Zorginstituut Nederland

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Datum
24 oktober 2023

Onze referentie
2023018177

Managed access for and appropriate use of givosiran in the Netherlands

Stakeholders
Porphyria Expert Center Rotterdam, Erasmus MC;
Patiëntvereniging Acute Porfyrie (PVAP);
Zorgverzekeraars Nederland (ZN);
National Health Care Institute.

Aim of this document
The aim of this document is to standardize evidence based decision making for initiation, monitoring and cessation of treatment givosiran in the Netherlands, in patients who are expected to benefit from treatment. This is essential since AHP is rare and needs specialist care and costs of givosiran per patients are substantial.

Erasmus MC Universitair Medisch Centrum Rotterdam

PVAP

Zorgverzekeraars Nederland

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Background

Acute hepatic porphyria (AHP)

AHP is a group of rare inborn errors of heme metabolism, with an estimated prevalence of 0.24 per million. Symptomatic AHP patients may suffer from recurrent acute attacks characterized by severe neuropathic abdominal pain, constipation, nausea/vomiting, back pain, hypertension, muscle weakness, a rapid heartbeat (tachycardia), behavioral changes, and seizures, which in some cases may lead to death. These attacks are caused by supraphysiological increases in the neurotoxic delta-aminolaevulinic acid or d-ALA. The majority of patients suffering attacks are young females. Recurrent attacks occur in 3-5% of patients with AHP whom have presented with attacks.
The only curative treatment for AHP is liver transplantation, which is rarely performed because of morbidity and mortality associated with the procedure.
Standard treatment of AHP primarily aims to reduce the number and/ or duration of acute attacks. This can be achieved by counseling patients about those factors, which may luxate an attack and can be avoided. Attacks can be provoked by drugs (www.drugs-porphyria.org and alcohol), hormonal changes (menarche and menstrual periods), fasting, carbohydrate reduced diets, surgery and infections. It is not exceptional that attacks occur without an obvious provoking factor. The effects of the provoking factors and the development of recurrent attacks (without an evident provoking factor) is unpredictable.
In case of an attack, medical treatment is initiated (see current treatment options below).
With family counseling, asymptomatic gene mutations carriers (never had an attack) can be identified and whom are at risk for an attack, can be counseled in order to prevent attacks. For them the main goal of treatment is to reduce the risk of attacks with reliable information on provocative factors and potential complications.
A secondary treatment target is to screen for secondary long term complications like hypertension, renal insufficiency and hepatocellular carcinoma. These complications can also occur in asymptomatic and low attack frequency patients, though the prevalence seems higher in patients with frequent attacks. The screening and treatment of hypertension is mostly performed by the general practitioner; whilst occurrence of the latter two complications are monitored by the expert center.

Acute hepatic porphyria
Phenotypes
-asymptomatic carriers (majority of patients, approximately 80%)
-a single of few attacks over a life time (~18% of patients)
-recurrent attacks; 2 or more attacks in the last 6-12 months (~0.5% of patients)
-on heme prophylaxes because of previous frequent attacks; currently with or without attacks (~1% of patients)

Long-term complications
-hypertension
-renal insufficiency, irrespective of hypertension
-hepatocellular carcinoma (comparable risk to hepatitis C related liver cirrhosis)

Current treatment options
Prevention and treatment of attacks are the cornerstone of treatment. Mild attacks may be treated with oral carbohydrate administration and pain relief.

Heme arginate (Recordati Rare Diseases®), which is available since the 1980's, is indicated for the amelioration of severe attacks of acute porphyria, after initial carbohydrate therapy is known or suspected to be insufficient. Heme is administered intravenously daily during an acute attack, for at most 4 subsequent days. A small number of patients develops recurrent attacks, which cannot be avoided by avoidance of precipitating factors. Although off label, widely accepted standard clinical practice is to treat these patients with recurrent severe attacks prophylactically with heme (e.g., weekly, once every two weeks, or monthly) in order to prevent morbidity or even mortality. Case studies have shown a reduction in attack frequency when patients without prophylaxis treatment are switched to prophylaxis treatment with heme.
Patients with recurrent attacks of AHP use a wide range of healthcare resources, and acute attacks are generally associated with urgent care or emergency room (ER) visits and inpatient hospitalizations. For patients that present to the hospital with an attack, 20-30% have severe hyponatremia, uncontrolled systemic arterial hypertension, and/or seizures and often are admitted to the intensive care unit (ICU). The median inpatient length of stay for an acute attack is expected to be approximately 5 days for patients with AHP who experience recurrent attacks. Depending on the severity of an attack, the recovery of an attack may take months to years (and is not always complete), and in between attacks chronic complaints, such as fatigue and chronic pain, remain present. Side effects of heme are also well known. Heme contains iron, after years of treatment patients can develop pathological iron accumulation. And, several patients require a port-A-caths when intravenous access has become problematic, infections and thrombosis are known problems related to port-A-caths. Heme arginate is also considered to induce dependence, heme can stimulate HO-1 enzyme that is involved in the breakdown of heme.

Givosiran for treatment of AHP
On March 3 2020 the European Commission (EC) authorized givosiran for the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older. Givosiran is synthetic small interfering RNA (siRNA) molecule directed against 5-aminolevulinic acid synthase. The pharmaceutical company (Alnylam®) performed several clinical studies to evaluate the safety and efficacy of Givosiran at different doses. The final dose was 2,5 mg/kg of body weight administered once every month by subcutaneous injection.

