were diagnosed on the basis of a test confirming a mutation in a gene relevant to AHP subtype. The requested PBS restriction does not require diagnosis by genetic testing, only on clinical features and biochemical markers. Although patients whose genetic testing did not identify a mutation in a porphyria-related gene may have been enrolled if they had both clinical features and diagnostic biochemical criteria consistent with AHP (as suggested for the PBS population), only two patients with AHP without an identified mutation were randomised in ENVISION.
- Although patients aged ≥12 years are included in the requested PBS restriction, no patients aged ≥12 to <18 years were enrolled in the trials, thus the safety and effectiveness of givosiran in this patient subset is not known.
- The definition of an 'acute attack' had implications on the estimated incremental treatment effect of givosiran versus BSC, with rate ratios (95% CI) ranging from (95% CI) of 0.25 (0.16, 0.40) to 0.43 (0.29, 0.65).

6.31 The Sub-Committees agreed with the Commentary that the conclusion of non-inferior safety was not adequately supported by the evidence presented in the submission. Patients randomised to givosiran in the ENVISION trial reported statistically significantly increased incidences of injection-site reactions, nausea and chronic kidney disease. The renal and hepatic signals observed with givosiran need to be carefully considered, as they raise potential long-term safety concerns and patients should be monitored for LFTs and GFR during treatment. Given that the duration of ENVISION was only six months, it does not provide sufficient insight into long-term risks—particularly in populations with pre-existing renal or hepatic conditions. The Sub-Committees considered a claim of inferior safety would be appropriate.

6.32 The PBAC considered that the claim of superior comparative effectiveness was reasonable and that the trial population and supportive treatments received were likely to be representative of AHP patients in Australian clinical practice.

6.33 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.34 The submission presented a modelled economic evaluation based on the clinical data from the ENVISION trial, supported by extrapolation from the ENVISION OLE study, literature, and inputs from Australian clinical experts. The type of economic evaluation presented was a cost-utility analysis (CUA), comparing givosiran to BSC. A CUA was consistent with the submission's clinical claim that givosiran was superior in efficacy

compared to BSC. The key components of the economic model are presented in Table 8.

6.35 The submission noted that NICE (HST16, published 24 November 2021) had previously considered givosiran for the treatment in AHP. Additionally, during the evaluation, a consideration by CADTH (project number SR0679-000)[2] was identified.

6.36 The submission adopted a lifetime time horizon of 61 years (122 six-month cycles), as AHP is a chronic and incurable hereditary condition requiring long-term specialist management. While this may be reasonable given the nature of the condition, the model was informed by the ENVISION trial (6-month duration) and its 36-month OLE only. Extrapolating outcomes over such an extended period from relatively limited trial data introduces significant uncertainty. Comparative data were only available to inform transitions in cycle 1 of 122 in the model. Reducing the time horizon to 30 years increased the ICER by [redacted]%. The Pre-Sub-Committee Response (PSCR) argued that AHP is a chronic disease and attacks may occur throughout a patient's lifetime, and therefore a lifetime time horizon is appropriate to capture the clinical and HRQoL benefits. The Sub-Committees considered that a time horizon of 40 years should be included in a respecified base case given the short duration of the trial data and the expected diminishing of symptoms beyond menopause.

6.37 The economic evaluation utilised a four-health state Markov model to conduct a cost-utility analysis comparing givosiran with BSC. The model appeared to be similar to the model considered by NICE and CADTH.

Table 8: Summary of model structure, key inputs and rationale

Component	Description	Justification/comments
Type of analysis	CUA	Reasonable and consistent with the claim of superior effectiveness in terms of reducing the frequency/severity of porphyria attacks.
Population	Patients aged 12 years and older with a documented diagnosis of AHP using clinical features and biochemical results and recurrent disease, defined as ≥2 porphyria attacks requiring hospitalisation, presentation at an emergency department or medical intervention via a porphyria clinic within the 6 months prior to treatment initiation.	Consistent with the inclusion criteria of the ENVISION trial and the proposed PBS-eligible population.
Outcomes	Life Years (LY) gained, Quality-adjusted life years (QALYs), and costs	Reasonable
Time horizon	Lifetime horizon	ENVISION included only 6-months of comparative evidence. Extrapolation highly uncertain.
Perspective	Australian healthcare system	Reasonable
Discount rate	5% applied to cost and outcomes	Reasonable
Methods used to generate results	Markov model	Reasonable
Health states	The model incorporates four health states, assigned by AAR: AAR = 0 ('asymptomatic') AAR >0 to ≤4 ('symptomatic') AAR >4 to ≤24 ('recurrent') AAR >24 ('severe') Additionally, death is an absorbing state. A further health state of 'asymptomatic post menopause' which is identical to AAR = 0 except no drug treatment costs was also modelled	With the exception of the AAR>24 health state, health states were based on Neeleman 2018. The Commentary noted it was unclear whether the inclusion of the AAR>24 health state was reasonable and was a key driver of the model.
Cycle length	6 months (182.63 days)	Given the ENVISION trial duration was only six months, there was only comparative evidence for one cycle of the model.
Transition probabilities	Transition probabilities for givosiran and BSC: A patient can transition between any of the four health states (i.e., AAR = 0, AAR >0 to ≤4, AAR >4 to ≤24, AAR >24) based on the transition probabilities obtained from the ENVISION trial and the additional 36 months of the ENVISION OLE data. The cohort may transition to death from any alive health states based on population-adjusted norms.	Application of transition probabilities was reasonable however there were limitations with the data used to inform the transition probabilities (see paragraphs 6.44 to 6.47).
Software package	Microsoft® Excel® for Microsoft 365	Reasonable

Source: Table 3.1, p79 of the submission.

AAR = Annualised Attack Rate, AHP = Acute Hepatic Porphyria, ALA = Aminolevulinic Acid, BSC = Best Supportive Care, CUA = Cost-Utility Analysis, HRQoL = Health-Related Quality of Life, LY = Life Year, OLE = Open-Label Extension, PBG = Porphobilinogen, PBS = Pharmaceutical Benefits Scheme, QALYs = Quality-Adjusted Life Years, ULN = Upper Limit of Normal,

6.38 In the absence of a standard classification system to define disease severity in AHP, the submission categorised patients as follows: 'Recurrent' (>4 attacks per year), 'Symptomatic' (≥1 attack per year), and 'Asymptomatic' (no attacks) based on Neeleman 2018. The submission considered it crude to group all patients with >4

attacks together, therefore a fourth health state of AAR >24 was included. The model also includes an additional health state of 'asymptomatic post menopause' which patients may transition to at the cycle post menopause. Patients in this health state are assumed to be the same as the asymptomatic (AAR=0) health state but will not receive any active treatment. The Commentary noted that there was a lack of correlation between AAR and health related quality of life (HRQoL) in ENVISION, which undermined the validity of using AAR to inform health states in the economic model.

6.39 While the submission cited Neeleman 2018 to justify its classification of disease severity, noting that the study demonstrated a relationship between attack frequency and overall disease burden, the applicability of Neeleman 2018 to the model may be uncertain as:

- The definition of an attack in Neeleman 2018 (an episode of abdominal pain in parallel with a significant rise in urinary ALA and PBG levels of ≥ 4 times upper limit of normal and a verified visit or admission to a hospital for diagnosis and treatment) was narrower than the definition of an attack in ENVISION (an attack requiring hospitalisation, an urgent healthcare visit, or IV hemin administration at home) and the requested restriction (attack requiring hospitalisation, presentation at an emergency department or medical intervention via a porphyria clinic) due to the inclusion of biochemical measurements and a specific symptom (abdominal pain) and setting (hospital only).
- The definition of 'symptomatic' and 'recurrent' in Neeleman 2018 was misrepresented by the submission and was not aligned with the submission's assumptions:
    - 'Symptomatic' in the submission's economic model was assumed to reflect an AAR >0 to ≤4. In Neeleman 2018, 'symptomatic' was defined as having experienced one or more confirmed acute porphyric attacks, and not as an annualised rate, i.e. any patient with at least one attack ever during the follow up period would be considered symptomatic. Some patients with only one attack from 60 years of follow-up were considered as 'symptomatic' in Neeleman 2018, whereas these patients would likely be considered 'asymptomatic' for the majority of their life in the model.
    - 'Recurrent' in the submission's economic model was assumed to reflect an AAR >4 to ≤24. In Neeleman 2018, recurrent cases were defined as having more than four attacks in any year, or on prophylactic haem therapy, which was a broader definition than the submission. Neeleman 2018 also did not include an upper limit of 24 attacks per year.

6.40 The inclusion of an AAR >24 health state was not consistent with Neeleman 2018 and its inclusion favoured givosiran. In the base case, the model estimated that patients in the BSC arm would experience 672 attacks compared to 15 attacks in the givosiran arm during the modelled time horizon of 62 years. The high number of attacks in the BSC arm was driven by the AAR >24 health state in which patients were assumed to have 33.1 attacks per year (see Table 9), or a total of 672 attacks over the lifetime

horizon in the BSC arm. Comparatively, among the 11 patients classified as 'recurrent' in Neeleman 2018, the highest number of attacks reported in any one patient in any given year was 13 attacks, and only one other patient had any one-year period during which they experienced more than four attacks (which was five). No patient in Neeleman 2018 experienced more than 54 attacks in their lifetime.

6.41 The PSCR and Pre-PBAC response reiterated that it was important to include a separate health state with annualised attack rate (AAR) >24 because there was a subset of patients with AHP who experience a very high AAR. The Sub-Committees noted that Neeleman 2018 studied the lifetime probability of attacks, and commented that porphyria is a relapsing disease and not all patients would experience an attack every year. The Sub-Committees noted that the number of attacks per year was a proportion of the number per lifetime, and commented that the number of attacks in the model was substantially overestimated, favouring givosiran.

6.42 The PSCR noted that, "Grouping all patients with >4 attacks per year in one health state would not allow the model to differentiate the burden of disease for a patient with an AAR of 5 from a patient with an AAR of 25. HRQoL data from ENVISION shows that patients with >24 attacks per year experience clinically meaningfully worse disease than patients who have >4 but ≤24 attacks per year." The Sub-Committees noted that despite this argument, the QoL decrement for chronic symptoms in the model was the same for recurrent and severe health states (0.617).

6.43 Assuming no patients started the model in the AAR >24 health state increased the ICER by [redacted]%, and reducing the assumed number of attacks in the AAR >24 health state from 33.1 to 28.22 (the lower 95% CI calculated by the submission) increased the ICER by [redacted]%. Notably, CADTH removed the health state of 'severe' (corresponding to AAR >24) in the respecified base case.

6.44 Transition probabilities for givosiran were derived from the 0 to 6 months of the ENVISION (cycle 1) and the 36-month follow-up of ENVISION OLE (cycles 2–6). The transition probabilities from cycle 6 (corresponding to 30-36 months in ENVISION OLE) were assumed to apply until year 5 (cycle 10), after which all patients were considered to remain in their respective health states until death, except for the transition from asymptomatic (AAR=0) to asymptomatic post menopause at the cycle post menopause, which had the same utility and costs associated with the AAR=0 health state. Only cycle 1 of the 122-cycle model included evidence from the comparative ENVISION trial. The transition probabilities afterwards were based on a small number of patients (n=48) who were randomised to givosiran in ENVISION and ENVISION OLE. It was unclear why patients (n=44) who were randomised to placebo in the randomised ENVISION trial who subsequently were enrolled in the open label ENVISION OLE were not included in these transitions. The number of patients within each AAR health state in ENVISION and ENVISION OLE could not be independently verified during the evaluation.

6.45 With regards to the transition probabilities in the givosiran arm:

- Most transitions occurred in the first 6 months and the number of patients informing transitions beyond 6 months (except for in the AAR=0 health state) was relatively small. For example, in cycle 2, almost 50% (23/47) of patients were in the AAR=0 health state, with more and more patients in the AAR=0 health state thereafter until by cycle 6, only eight patients remained in the non-AAR=0 health state. These eight patients informed transitions between all the health states (all patients in AAR=0 health state were assumed to remain in the health state) until cycle 10. This introduces considerable uncertainty in some of the transition probabilities.
- Based on the transition probabilities applied, the model estimated that the majority of patients treated with givosiran will eventually transition to the AAR=0 health state, with no patients remaining in the AAR >24 health state. After 18 months in the givosiran arm (i.e. cycle 3), more than 70% of patients were estimated to be asymptomatic with a 95%+ probability of remaining asymptomatic until cycle 10 (5 years) after which it increased to 100%. This may be a strong and optimistic assumption given the small patient numbers used to inform the transition probabilities and the fact that only results from the first cycle were informed by the double blind ENVISION trial, and all subsequent transition probabilities were informed by the single arm open label ENVISION OLE. This may underestimate disease management costs in the givosiran arm and overestimate its long-term benefit.
- Only six patients were initially in the severe (AAR >24) health state, all of whom transitioned out after cycle 1 (0-6 months) in the givosiran arm. This health state is, therefore, unoccupied in the model in the givosiran arm beyond this point, which was highly favourable to givosiran.

6.46 Transition probabilities for BSC were based on the AAR of patients randomised to placebo (n=44) in ENVISION at baseline compared to at six months. The same transition was applied each cycle until cycle 10 (year 5). Beyond year 5 the model assumed no further transitions between AHP severity health states until death, except for the transition from asymptomatic (AAR=0) to asymptomatic post menopause at the cycle post menopause. This transition was applied to 95% of all female patients in the AAR=0 state alive at the first cycle past the age of menopause (51 years old in the base case). The asymptomatic post menopause health state had the same utility and costs associated with the AAR=0 health state but all patients were assumed to be not using active treatment.

6.47 Based on six-month data from only three patients in ENVISION, the model assumed that any BSC patients in the AAR >24 health state would remain in this state until death. Similarly, BSC patients in the AAR >4 to ≤24 state had only a 13% chance of improving (3% to AAR=0 and 10% to AAR >0 to ≤4) each cycle. Notably, the number of patients in the AAR >24 health state increased from 10% at baseline to around 29% by cycle 2 before gradually declining due to death (see Figure 4). While the submission acknowledged that no further data were available beyond the 6-month double-blind

period, the assumption that these short-term transition probabilities could be applied consistently up to 5 years and beyond introduced significant uncertainty and the assumption that patients' disease severity might worsen considerably over time under BSC was not well-supported.

6.48 Female patients who experienced an attack just before menopause onset were assumed to continue experiencing attacks post-menopause and did not transition to the asymptomatic health state at menopause. The Sub-Committees agreed with the Commentary that this was inconsistent with clinical expectations of the impact of menopause on AHP symptoms, which typically improve at the time of menopause for all female patients (i.e., severity and frequency of attacks is expected to decrease) regardless of which treatment is administered, given that the likely trigger for the attacks (hormone levels at the time of menstruation) would no longer be present. The Sub-Committees acknowledged that there can be other triggers for some patients but noted that post-menopausal patients are unlikely to require hospitalisation or rescue medication for attacks. In the CADTH base case, all female AHP patients in the symptomatic and recurrent health state were assumed to become asymptomatic at onset of menopause. A similar sensitivity analysis was conducted during the evaluation and increased the ICER by [redacted]%.

6.49 Within each of the four health states, the model estimates the impact of both acute and chronic AHP consequences (costs and utility impacts).

6.50 Acute attacks were included in the model as discrete events that may occur at every cycle in any of the health states, over the entire time horizon of the model. Acute attacks were defined based on the definitions of the ENVISION trial i.e. comprising attacks requiring hospitalisation, urgent healthcare visits or IV hemin administration at home (Balwani 2020). Each acute attack was associated with a one-off utility decrement weighted by the average attack duration and a one-off cost, based on healthcare resource use and setting informed by the EXPLORE study data and Australian clinical input. The use of EXPLORE data to inform the proportion of healthcare resource use for acute attacks may not be justified when data from ENVISION, which was the primary source of data in the model, was available. Given that the AAR were all based on ENVISION, the healthcare setting for treatment of acute attacks from ENVISION would be most applicable. Use of healthcare setting for treatment of acute attacks from ENVISION instead of EXPLORE increased the ICER by [redacted]%.

6.51 Each health state was also assigned a disutility decrement and cost per cycle associated with chronic conditions, which were assumed to be more severe at higher AAR. The submission noted that chronic conditions are more prevalent in AHP patients with frequent attacks, as reported by Neeleman 2018. Age adjusted utility values from the general population (informed by McCaffery 2016) were used as the baseline, with AHP-related disutilities applied as decrements to account for both acute attacks and chronic conditions. Utilities in each health state were estimated by subtracting the disutilities associated with chronic and acute attacks from a baseline utility.

6.52 The disutility decrements for chronic conditions and acute attacks and the resultant utilities applied in the model are summarised in Table 9.

Table 9: Health utility decrements accounting for chronic disutility used in the base-case analysis

Age group	Mean baseline utility	Asymptomatic AAR = 0	Symptomatic AAR >0 to ≤4	Recurrent AAR >4 to ≤24	Severe AAR >24
Chronic condition utility decrement	-	-0.198	-0.502	-0.617	-0.617
Acute attack decrement per attack	-0.0043 (Average duration of attack 7.29 days, -0.22 attack disutility, adjusted for 365.25 days)				
Number of acute attacks per year [a]	-	0	2.27	10.90	33.10
Estimated utility by health state [b]					
18-24 years [c]	0.96	0.762	0.426	0.296	0.200
25-34 years [c]	0.95	0.752	0.422	0.286	0.190
35-44 years	0.92	0.722	0.408	0.256	0.160
45-54 years	0.89	0.692	0.394	0.226	0.130
55-64 years	0.89	0.692	0.394	0.226	0.130
65-74 years	0.87	0.672	0.385	0.206	0.110
≥75 years	0.83	0.632	0.367	0.166	0.070

Source: calculated during the evaluation using information from Table 3.6, p86, Table 3.20, p95 and Table 3.24, p98 of the submission

[a] based on ENVISION pooled data from givosiran and placebo arms

[b] Calculated by adding mean baseline utility at the age range, with the chronic condition utility decrement multiplied by the ratio of the mean baseline utility at the age range divided by the mean baseline utility at the starting age of the model, and with utility decrement from acute attacks

[c] Not in model as baseline starting age was 38.8 years in the base case

6.53 The submission derived the acute attack disutility from the EXPLORE study, which collected EQ-5D-5L data at scheduled 6-month intervals and during acute attacks. The submission justified the use of EXPLORE on the basis that it captured a higher proportion of EQ-5D-5L assessments during attacks (10.1%) compared to the ENVISION trial (0.4%), allowing a more reliable estimate.

6.54 Utility decrements for chronic AHP symptoms (pain, neurological, and psychiatric) were derived from non-AHP-specific published literature due to limited direct trial data:

- For chronic pain, the submission used a disutility value sourced from McDermott 2006, a cross-sectional study exploring the burden of neuropathic pain across 6 European countries (n=602, mean age: 62.9 years) which reported utility estimates for mild, moderate, and severe neuropathic pain. It was unclear whether chronic pain in AHP is clinically comparable to the pain profiles observed in other progressive or neurological conditions. Further, McDermott 2006 had other applicability issues as the mean age of the study population was 62 years, approximately 49% were male, and the majority of patients experienced neuropathic pain secondary to diabetes (23%) whereas the model assumed a baseline age of 38.8 years and 89.4% female.
- For neurological disutility, the submission used a disutility value from Sullivan 2011, a study that presents a catalogue of EQ-5D scores for the United Kingdom pooled from 79,522 individuals with complete EQ-5D scores. The utility decrement reported for “other hereditary and degenerative neuropathy”

(- 0.097) was selected. The rationale provided was that this category captures a broader range of neurological impairments without restricting disutility to a specific clinical presentation. The applicability to the AHP population remains uncertain.

- For psychiatric disutility, the submission stated that patients with AHP may experience a spectrum of psychiatric symptoms, including depression, anxiety, insomnia, and psychosis. To reflect this, the submission used data from Ara and Brazier 2011, a study that provides EQ-5D scores obtained from noninstitutionalised residents (n=41,174; mean age: 48.6 years) in England stratified by self-reported history of prevalent health conditions and age, when condition specific data are not available. This study included HRQoL impacts for a range of psychiatric conditions. There is uncertainty regarding the applicability of these values to the AHP population, as the utility decrements were derived from populations with differing demographic and clinical profiles, and the underlying conditions may not fully capture the severity, pattern, or interaction of symptoms experienced in AHP.

6.55 These values were weighted by the prevalence of chronic symptoms from Neeleman 2018 and adjusted for co-occurrence using a multiplicative method (Ara and Brazier 2011). While the use of literature-based utility decrements is reasonable when condition-specific trial data are not available, it introduces potential uncertainty regarding the applicability of the selected disutilities to the AHP population, particularly given that the sourced utility values are not specific to AHP and may not be representative of the HRQoL associated with AHP.

6.56 Notably, the 'out of attack' utility in EXPLORE of 0.577 was higher than the utility in the AAR >0 to ≤4 health state assumed in the model when considering only chronic condition decrements (0.92- 0.502 = 0.418). This suggests that the chronic utility decrements assumed by the submission were overestimated, favouring givosiran. The differences in utility between each health state were also substantial. The utility in the AAR>0 to ≤4 (0.408) was almost half of AAR=0 (0.722) in the 35-44 age group– suggesting that if a previously asymptomatic patient has one attack, they will subsequently be classified as AAR >0 to ≤4 and will have a significant loss of HRQoL.

6.57 Utilities were identified as a source of uncertainty by both CADTH and NICE. CADTH stated in relation to the HRQoL measures in ENVISION, "none of these measures have been validated in this patient population, and all related results were not adjusted for multiple testing. Other symptom-related outcomes, including pain, fatigue, and nausea, either did not show a statistically significant result or were outside of the statistical testing hierarchy and not adjusted for multiple testing. As such, no conclusion could have been made on the effect of givosiran on these outcomes. There is no conclusive evidence to support any effect of givosiran on chronic neurologic or psychiatric complications of AHP" (p5, CADTH 2021). Given this, it might not be reasonable to model such a large utility difference due to different prevalence in these conditions. A sensitivity analysis in the submission's model assuming all health states

had the utility decrement equal to the asymptomatic health state (- 0.198) increased the ICER by [redacted]%.

6.58 NICE suggested the use of utilities from relapsing-remitting multiple sclerosis (RRMS) may be a reasonable proxy for AHP health states, on the basis that the condition is chronic and progressive in nature and patients have the potential to relapse/experience recurrence. Using RRMS utilities from Hawton 2016 (as used by NICE) increased the ICER by [redacted]%. Using the utility decrements from Orme 2007, which was considered by the PBAC in the consideration of ofatumumab in RRMS (Table 9, ofatumumab Public Summary Document, March 2024 PBAC meeting) increased the ICER by [redacted]%.

6.59 The PSCR argued that "the preference for conservative utility values by CADTH and NICE does not align with clinical reality or patient experience. Given the severity of the disease and the evidence for a negatively impacted HRQoL with increasing attack frequency and chronic conditions in AHP, the values used in the CEA are reasonable in the context of the disease. The proposed alternatives by CADTH and NICE are no more clinically plausible than those used in the submission given the severe impact of AHP on HRQoL." The Sub-Committees considered that the chronic utility decrements in the submission base case were poorly justified and appeared substantially overestimated. The Sub-committees considered that the assumption all health states had the utility decrement equal to the asymptomatic health state (- 0.198) should be included in a respecified base case ICER.

6.60 The submission excluded mortality from acute attacks, stating deaths from acute attacks are now exceedingly rare due to improved management and hemin use, with no such deaths reported in ENVISION or EXPLORE study. The cohort could transition to death from any alive health state based on population-adjusted norms, with the same mortality risk across all health states. Overall, mortality assumptions had a limited impact on the ICER and appropriately the model did not estimate any differences in life years gained in the base case.

6.61 The model applied a time-on-treatment (ToT) curve based on ENVISION and ENVISION OLE to simulate givosiran discontinuation. Parametric extrapolation was used to inform long term discontinuation. Patients who discontinue givosiran were assumed to remain in the same health state but have the BSC transition probabilities applied to them in subsequent cycles. It may be unreasonable to assume that patients who discontinue from givosiran would not experience a worsening of AHP in the same cycle, particularly as the requested continuing restriction requires patients to have improvement in frequency or severity of AHP attacks, which would imply that those who discontinue did not experience any improvement or worsened and should transition to a more severe AAR health state in the cycle which they discontinued. This assumption also favoured givosiran but could not be tested during the evaluation.

6.62 Beyond the assumption of no worsening in AAR at discontinuation, the majority of patients who discontinued givosiran did so in the AAR=0 health state, and the BSC transition assumes all patients in the AAR=0 health state will remain in it. As such, the

model effectively assumed that the majority of patients who discontinue givosiran will retain the treatment benefit despite not receiving any treatment, which was not plausible and favoured givosiran. The magnitude of this bias was demonstrated in the sensitivity analysis which assumed that 99.9% of givosiran patients discontinued after cycle 1, which returned a QALY gain of 3.93 associated with givosiran, which was highly implausible.

6.63 In the base case, the exponential model was nominated for the ToT extrapolation. While the choice of the exponential model for extrapolating ToT appears reasonable based on AIC and BIC fit statistics, the exponential function predicts ~15% of patients remain on treatment after 30 years and ~2% after 60 years. The reasonableness of assuming most patients discontinue (as per the exponential extrapolation) was unclear. NICE noted that while lifelong treatment may be needed for some, the proportion was uncertain.

6.64 CADTH considered that assuming a gradual discontinuation rate over time was not reasonable and it was unlikely that the discontinuation observed during the trial would hold over the course of a lifetime time horizon, as a greater rate of discontinuation is likely to occur during the trial rather than beyond the trial period, given that only patients demonstrating good tolerability and response will remain on treatment. As such, the model's assumption of discontinuation may underestimate givosiran utilisation, favouring givosiran. The CADTH base case therefore assumed that all patients remained on givosiran treatment for the remainder of the model. A sensitivity analyses conducted during the evaluation which assumed discontinuation from cycle 8 onwards to be 0% increased the ICER by [redacted]%. The Sub-Committees agreed with the Commentary that discontinuation is likely to reflect the trial rates initially, but is likely to reduce as responders stay on treatment. The Sub-Committees considered that a revised base case should assume no discontinuation beyond cycle 8. The Pre-PBAC response argued that this scenario is clinically implausible and proposed reducing the probability of discontinuation by 50% in an alternative base case.

6.65 The cost of treatment of acute attacks was a key component of the costs in AHP. These are summarised in Table 10. As discussed in paragraph 6.50, the assumptions behind the treatment settings for acute attacks (hospitalisation, urgent healthcare visits or IV hemin administration at home) favoured givosiran, and using the distribution of settings from ENVISION instead of EXPLORE increased the ICER by [redacted]%.

Table 10: Cost estimation per acute AHP attack:

Attack treatment (Total attacks=483)	Attacks	Utilisation per attack (%)	Utilisation per attack (n)	Unit cost	Total cost per attack	Source
Setting						
Inpatient ward	161	59%	1	$12,563.00	$12,563.00	Inborn Errors of Metabolism, Major Complexity. AR-DRG item K63A
Infusion centre	64	24%	4	$111.60	$446.40	MBS item 14245
ED	47	17%	1	$724.00	$724.00	NHCDC 2021-22 ED visit, left without being admitted
Medications						
Hemin (product only)	332	69%	4	$1,214.00	$4,856.00	Local clinician. Dosed 1 vial x4 days
Opioids	262	54%	1	$23.08	$23.08	PBS item 12054K, 10 tablets
NSAIDs	217	45%	1	$16.15	$16.15	PBS item 3192B, 30 tablets
Hemin AE costs	332	69%	1	$168.24	$168.24	Anderson 2006.
Cost per attack					**$11,139.62**	Weighted mean

Source: Table 3.29 of the submission

AE= adverse event; ED= emergency department; MBS = Medical Benefits Schedule; NSAIDs =non-steroidal anti-inflammatory drugs; PBS =Pharmaceutical Benefit Scheme

6.66 A substantial component of the cost of managing acute attacks was the use of hemin. The cost per vial of hemin was assumed to be $1,214, based on local clinician input and from the Porphyria Association of Australia; however, this could not be independently verified. The cost of serious and non-serious AEs associated with hemin use was also modelled based on Anderson 2006, an open label study of hemin for acute porphyria. The assumed utilisation (four vials over four days) was substantially higher than what CADTH clinical experts reported (one vial per day, with an urgent health care visit not lasting more than one day). Since a greater proportion of BSC patients required hemin, this favoured givosiran. Decreasing the assumed hemin use to 2.5 vials for infusion centre visits (which was used in the base case for the sponsor's model to CADTH for urgent care) increased the ICER by [redacted]%. The Sub-Committees noted that patients are likely to receive up to 5 days hemin use to manage acute attacks, though they would not be hospitalised during all of this time. The PBAC noted that these modelled costs do not necessarily reflect advice from the sponsor hearing that in some cases patients require extended hospitalisation, which is associated with a high cost, especially where patients with seizures or respiratory paralysis require treatment in the ICU and where long-term neurological damage requires lengthy rehabilitation.

6.67 Another factor which affected the cumulative cost for acute attacks was the number of acute attacks (see Table 9). As discussed in paragraph 6.43, this had most impact in the AAR >24 health state, as reducing the assumed number of attacks in the AAR >24 health state from 33.1 to 28.22 (the lower 95% CI calculated by the submission) increased the ICER by [redacted]%.

6.68 The costs of chronic conditions were derived by multiplying the prevalence of symptoms reported by Neeleman 2018 with associated unit costs sourced from various Australian data sources. The costs per cycle of chronic conditions by health state were:

- AAR=0: $2,094.60
- AAR>0 to ≤4 = $6,059.63
- AAR >4 to ≤24 = $9,090.92
- AAR >24 = $9,090.92

6.69 The sources used to estimate chronic condition costs were not specific to AHP and were largely drawn from studies involving older, hospital-based populations or general pain-related conditions. In addition to demographic differences, the severity of symptoms reported, such as ambulance-attended chest pain or hospital-managed back pain, which may not reflect the typically less acute, chronic nature of AHP symptoms. These differences increased the uncertainty of the chronic condition costs applied in the model.

6.70 The submission also assumed that 82% of all patients in the AAR >4 to ≤24 and AAR >24 health states would be treated for opioid addiction. This was based on 9 out of 11 recurrent cases having analgesic dependence in Neeleman 2018. Opioid addiction was not a reported outcome in ENVISION. CADTH clinicians expressed that inclusion of opioid addiction in the model implied inappropriate use of opioids among AHP patients, and while AHP patients do receive management with opioids they would not be classified as addicted. The CADTH base case therefore assumed 0% of patients would be treated for opioid addiction in the AAR >4 to ≤24 and AAR >24 health states. A sensitivity analysis showed that removing this cost increased the ICER by [redacted]%.

6.71 Half-cycle correction was applied to all costs and outcomes. Inappropriately, half cycle correction was applied to the drug costs. A sensitivity analysis was conducted to remove the half cycle correction applied to drug costs, which led to an [redacted]% increase in the ICER.

6.72 A 5% annual discount rate was applied to both to costs and outcomes in the model. The undiscounted and discounted ICERs were substantially different. In the base case, undiscounted results showed givosiran was dominant compared to BSC (16.14 QALY gained with $[redacted] million in savings) whereas discounted results showed givosiran was more effective but more costly compared to BSC $155,000 to < $255,000/QALY). This was mainly attributed to the substantially greater cost of acute attacks in the BSC arm compared to the givosiran arm. Acute attack costs were more heavily impacted by discounting as they accrued over the time horizon. As such, the costs in the BSC arm were substantially discounted ($8.6 million undiscounted vs $3.5 million discounted) compared to givosiran ($[redacted] million undiscounted vs $[redacted] million discounted).

6.73 The baseline characteristics of the cohort in the model were based on characteristics of patients in ENVISION. A mean starting age of 38.80 years was assumed, with 89.4%

female patients having a mean onset of menopause at 51 years, and 23.4% of patients having a weight >75.6 kg. Changes in baseline characteristics had sizeable impacts on the ICER:

- Based on ELEVATE, an international AHP registry, among 151 patients with symptoms, the median age of symptom onset was 29 years (range 6-69 years). This suggested that the starting age of 38.8 years in the model may be overestimated. Assuming a starting age of 29 years in the model increased the ICER by [redacted]%.
- A reduction in the proportion of females in the model from 89.4% to 80% led to a [redacted]% increase in the ICER, which was attributed to fewer patients impacted by menopause.
- While the weight of AHP patients in Australia was unknown, ABS data[5] indicated that in 2022, 58.3% of females aged 35-44 in Australia were considered overweight or obese based on waist circumference and BMI. Assuming 58.3% of patients weighed >75.6kg increased the ICER by [redacted]%.
- The model assumed that 95% of female patients in the AAR=0 health state would discontinue treatment and experience no more attacks once they pass menopause. Increasing the age of menopause onset by 1 year (52 years old) led to a [redacted]% increase in the ICER, mostly attributed to an increase in incremental costs from givosiran.

6.74 Regarding the likely proportion of patients >75.6 kg, the PSCR noted that, "The ENVISION trial provides the most robust, patient-level weight data specifically in individuals with AHP, the target population for this submission". The PSCR also noted ENVISION was an international trial (including three Australian sites). The Sub-Committees noted there is uncertainty associated with this estimate, which is difficult to resolve, but considered the submission's use of trial data was a reasonable approach.

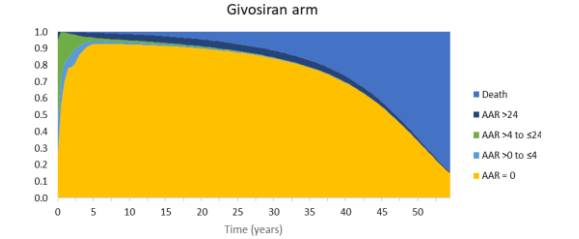
6.75 The cost of givosiran did not include any relevant mark-ups and therefore was underestimated. A sensitivity analysis conducted during the evaluation found the ICER increased by [redacted]% when mark-ups were applied to each dose of givosiran.

6.76 The Markov trace for the economic model is presented in Figure 4. Two additional traces showing the proportion of patients in the asymptomatic post menopause state were constructed during the evaluation.

5 https://www.abs.gov.au/statistics/health/health-conditions-and-risks/waist-circumference-and-bmi/latest-release

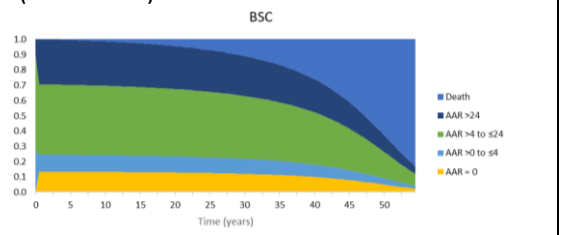
Figure 4: Markov trace for the base case of the economic model

Proportion of the patient cohort across all health states over time (Markov trace) for the givosiran arm



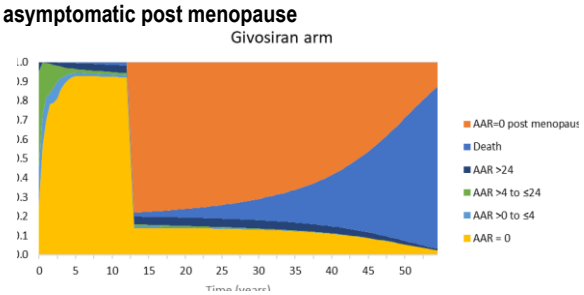
Source: Figure 3.7 of the submission

Proportion of the patient cohort across all health states over time (Markov trace) for the BSC arm



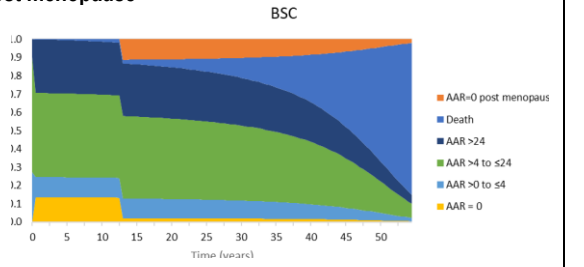
Source: Figure 3.8 of the submission

Proportion of the patient cohort across all health states over time (Markov trace) for the givosiran arm showing asymptomatic post menopause



Source: Figure generated during evaluation

Proportion of the patient cohort across all health states over time (Markov trace) for the BSC arm showing asymptomatic post menopause



Source: Figure generated during evaluation

6.77 The model, despite having a large number of cycles, has very few instances of transition between health states. There was effectively only one transition in BSC at cycle 1, and only 10 cycles with transitions in the givosiran arm, and after cycle 3, the majority of patients in the givosiran arm were assumed to be in the AAR=0 health state and remained there until death, regardless of whether they remained on treatment or not. This can be observed clearly in the Markov traces where the relative proportions of health states do not change in the BSC arm after cycle 1 (except for deaths and transition from asymptomatic to asymptomatic post menopause at age 51) and in the givosiran arm, the majority of patients are in the AAR=0 arm until moving to the post menopause state. As such, even small changes to inputs can have their impacts magnified due to the lack of interaction in the model, and the model being sensitive to a number of parameters.

6.78 No external validation was provided by the submission. The base case model estimates that, even post menopause, only 10% of patients (from an 89.4% female cohort) would be asymptomatic, which was not consistent with the natural history of AHP. Moreover, it was unclear whether it was reasonable to have estimated that 28-29% of patients will have severe AHP, given that at baseline (prior to ENVISION, in which all patients would be treated with BSC since their diagnosis) only 10% of patients had an AAR >24.

6.79 The key drivers of the model are presented in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact [Base case: $[redacted]/QALY gained.]
Utility decrements from chronic symptoms	The utility decrements related to chronic symptoms were based on non-AHP patients.	High, favours givosiran Applying the CADTH or NICE preferred utility estimates increased the ICER by [redacted]% and [redacted]%, respectively.
Assumption around givosiran discontinuation	The model assumed discontinuation of givosiran based on extrapolated time on treatment extrapolated from ENVISION, based on only six months of randomised comparative data and up to 36 months of open-label data from the OLE.	High, favours givosiran The Sub-Committees considered that this likely underestimates the use of givosiran. Assuming no further discontinuation after cycle 8 increased the ICER by [redacted]%.
Maintenance of response	The majority of patients who discontinue were effectively assumed to maintain treatment benefit as majority discontinued from the AAR=0 health state and were assumed to remain in the AAR=0 health state after discontinuation.	High, favours givosiran. Assuming 99.9% of patients discontinue after cycle 1 results in a dominant ICER with 3.93 QALY gain. Alternative approaches could not be tested.
Assumption of post menopause transition.	Only patients who are asymptomatic (AAR=0) prior to the onset of menopause were assumed to transition to the asymptomatic post menopause health state in the model. This assumption was inconsistent with the natural course of the disease in post menopause women.	High, favours givosiran Assuming 95% of all female patients in symptomatic and recurrent states become asymptomatic post-menopause increased the ICER by [redacted]%.
Proportion of acute treatment setting	The model used data from the EXPLORE study to determine the proportion of treatments required for acute attacks (hospitalisation 59%, emergency department visits 17%, or infusion centre 24%), which was inconsistent with the results from the ENVISION trial (hospitalisation 30%, emergency department visit/urgent healthcare 60%, or infusion centre/hemin at home 10%).	High, favours givosiran Applying the acute attack treatment data from ENVISION increased the ICER by [redacted]%.
Time horizon	The lifetime time horizon (62 years) based on 6 months of comparative data for givosiran from ENVISION and up to 36 months from ENVISION OLE.	High, favours givosiran Use of a 30-year time horizon increased the ICER by [redacted]%.
Inclusion of AAR >24 health state	The model included an AAR >24 health state which was not supported by clinical evidence and resulted in a substantially greater modelled number of acute attacks in BSC patients than the known number of attacks in AHP patients.	High, favours givosiran. Assuming no patients started the model in the AAR >24 health state increased the ICER by [redacted]%.
Number of attacks in the AAR>24 health state	The model assumed patients in the AAR>24 health state would have 33.1 attacks per year.	Changing the number of attacks per year to 28.22 increased the ICER by [redacted]%.
Age of initiation	The model assumed patients started the model at 38.8 years of age, based on the baseline characteristics of ENVISION.	Moderate. May favour givosiran though some uncertainty. Assuming an age of initiation of 29 years (as per ENVISION) increased the ICER by [redacted]%.
Proportion of patients weighing >75.6kg	The model assumes that 23.4% of patients would weigh more than 75.6kg (i.e. require two vials per dose).	Uncertain, may favour givosiran. In 2022, 58.3% of females aged 35-44 in Australia were considered to be overweight or obese when considering waist circumference and BMI. Using this percentage as a proxy for proportion >75.6kg, the ICER increased by [redacted]%.

Source: Constructed during evaluation

AAR = Annualised Attack Rate, ABS = Australian Bureau of Statistics, AHP = Acute Hepatic Porphyria, BSC = Best Supportive Care, CADTH = Canadian Agency for Drugs and Technologies in Health, ED = Emergency Department, ICER = Incremental Cost-Effectiveness Ratio, NICE = National Institute for Health and Care Excellence, OLE = Open-Label Extension, RRMS = Relapsing-Remitting Multiple Sclerosis.
The redacted values correspond to the following ranges:
[1] $155,000 to < $255,000

6.80 The base case summary of the results of the economic evaluation base-case ICER is presented in Table 12.

Table 12: Results of the economic evaluation

Component	Givosiran	BSC	Increment
Undiscounted costs	$[redacted]	$8,646,350	$-[redacted]
Discounted costs	$[redacted]	$3,482,891	$[redacted]
Undiscounted LYs	44.70	44.70	0.00
Discounted LYs	18.13	18.13	0.00
Undiscounted QALYs	29.09	12.95	16.14
Discounted QALYs	11.81	5.38	6.43
Incremental cost/QALYs gained (undiscounted)			-$[redacted]
Incremental cost/QALYs gained (discounted)			**$[redacted]**

ICER = incremental cost-effectiveness ratios; LY = life year; QALYs = quality adjusted life years; BSC= Best supportive care
Source: Table 3.38 and table 3.39, p107 of the submission
The redacted values correspond to the following ranges:
[1] Dominant
[2] $155,000 to < $255,000

6.81 The results of key sensitivity analyses are summarised in Table 13.

Table 13: Sensitivity analysis around the economic evaluation

Variables altered in sensitivity analysis	Incremental costs	Incremental QALY	ICER ($/QALYs)	% change from base case
Base case (BC)	$[redacted]	6.43	$[redacted][1]	0%
Discount rate (BC 5% costs and outcomes)				
0 % (costs and outcomes)	-$[redacted]	16.14	dominant	
3.5% (costs and outcomes)	$[redacted]	8.08	$[redacted][2]	-[redacted]%
Time horizon (BC lifetime; 63 years)				
30 years	$[redacted]	5.57	$[redacted][3]	[redacted]%
40 years	$[redacted]	6.14	$[redacted][1]	[redacted]%
Include PBS markup of $162.60 per script (BC not included)	$[redacted]	6.43	$[redacted][1]	[redacted]%
Removing half cycle correction to givosiran drug cost	$[redacted]	6.43	$[redacted][1]	[redacted]%
Menopause onset age (BC: 51 years)				
52 years	$[redacted]	6.43	$[redacted][1]	+[redacted]%
50 years	$[redacted]	6.43	$[redacted][4]	-[redacted]%
Assume 95% of female patients alive in the AAR=0, AAR >0 to ≤4 and AAR >4 to ≤24 health states will become asymptomatic (AAR=0) post menopause (BC: only patients who were asymptomatic pre-menopause assumed to become asymptomatic post menopause)	$[redacted]	4.76	$[redacted][3]	[redacted]%
Mean start age 39.8 years (BC = 38.8 years)	$[redacted]	6.37	$[redacted][4]	-[redacted]%
Mean start age 29 years as per ELEVATE median age of symptom onset (BC = 38.8 years)	$[redacted]	6.96	$[redacted][1]	[redacted]%

Variables altered in sensitivity analysis	Incremental costs	Incremental QALY	ICER ($/QALYs)	% change from base case
Proportion of females 80% (BC = 89.4%)	$[redacted]	6.41	$[redacted]1	[redacted]%
Assume baseline % of AAR >24 initiated in AAR >4 to ≤24 instead i.e. 0% start in AAR > 24 (BC: 10% start in AAR>24)	$[redacted]	6.25	$[redacted]1	[redacted]%
Change number of acute attacks per year in AAR >24 health state to 28.22 (BC 33.1 attacks per year)	$[redacted]	6.33	$[redacted]1	[redacted]%
Proportion of acute treatment setting informed by ENVISION (BC informed by EXPLORE)	$[redacted]	6.43	$[redacted]3	[redacted]%
No discontinuation of givosiran after cycle 8 (BC: discontinuation based on extrapolation)	$[redacted]	6.42	$[redacted]3	[redacted]%
Assume 99.9% discontinue treatment after 1 cycle (BC exponential extrapolation)	-$[redacted]	3.93	dominant	-
Assume AAR >0 to ≤4 health state chronic utility to be the same 'out of attack' utility (0.577) in EXPLORE in patients aged 35-44 [a]	$[redacted]	4.31	$[redacted]1	[redacted]%
Use chronic utility decrement for asymptomatic in all health states (i.e. -0.198 for all health states) as per CADTH	$[redacted]	1.02	$[redacted]5	[redacted]%
2.5 vial of hemin use per acute attack for infusion centres as per Sponsor's submission to CADTH (BC 4 vials)	$[redacted]	6.43	$[redacted]1	[redacted]%
Assume 58.3% patients weighted >75.6 kg (base case 23.4%)	$[redacted]	6.43	$[redacted]6	[redacted]%
Removing opioid addiction costs (BC included)	$[redacted]	6.43	$[redacted]1	[redacted]%
ESC revised base case				
40-year time horizon; no discontinuation of givosiran after cycle 8; chronic utility decrement of -0.198 for all health states. [b]	$[redacted]	0.98	$[redacted]5	[redacted]%
ESC requested additional univariate sensitivity analyses				
Assume givosiran discontinuation associated with progression to next worse health state (except for discontinuation at AAR >24) at time of discontinuation, then BSC transitions apply thereafter [c]	$[redacted]	2.86	$[redacted]5	[redacted]%
Remove AAR>24 Health State [d]	$[redacted]	6.17	$[redacted]3	[redacted]%
95% of all females progress to AAR =0 (asymptomatic) post menopause, including AAR>24 (commentary sensitivity did not include AAR>24 patients) [e]	$[redacted]	3.62	$[redacted]7	[redacted]%
ESC requested additional multivariate sensitivity analyses				
MVSA1: Remove ARR >24 health state; assume 95% of female patients will become asymptomatic post menopause	$[redacted]	3.56	$[redacted]8	[redacted]%
MVSA2: As above, plus 40-year time horizon; no discontinuation of givosiran after cycles 8; chronic utility decrement of -0.198 for all health states	$[redacted]	0.34	$[redacted]5	[redacted]%
MVSA3: As above, plus assume givosiran discontinuation associated with progression to next worse health state (except for discontinuation at AAR >4 to ≤24 as it is most severe health state in this analysis) at time of discontinuation, then BSC transitions apply thereafter	$[redacted]	0.28	$[redacted]5	[redacted]%

Source: Table 3.47, p113 of the submission and sensitivity analysis performed during the evaluation (see footnotes).

Abbreviations: AAR = annualised attack rate; AE = adverse events, BC = base case; BSC = best supportive care; CADTH = Canadian Agency for Drugs and Technologies in Health; CSR = clinical study report; DB = double blind; HR = hazard ratio; NICE = National Institute for Health and Care excellence; RRMS = relapse remitting multiple sclerosis; ToT = time on treatment

a Base case utility in AAR >0 to ≤4 health state was 0.418 (0.92-0.502). The chronic symptom utility decrement for AAR >0 to ≤4 changed to 0.343, which will give a utility of 0.577, based on baseline utility of 0.92. AAR >4 to ≤24 (and AAR >24) assumed to have utility decrement of 0.458 (based on 0.343+0.115, with 0.115 being the difference in the utility decrement between AAR >4 to ≤24 and AAR >0 to ≤4 in the base case).

b Three changes made: 1)'Settings' sheet E20 clicked to "Others, please include number of years" and H20 to 40; 2)'HRQoL' sheet D34:36 values set to equal that of D33 and 3)'ToT' sheet AI17:AI209 values set to 0.

c Transitions in BSC after discontinuation changed. In sheet 'Markov Givosiran', values in AG213:AG412 set to 0; formula in AH213 changed to "=U213*(1-L213-Q213)+U7*$S7" and dragged down to AH412; formula in AI213 changed to "==V213*(1-M213)+V7*$S7" and dragged down to AI412; and formula in AJ213 changed to =(W213*(1-N213)+W7*$S7)+(X213*(1-O213)+X7*$S7)" and dragged down to AJ412

d All patients who start in AAR>24 health state (sheet 'Clinical data' D8) moved to recurrent (sheet 'Clinical data' D7). Transition probabilities associated with AAR>24 health state combined with AAR >4 to ≤24 health state

e As noted in the PSCR response, the sensitivity analysis presented in the commentary was mislabelled. The sensitivity analysis presented in the commentary only assumed that 95% of females who were in the AAR =0, AAR >0 to ≤4 and AAR >4 to ≤24 health states become asymptomatic post menopause, which was consistent with CADTH's approach. However, it was not acknowledged that as CADTH's respecified base case did not include an AAR>24 health state, then effectively, all female patients, irrespective of AAR, could become asymptomatic post menopause.

The redacted values correspond to the following ranges:

[1] *$155,000 to < $255,000*
[2] *$75,000 to < $95,000*
[3] *$255,000 to < $355,000*
[4] *$135,000 to < $155,000*
[5] *> $1,055,000*
[6] *$355,000 to < $455,000*
[7] *$555,000 to < $655,000*
[8] *$755,000 to < $855,000*

6.82 The PSCR referred to a publication not included in the submission (Andersson et al 2003)[6], a large Swedish population-based study found that reported half of female patients reported a reduction in porphyria symptoms after menopause, with the remainder reporting no change. The PSCR argued that the approach taken in the submission was consistent with expert clinical input and that the sensitivity analysis modelling 95% of all female patients in the AAR >0 to ≤4 and >4 to ≤24 health states becoming asymptomatic post menopause is clinically unrealistic because not all women with AHP experience a positive effect of menopause on their disease. The Sub-Committees considered that the majority of patients who are not attack free prior to menopause would be likely to have less severe and less frequent attacks following menopause, and likely not require hospitalisation, and noted the submission's approach favoured givosiran. The Sub-Committees also noted that the financial estimates assumed that 5% of post-menopausal women would remain eligible for active treatment.

6.83 The Sub-Committees considered a respecified base case ICER should include a 40-year time horizon, no discontinuation of givosiran after cycle 8, and that the utility decrement for asymptomatic patients should apply to patients in all health states (i.e. -0.198). The Sub-Committees noted that the resulting ICER was $>

[6] Andersson C, Innala E, Bäckström T. Acute intermittent porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. J Intern Med. 2003;254(2):176-183.

$1,055,000/QALY. The Sub-Committees noted that multivariate sensitivity analyses further increased the ICER to up to $> $1,055,000/QALY.

6.84 The pre-PBAC response provided an alternative sensitivity analysis which the pre-PBAC response described as being more realistic than the ESC respecified base case. The scenario presented included a 40-year time horizon, utilities from the PBAC's consideration of ofatumumab in RRM and reduced continuation of treatment by 50% after year 4 of the model. This resulted in an ICER of $355,000 to < $455,000.

6.85 Overall, the Commentary noted that the results from the economic model presented in the submission were uncertain, likely underestimated and favoured givosiran. Given the large number of issues and the potentially high impact of these assumptions (e.g. assumptions around the time horizon, transition to asymptomatic post menopause, discontinuation, utilities, type of treatment setting for acute attacks and treatment benefit while off treatment could all change the ICER by more than [redacted]% individually) and given the interacting effects of multiple sensitive variables, the true ICER was likely to be substantially higher than the submission's base case ICER. The Sub-Committees advised the model structure was not reliable for decision-making.

Drug cost/patient/year

6.86 The drug cost per patient for givosiran and BSC in the trial, model and financial estimates are presented in Table 14.

Table 14: Cost per patient for givosiran and BSC

	Trial dose and duration	Givosiran Model	Givosiran Financial estimates
Mean dose	2.5 mg/kg SC monthly	2.5 mg/kg SC monthly (1.2 vials per administration at 99% RDI and 12 doses a year)	2.5 mg/kg SC monthly (1.2 vials per administration at 100% compliance and 12 doses a year)
Mean duration	Lifetime	118.71 months	Lifetime
Cost/patient/month	$[redacted] a	$[redacted] b	$[redacted] a
Cost/patient/year	$[redacted] c	$[redacted] c	$[redacted] d

Source: Constructed during evaluation

a DPMQ per script estimated as 1.2 vials at effective AEMP plus $162.60 (Total mark-ups/fee per script including wholesaler mark-up of $54.14, pharmacy mark-up of $99.79, and dispensing fee of $8.67)

b Estimated by dividing undiscounted costs associated with givosiran by mean duration of treatment in months, accounts for 99% relative dosage intensity; as discussed in paragraph 6.69, the cost of givosiran did not include mark-ups in the model.

c Cost per patient per month multiplied by 12

d Calculated by multiplying cost for 1.2 vials of givosiran (DPMQ $[redacted], Cell C65, 'Medison BIM' sheet of financial estimates') by 12.

e Did not include cost offsets in the financial model.

BSC = best supportive care, NA = not applicable

Estimated PBS usage & financial implications

6.87 This submission was considered by DUSC at a joint meeting of ESC and DUSC.

6.88 Table 15 presents the key inputs relied on in the financial estimates. The submission took an epidemiological approach to derive the financial estimates.

Table 15: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comments
Total Australian Population	2026: 26,152,276 2027: 26,432,595 2028: 26,832,733 2029: 27,231,553 2030: 27,622,493 2031: 28,004,790	Source: ABS 2023	The Sub-Committees agreed with the Commentary that this should be the population that the prevalence be applied to.
Total Australian population aged ≥12	2026: 22,357,918 2027: 22,616,601 2028: 22,987,425 2029: 23,357,001 2030: 23,716,600 2031: 24,066,169	Source: ABS 2023. The submission excluded patients aged below 12 years from the analysis to align with the TGA indication of givosiran.	Sub-Committees agreed with the Commentary the application of prevalence to this population only underestimated the number of AHP patients as prevalence estimates were based on whole country populations.
Average age of menopause	51 years	Gold 2011; Xu 2020	The assumed average age of menopause at 51 years aligns with data from Gold 2011 and Xu 2020, which report an average range of 50–52 years. Age of onset of menopause is consistent with the submission's economic model.
Estimated population of post-menopausal women (i.e. 51 years and above).	2026: 5,021,462 2027: 5,119,250 2028: 5,215,296 2029: 5,309,932 2030: 5,406,019 2031: 5,502,436	Source: ABS 2023. The submission applied a different uptake rate to this sub-population group compared to those ≥ 12 to 50.	The Sub-Committees considered that it was not appropriate to split the eligible population into pre- and post-menopausal. This split as applied to the estimates will result in an underestimate of patient numbers.
Total population aged ≥12 (excluding post-menopausal women)	2026: 17,336,456 2027: 17,497,351 2028: 17,772,129 2029: 18,047,069 2030: 18,310,581 2031: 18,563,733	Source: ABS 2023 (calculated by subtracting the estimated number of post-menopausal women (aged ≥ 51 years) from the total population.	
Prevalence rate of symptomatic/ diagnosed AHP (all types)	10.6/million (0.001006%) AIP: 5.9/million VP: 3.2/ million HCP: 0.8 /million Other (e.g. ADP and homozygous VP): 0.16/ million.	Elder 2013; The estimated prevalence of 10.6 per million was derived by summing the prevalence of each AHP subtype reported in the study. These subtype prevalences were calculated using reported incidence rates and assumed mean disease duration.	Elder 2013 reported the incidence (n=335) of AHP from 11 European countries over a three-year period. Elder 2013 focused on symptomatic cases and excludes asymptomatic gene carriers or undiagnosed individuals. The estimates were not based on direct observation but calculated by multiplying incidence rates by assumed disease durations (e.g. 40–60 years depending on AHP subtype) to the total population of each country. These durations are not aligned with the lifetime treatment horizon assumed in the PBS listing, which may limit the applicability of these figures to the Australian context. The Sub-Committees noted that the prevalence is in alignment with other studies presented in submission.
Prevalence of AHP in aged ≥12 (excluding post-menopausal women)	2026: 174.4 2027: 176.02 2028: 178.79 2029: 181.55 2030: 184.20 2031: 186.75	Calculated by applying the prevalence rate to the total population aged ≥12 (excluding post-menopausal women)	It was unreasonable to expect that the incidence of AHP in patients aged <12 would be the same as those aged ≥12 and these calculations therefore underestimate the population. Financial estimates using the whole Australian population were calculated during the evaluation as sensitivity analysis.

Data	Value	Source	Comments
Prevalence of AHP in post-menopausal women	2026: 50.52 2027: 51.50 2028: 52.47 2029: 53.42 2030: 54.38 2031: 55.35	Calculated by applying the prevalence rate to post-menopausal women (i.e. 51 years and above).	The Commentary considered calculation of these patient numbers seems reasonable.
Total eligible population with AHP (aged ≥12, including post-menopausal women)	2026: 225 2027: 228 2028: 231 2029: 235 2030: 239 2031: 242	Adding the above two population subgroups.	Given issues with calculation of prevalence of AHP (not using whole Australian population), likely underestimated.
Estimated proportion presenting with acute attack	73.7% (weighted average)	Elder 2013. The study presented data across different types of AHP patients, categorised by mode of presentation—those experiencing acute attacks (with or without hospital admission) and patients presenting with cutaneous symptoms were excluded.	The definitions of attacks used in Elder 2013 was broad and not standardised, not necessarily requiring hospitalisation or urgent medical care as opposed to the stricter criteria proposed for PBS listing. While this may lead to an overestimation, given the limited data on the condition these inputs may be reasonable. The Sub-Committees considered that this estimate was uncertain given variability in prevalence estimates.
Estimated proportion meeting the definition of "recurrent attacks"	31.4%	Neeleman 2018 - 11 out of 35 total symptomatic (defined as having had one or more confirmed acute attack in their life) patients were "recurrent" (defined as having had four attacks in any 12-month period or are on prophylactic haem therapy).	The definition of attacks in Neeleman 2018 differed to ENVISION and the requested restriction and this has potential applicability issues. This difference in definitions may introduce some uncertainty in the number of 'recurrent' patients who would be eligible for givosiran. The Sub-Committees noted that as Neeleman 2018 provided lifetime estimates, and not annualised rates of recurrent attack in any six-month period, the lifetime estimate will be an overestimate if applied as an annual estimate (as undertaken in the submission). However, it is apparent from individual patient data in the study that more people are eligible than the 31%, suggesting that this is an underestimate of the proportion of patients who would meet this definition at some point in their life.
Proportion meeting the proposed attack-based eligibility criterion	23.2%	Neeleman 2018 and Elder 2013. The submission combined the estimated proportion presenting with acute attack of 73.7% with the estimated proportion meeting the definition of "recurrent attacks" i.e. 31.4%. (73.7%*31.4%)	While Neeleman 2018 and Elder 2013 had applicability issues, if accepted, the proportion is arithmetically accurate. However, there are other published sources (e.g. Stölzel 2024) which were tested in sensitivity analyses. The Sub-Committees considered that this was uncertain given the uncertainties in the related inputs.
Subgroup: estimated patients aged ≥12 years, (excluding post-menopausal women)	2026: 40 2027: 41 2028: 41 2029: 42 2030: 43 2031: 43	This is calculated by applying the above proportion of meeting the attack-based eligibility criteria.	As above, the estimates are likely underestimated.

Data	Value	Source	Comments
Subgroup: estimated number of post-menopausal women	2026: 11.69 2027: 11.92 2028: 12.14 2029: 12.36 2030: 12.59 2031: 12.81	This is calculated by applying the above proportion of meeting the attack-based eligibility criteria.	It was unclear whether using the same proportion of meeting attack-based eligibility criteria for post-menopausal women was reasonable as post-menopausal women are expected to experience fewer attacks. May be overestimated.
Compliance	100%	Assumed by the submission	The assumption of 100% compliance in the financial model may overestimate medicine usage. Inconsistent with the economic model which used a 99% RDI. The Sub-Committees agreed with the Commentary but considered that it's likely to be very high.
Discontinuation and treatment duration	Implicitly 0% discontinuation	-	Not consistent with economic evaluation which assumed a discontinuation rate based on ENVISION. Omission will lead to overestimation of utilisation. The Sub-Committees considered that this was not necessary because a prevalent approach has been used.
Uptake rate	2026: [redacted]% 2027: [redacted]% 2028: [redacted]% 2029: [redacted]% 2030: [redacted]% 2031: [redacted]%	Sponsor assumption: These uptake rates are taken as the proportion of prevalent patients receiving the treatment each year (full 12-month treatment), hence pro rata adjustments may be necessary in interpreting the presented estimates.	The submission estimates that 50% of eligible pre-menopausal patients will receive treatment in Year 1, which may be too low given the high unmet clinical need for an effective treatment. The Sub-Committees considered that as this was a small patient group being treated by a specialist, with the requirement to have had two attacks requiring intervention, the uptake is likely to be higher in those with attacks. However, lifetime eligibility is not equivalent to annualised eligibility and as such not all eligible patients will be having attacks in same year which will affect the uptake initially.
Number treated	2026: [redacted]1 2027: [redacted]1 2028: [redacted]1 2029: [redacted]1 2030: [redacted]1 2031: [redacted]1	This is calculated by applying the above uptake rate each year.	Arithmetically accurate based on inputs but likely underestimated as AHP patient number and uptake rate in earlier years may be underestimated.
Uptake rate	2026: [redacted]% 2027: [redacted]% 2028: [redacted]% 2029: [redacted]% 2030: [redacted]% 2031: [redacted]%	Assumed only 5% of patients post-menopause will be treated, with same uptake rate for patients aged ≥12 years applied ([redacted]% in year 1 increasing to [redacted]% in year 6)	The assumption that 5% of post-menopausal women will be treated already includes an uptake rate and as such, this may be double counting and further reduction in uptake in this subgroup may lead to an underestimation of potential treatment costs.
Number treated	2026: [redacted]1 2027: [redacted]1 2028: [redacted]1 2029: [redacted]1 2030: [redacted]1 2031: [redacted]1	This is calculated by applying the above uptake rate	Arithmetically accurate if uptake rate accepted.

Data	Value	Source	Comments
Total estimated patients treated each year	2026: [redacted][1] 2027: [redacted][1] 2028: [redacted][1] 2029: [redacted][1] 2030: [redacted][1] 2031: [redacted][1]	Calculated by including both population subgroups.	Likely underestimated as AHP patients underestimated, and uptake rates may be underestimated.
Total vial usage	2026: [redacted][1] 2027: [redacted][1] 2028: [redacted][1] 2029: [redacted][1] 2030: [redacted][2] 2031: [redacted][2]	Calculated by multiplying the total number of treated patients by the total vials per patient per year (14.4 vials, based on 1.2 vials/month which was based on an assumption of 23.4% of patients being >75.6kg)	Consistent with estimated patient numbers. As dosing is weight-based, actual vial usage may vary across individuals, which could impact the accuracy of the projected vial estimates, and the proportion weighing >75.6kg in the Australian population was uncertain.
Scripts dispensed *	2026: [redacted][1] 2027: [redacted][1] 2028: [redacted][1] 2029: [redacted][1] 2030: [redacted][1] 2031: [redacted][1]	These were calculated by applying the assumed split of 10% initiation and 90% continuation to total treatment usage.	The calculation of the estimated scripts dispensed based on vial usage and assumption of initiation/continuation was accurate.
Givosiran	Average per script: AEMP = $[redacted] DPMQ = $[redacted]	DPMQ per script estimated as 1.2 vials at effective AEMP plus $162.60 (Total mark-ups/fee per script including wholesaler mark-up, pharmacy mark-up, and dispensing fee)	The AEMP was consistent with the submission's requested price per vial and calculations appear reasonable.
Total mark-ups/fee per script	$162.60	Including wholesaler mark-up of $54.14, AHI fee of $99.79 and dispensing fee $8.67.	This was consistent with the submission's economic model.
Patient copayment	PBS: $23.24 RPBS: $3.85 (not considered)	Based on trientine (250 mg capsule, PBS items 13124R)	The impact the copayment is likely minimal given the relatively low value of the co-payment compared to the drug cost. The Sub-Committees considered this reasonable.
MBS costs	$49.75 per administration of Givosiran	MBS item 105, with 80% rebate assumed in the base case.	Applied to each givosiran script

Source: Excel workbook 'Budget Impact Model' Table 4.1, p116, Table 4.3, p118, Table 4.4, p119, Table 4.6, p120, Table 4.7, p122, Table 4.8, p123, Table 4.9, p124, Table 4.13, p127 of the submission

ABS, Australian Bureau of Statistics; AEMP = approved ex-manufacturer price; AHP, Acute Hepatic Porphyria; AIP, Acute Intermittent Porphyria; ; DPMQ, Dispensed Price for Maximum Quantity; HCP, Hereditary Coproporphyria; PBG, Porphobilinogen; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RDI, Relative Dose Intensity; RPBS, Repatriation Pharmaceutical Benefits Scheme TGA, Therapeutic Goods Administration; VP, Variegate Porphyria;

*Scripts dispensed: twelve-month totals are presented; pro rata adjustments may be necessary in interpreting the presented estimates. No rounding is applied in translating to the usage / cost estimates.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *500 to < 5,000*

6.89 The estimated net financial impact of givosiran is presented in Table 16.

Table 16: Estimated use and financial implications (submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of givosiran						
Cost to PBS less copayments (effective)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][3]
Estimated financial implications for other medicines						
Cost to PBS less copayments [b]	NA	NA	NA	NA	NA	NA
Net financial implications						
Net cost to PBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][3]
Net cost to MBS [c]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to PBS and MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][3]

Source: Table 4.10 and Table 4.11, p 124; Table 4.13, p 127 of the givosiran submission

[a] Assuming 12 scripts (each script an average of 1.2 vials) per year as estimated by the submission.

[b] no cost offsets from potential reduction in acute or chronic treatments considered in financial estimates

[c] Assuming 80% rebate from MBS item 105 (80% of $49.75) per MBS service applied to each script. Does not include any cost offsets from potential reduction in acute or chronic treatments as assumed in economic evaluation.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *$10 million to < $20 million*

[3] *$20 million to < $30 million*

[4] *$0 to < $10 million*

6.90 The total cost to the PBS of listing givosiran was estimated in the submission to be $20 million to < $30 million in Year 6, and a total of $90 million to < $100 million in the first six years of listing.

6.91 The total number of patients with AHP was likely underestimated as the prevalence from Elder 2013 was applied only to the population aged ≥12 and above, despite the prevalence from Elder 2013 being calculated based on the whole populations of 11 European countries. Given that symptoms are rare before onset of menses and the majority of AHP patients are female, the proportion of symptomatic AHP under 12 years is likely to be substantially lower than the ≥12 years population. In addition, the prevalence rate in Australia is uncertain. The Pre-PBAC response noted that estimates provided by Australian clinicians suggested approximately 20 patients would be eligible in Year 1, increasing by around 5 patients annually. The Year 1 estimate was a sum of current patients from specialist clinicians and comprises 5-10 prevalent patients each in NSW and Victoria, 3-5 in Queensland and 0.5-1 in the remaining states and territories. The annual increase of 4-6 patients per year is based on the clinicians' experience and their review of epidemiology publications.

6.92 No cost offsets were included in the financial estimates. While this was appropriate for the financial estimates, there may be significant cost offsets to the health system, such as those from reduced hospitalisations and emergency presentations.

6.93 The Commentary noted that the comparability of the study population from Neeleman 2018 (AIP only and from Netherland patients) to the Australian AHP population is uncertain (see paragraph 6.39). The Sub-Committees considered that the estimates drawn from the literature are likely to provide an underestimate because 1) the definition of attack used in Neeleman 2018 reflects more stringent

criteria than the proposed indication, 2) attacks are likely to be irregular, and 3) the severity of attacks can vary. The Sub-Committees considered that the method used to estimate the number of patients meeting the clinical criterion in relation to the number of attacks of appropriate severity in the relevant period (2 attacks within 6 months) was flawed as it utilised a lifetime rate of attack, where it is possible to have 4 attacks in any year while not having 2 attacks (of the appropriate severity) within the previous 6 months. The estimates derived from Neeleman 2018 may be inappropriate as some 'recurrent' cases which were included in the estimates maybe excluded under the proposed restriction while some 'symptomatic' cases which were excluded from the estimates maybe eligible under the proposed restriction. In addition, Neeleman 2018 reported a substantially lower rate of patients experiencing acute attacks than the assumptions made in the submission (39.7% compared to 73.7% in the submission). The Sub-Committees also noted the age of the data in Neeleman 2018 and considered that more up to date data would be beneficial. Overall, the proportion of AHP patients eligible for treatment was uncertain and may be overestimated, as Stölzel 2024 reported a substantially lower rate of patients with at least two attacks in the previous six months (7.4% compared to the 23.2% assumed in the submission).

6.94 The submission estimated that 40-43 patients annually (who were not post-menopausal women) would meet the proposed eligibility for PBS-subsidised givosiran. In the post-menopausal population, it is estimated that 12-13 patients currently meet or previously met the eligibility criteria. The submission noted that the requested eligibility criteria do not impose a specific exclusion criterion (or a discontinuation requirement) once patients reach menopause; some patients remain at risk of AHP attacks/symptomatic relapse post-menopause, and there exists a clear clinical need for givosiran among these patients. The submission assumed that 5% of post-menopausal women would remain eligible for active treatment. The submission expected that givosiran usage in this subgroup would mostly be among patients who commenced treatment prior to menopause (i.e., patients continuing on the treatment into post-menopausal years). No distinction is made between patients initiating treatment post-menopause and prior to menopause in terms of usage in the current prevalence model. The Sub-Committees considered that the inclusion of separate estimates for the post-menopausal sub-population to be unnecessary and could lead to the prevalence estimates being underestimated.

6.95 The proportion of patients who weigh >75.6kg was uncertain and had a substantial impact on the financial estimates.

6.96 Sensitivity analyses around the financial estimates were conducted during the evaluation (Table 17).

Table 17: Results of one-way sensitivity analyses (Net cost to PBS and MBS)

Scenario Analysis	2026	2027	2028	2029	2030	2031	%Δ
Base Case							
Effective price	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][3]	
Total AHP population by applying 10.6% to the whole population instead of ≥12 years and above							
Effective price	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][4]	$[redacted][4]	$[redacted][3]	17%
Eligibility Criteria Based on Attack Frequency – Reduced the proportion from 23.16% to 7.4% in Stölzel 2024							
Effective price	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	-68%
Post-Menopausal Women Uptake Rate – Increased to 5%							
Effective price	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][3]	1%
Proportion of AHP patients with acute attacks– Adjusted from 73.7% to 39.7% based on Neeleman 2018							
Effective price	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][1]	$[redacted][1]	-46%
Overall Uptake Rate – Increased from 50% in year 1 to 75%							
Effective price	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][3]	$[redacted][3]	17%
Assume 58.3% patients weighted >75.6 kg							
Effective price	$[redacted][1]	$[redacted][1]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	33%
Assume 11.8 % prevalence rate from Horie 2023							
Effective price	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][3]	$[redacted][3]	$[redacted][3]	17%

Source: Compiled during evaluation using 'Attachment 4.1- budget impact model' excel workbook

The redacted values correspond to the following ranges:

[1] $10 million to < $20 million

[2] $20 million to < $30 million

[3] $0 to < $10 million

6.97 In the PSCR the sponsor provided a sensitivity analysis for increased uptake in Years 1–3 (Table 18). The Sub-Committees undertook a sensitivity analysis (Table 19) removing the subpopulations (<12 years and post-menopausal) and applying the prevalence and uptake rates to the entire Australian population.

Table 18: PSCR sensitivity analysis with increased uptake rate in Years 1-3

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Patients treated[1]	[redacted]					
Scripts dispensed[1]						
Net cost to (R)PBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][3]

Source: Table 2, p6 of the PSCR.

The redacted values correspond to the following ranges:

[1] < 500

[2] $10 million to < $20 million

[3] $20 million to < $30 million

Table 19: DUSC sensitivity analysis applying prevalence to total Australian population

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total population	26,152,276	26,432,595	26,832,733	27,231,553	27,622,493	28,004,790
Prevalence	0.001006%					
Proportion of AHP total population[b]	263	266	270	274	278	282
Eligible (total population)	61	61	62	63	64	65
Uptake	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]

Cost to the PBS	$[redacted][3]	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][5]
Total costs to the PBS (less copayments)	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][5]**

[a]Assuming 12 scripts (each script an average of 1.2 vials) per year as estimated by the submission.
[b]Applying estimates to the population as a whole.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*
[3] *$10 million to < $20 million*
[4] *$20 million to < $30 million*
[5] *$30 million to < $40 million*

Quality Use of Medicines

6.98 The Sub-Committees noted that givosiran is a new type of medicine for which there is limited clinical experience and that givosiran has the potential to induce cytochrome P450 enzymes in the liver increasing the maximum serum concentration, and the clearance time of a number of other medications. Additionally, givosiran has a significant number of other drug and food interactions. The Pre-PBAC response noted that the Product Information specifies appropriate usage, potential drug and food interactions, and monitoring requirements. Educational materials will also be prepared to highlight these considerations and support quality use of givosiran.

Financial Management – Risk Sharing Arrangements

6.99 No risk sharing arrangement was proposed by the submission.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of givosiran for treatment of acute hepatic porphyria (AHP). The PBAC acknowledged the high unmet clinical need for treatments for AHP, which results in chronic symptoms and acute attacks that can include intense and persistent pain, muscle weakness, gastrointestinal, cardiovascular and neurological symptoms. The PBAC accepted the clinical claim of superior efficacy compared with best supportive care in reducing acute porphyria attacks. The PBAC considered that the incremental cost-effectiveness (ICER) was uncertain due to the limited data informing the model and range of disease severity for patients with AHP, but that in the context of this rare disease with very substantial impacts on patient quality of life, givosiran would be considered acceptably cost-effective with a price reduction that would result in an acceptable cost per patient per year, in line with other treatments for rare diseases funded on the PBS, accounting for clinical need, available evidence, nature of the benefits and size of the patient population. However, the PBAC considered that further clinical input is needed

regarding the patient numbers, likely circumstances of use, and treatment continuation, which are required for establishing a risk-sharing arrangement.

7.2 The PBAC noted that there was a high unmet clinical need for treatments to prevent attacks for patients with AHP, with current treatments for AHP described as ineffective, invasive, difficult to access and associated with serious side effects. The PBAC noted the substantial impact on QoL for patients and carers from both acute and chronic symptoms associated with AHP, as expressed in the consumer comments. The PBAC also noted the high cost to the health system for hospitalisations associated with severe and acute attacks.

7.3 The PBAC noted that the proposed restrictions were generally aligned with the inclusion criteria for the pivotal trial (ENVISION). The PBAC noted that the proposed restrictions did not require genetic confirmation of the diagnosis of AHP, but considered this was reasonable as diagnosis is based on a well-defined combination of clinical features and biochemical criteria (as proposed in the restrictions). The PBAC noted the restrictions required patients to have had at least two attacks within the six months prior to treatment initiation, with attacks defined as requiring hospitalisation, presentation at an emergency department or medical intervention via a porphyria clinic. While this was consistent with the inclusion criteria in ENVISION, the PBAC noted that attacks can be sporadic and vary substantially in severity. The PBAC considered that patients with less frequent but very severe attacks would want to access treatment, and patients with frequent but much less severe attacks could also access treatment under the proposed restrictions. The PBAC considered that the definition and frequency of attacks as proposed in the restrictions were appropriate and consistent with the ENVISION trial, but the nature of the condition means that it is unclear whether they are likely to capture patients most in need of treatment.

7.4 The PBAC considered it was appropriate for the restrictions to allow patients on prophylactic treatment, with a documented history of acute porphyria attacks (as per the initiation criteria), to receive treatment with givosiran without the need to demonstrate additional attacks and noted that the Secretariat revised restrictions addressed this concern. The submission requested a grandfathering restriction which will apply to patients currently receiving treatment through the Expanded Access Program (EAP). It was noted that grandfathered patients must also have had a documented history of at least two porphyria attacks prior to initiation of givosiran. Providing they meet the criteria for diagnosis of AHP, these patients would also be eligible for treatment under the initial treatment restriction with revisions proposed by the Secretariat.

7.5 The proposed continuation criteria require patients to demonstrate improvement in the frequency or severity of AHP attacks while on treatment. As the proposed continuation criteria were not specific or clearly defined in terms of outcomes, the assessment of response would rely on clinical judgement, which the PBAC considered was reasonable. The PBAC considered that it would be expected that patients would

trial discontinuation of treatment, but that the timing of this would be highly individualised and therefore not appropriate for incorporation into the restrictions.

7.6 The PBAC considered that the proposed clinical place for givosiran was appropriate and the population, although adequately captured in the proposed restrictions, potentially included patients with a range of symptom severity.

7.7 The PBAC considered the nominated comparator of BSC was appropriate. The PBAC noted that symptomatic treatments for AHP would not be replaced by givosiran, though their use may decrease with reductions in the number and severity of attacks.

7.8 The submission was based on one randomised, 6-month, double-blind, head-to-head, phase 3 trial of givosiran (ENVISION), supported by a 30-month open-label extension phase of ENVISION and other supplementary evidence from phase 1/2 trials. The PBAC noted that the RCT phase of the ENVISION trial had a low risk of bias. The PBAC noted that ENVISION included predominantly patients with the AIP subtype of AHP (95% of patients), whereas other subtypes could make up 20-40% of the likely PBS population. The PBAC considered that it is likely that treatment will be effective in all subtypes of AHP based on biological similarities and the mechanism of action of givosiran. Overall, the PBAC considered the trial population and supportive care received in ENVISION were likely to be representative of AHP patients in Australian clinical practice.

7.9 The PBAC noted that in the RCT phase of ENVISION givosiran demonstrated a statistically significant reduction of 74% in the primary outcome of mean AAR porphyria attack composite endpoint compared to placebo in AIP patients (rate ratio=0.26, $p<0.0001$). The PBAC noted that for most other secondary measures (including biochemical markers, annualised days of hemin use, and some patient reported outcomes) givosiran also demonstrated superiority over placebo. The PBAC noted that, although only 6 months of comparative data were available, the extension phase indicated that the treatment effect was maintained over 36 months. The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data.

7.10 The PBAC noted that patients randomised to givosiran in the ENVISION trial reported statistically significantly increased incidences of injection-site reactions, nausea and chronic kidney disease and noted that, as the duration of RCT phase of ENVISION was only six months, long-term risks of treatment with givosiran are unknown. The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data and a claim of inferior safety would be appropriate.

7.11 The PBAC noted the submission presented a modelled cost-utility economic evaluation based on the clinical data from the ENVISION trial, supported by additional data from the ENVISION OLE study, literature, and inputs from Australian clinical experts. The PBAC noted there was only 6 months of comparative data, in a limited number of patients to inform the economic model, with outcomes extrapolated to a 62-year time horizon, and many inputs drawn from literature not necessarily representative of AHP patients. This resulted in a high level of uncertainty in the modelled outcomes. The model also included a number of structural assumptions

which favoured givosiran and are likely to underestimate the ICER (inclusion of AAR >24 health state, assumptions regarding treatment benefit after discontinuation, transitions following menopause). Additionally, several inputs were not well-justified and had a substantial impact on the ICER, favouring givosiran (utility decrements for chronic symptoms, discontinuation rates, healthcare settings and costs for treatment of acute attacks). Further, the ICER was sensitive other inputs that were from the ENVISION trial but may not reflect the PBS population (the proportion of patients >75.6kg and age at diagnosis/treatment initiation). The PBAC noted that there was a high level of variation in the ICER, with interacting effects of multiple sensitive variables, and noted advice from the Sub-Committees that the model structure was not reliable for decision-making. However, given the paucity of data available for this rare condition, the PBAC acknowledged that revising the model structure or inputs is unlikely to resolve the uncertainty associated with the modelled outcomes. The PBAC considered that the value proposition was difficult to assess with a traditional ICER due to the limited long-term comparative clinical data, the small number of patients included in the trial, and the range of disease severity for patients with AHP.

7.12 The PBAC reflected on previous determinations made for other rare diseases where no effective alternative therapies were available. The PBAC compared the available evidence, nature of the benefits, ICERs, numbers of patients expected to be treated, and the cost per patient per year for givosiran at the proposed price, with other high-cost treatments for rare diseases funded on the PBS. The PBAC considered that in the context of this rare disease with very substantial impacts on patient quality of life, givosiran would be considered acceptably cost-effective at a cost of not more than $[redacted] per patient per year. In providing this advice, the PBAC acknowledged treatment with givosiran is likely to provide substantial reductions in cost to the healthcare system due to reduced hospitalisations and use of hemin.

7.13 The submission took an epidemiological approach to derive the financial estimates. The PBAC noted that, although the submission estimated that a relatively small number of patients would be eligible for treatment with givosiran, there were several important inputs to the estimates that led to uncertainty in patient and vial numbers, which were compounded by the high cost per vial for givosiran. The PBAC agreed with its Sub-Committees that the prevalence should be applied to the whole population, which would increase the total patient pool. The PBAC considered that it was unclear whether the data from Elder 2013 and Neeleman 2018 was appropriately applied in estimating the proportion of patients meeting eligibility criteria in terms of acute attack severity and frequency. The PBAC noted that the submission's estimated proportion of AHP patients meeting eligibility criteria appeared overestimated compared to estimates in the literature (Neeleman 2018 and Stölzel 2024). The PBAC also considered that uptake rates were uncertain. As noted in paragraph 7.3, attacks can be sporadic and vary substantially in severity and the PBAC considered it was unclear to what extent patients with less frequent but very severe attacks would access ongoing treatment. The PBAC also considered that the rate of discontinuation of treatment was unclear, especially with regard to the impact of menopause on the

need for ongoing preventive treatment. Further, the PBAC noted that the expected utilisation of givosiran was sensitive to the assumed proportion of patients weighing >75.6kg, who would require 2 vials of givosiran monthly. The PBAC considered that additional clinical advice regarding the patient population likely to be treated was required to give greater confidence in the estimated financial impact of listing givosiran.

7.14 The PBAC considered that an RSA would be required given the very high cost of givosiran, the uncertain cost-effectiveness and the uncertainty in patient numbers, duration of treatment given the broad continuation criteria, and the average number of vials required per dose. In addition, the PBAC considered there was a risk of use in patients with less severe or less frequent attacks where use is likely to be less cost-effective. The PBAC requested that the sponsor provide an RSA proposal based on revised utilisation estimates.

Outcome:
Deferred

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

The sponsor had no comment.