The studies all showed a significant effect of Givosiran on the urine concentration of d-ALA. The results for the functional outcomes were also effective, with an > 90% reduction in attack frequency, reduction in the number of heme infusions needed and reduction in morphine use.

<u>In summary trials:</u>
Phase III multi-centre, double blind, randomized, placebo-controlled trial (ENVISION):
Givosiran was more effective than placebo in reducing the yearly number of serious porphyria attacks. This study involved 94 AHP patients, who had experienced at least two attacks within 6 months before enrollment. Patients were treated every month with 2,5 mg/kg Givosiran or placebo for 6 months. Patients who received Givosiran had on average 3 symptomatic attacks per year compared to 13 in those receiving placebo (EMA). Attacks were based on the symptomatology in the individual patient, with a need for acute treatment of the

attack, without biochemical proof of the attack. Biochemical abnormalities strongly improved and the number of heme infusions strongly decreased. Physical Component Summary score or SF-12 (range 0=worst functioning to 100=best functioning), did not change. But overall health status according to patients in the givosiran group improved 'much or very much' in 59% versus 18% in the placebo group.

Phase III extension: open label extension studies with all patients in phase III
Still ongoing in the majority of patients who participated in the before mentioned ENVISION trial. The one year data are currently presented (summer 2020) on international congresses (www.Alnylam.com).

It is not so clear whether givosiran treatment also prevents or diminishes long-term complications like hypertension, renal insufficiency and hepatocellular carcinoma.

EMA Post marketing requirement of Givosiran
Acute hepatic porphyria is rare, and Givosiran was designated an 'orphan medicine' (a medicine used in rare diseases) on 29 August 2016. The phase III trial has demonstrated that Givosiran is effective in reducing porphyria attacks. The side effects of Givosiran treatment were mostly mild to moderate and most resolved during the study. The European Medicines Agency therefore decided that Givosiran's benefits are greater than its risks and it can be authorized for use in the EU.

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Givosiran have been included in the summary of product characteristics and the package leaflet. As for all medication, data on the use of Givosiran are continuously monitored. Side effects reported with Givosiran are carefully evaluated and any necessary action is taken to protect patients. EMA issued no specific obligations. (EMA/62114/2020; EMEA/H/C/004775)

Porphyria expert center Rotterdam, Erasmus MC
The Erasmus MC is the only recognized porphyria expert center in the Netherlands. The center is involved in the diagnosis and follow-up of patients with acute hepatic porphyria (and for erythropoietic protoporphyria and porphyria cutanea tarda).
We have a local acute porphyria registry and participate in the European registry (EPNET association). We collaborate with internists in other Dutch hospital to improve the care for individual patients.

The porphyria center Rotterdam experts have unanimously concluded, based on the results from the clinical studies and extensive experience with heme on demand and heme prophylactic treatment , that selected patients with AHP (with recurrent attacks or home prophylaxes) will strongly benefit from treatment with givosiran. We have observed that the quality of life of Dutch patients is severely impaired by recurrent attacks and accompanying chronic symptoms, and that the attacks induce psychiatric disorders and social limitations. Currently, evidence for efficacy and safety of Givosiran is sufficient to conclude that individual patients will likely benefit from treatment. Since Givosiran came available for selected patients via an early access program, we have already observed major beneficial

effects our patients on treatment. This early access program was made possible by the pharmaceutical company (Alnylam®) following approval by the Dutch health inspection.

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Purpose of this document
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References for supportive background

- Neeleman et al. 2018 Burden of recurrent AIP in JIMD of Journal of inherited metabolic disease
- Stölzel et al. 2019 review in Gastroenterology
- Sardh et al. 2019 Givosiran phase I in NEJM
- Neeleman et al. 2020 Review in Neth J Medicine
- Gouya et al. 2020 Explore natural history AIP in Hepatology
- Balwani et al. 2020 Givosiran ENVISION trial phase III in NEJM
- Massachi et al. Cost savings hemin versus givosiran AIP 2020 in Journal of Medical Economics

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Eligibility for treatment
Patients who match all following criteria are eligible for treatment with givosiran[1]:

- Patients with a confirmed diagnosis of acute hepatic porphyria: confirmed by conclusive biochemistry with either a confirmed gene mutation and/or decreased enzyme activity. Acute hepatic porphyrias are acute intermittent porphyria (AIP), Hereditary Coproporphyria (HCP), variegate porphyria (VP) en ALA-dehydratase deficiency (ALAD).
- Patients aged 12 years or older - with one exception: children/ babies with symptomatic autosomal recessive ALAD porphyria can start at any age (currently eight identified patients world-wide, one in the Netherlands)
- Patients that, in the 12 months preceding treatment initiation, suffered from at least two confirmed attacks or one severe confirmed attack, or treatment with heme prophylaxes. Severe is defined as an attack with neurological deficits lasting for more than 1 month despite heme therapy, convulsions, or debilitating or impairing new psychiatric symptoms. These findings should be confirmed by the treating neurologist or psychiatrist.
- A positive decision for start of treatment by the indication committee
- Patients should have sufficient cognitive function for basic daily activities and communication, as assessed by the indication committee.

Givosiran will not be started if any of the following apply:

- The patient is diagnosed with a second progressive life expectancy limiting condition where treatment would not provide benefit.
- The patient is unwilling to cooperate with suggested diminished use of heme or morphine, or unwilling to attend the Erasmus MC.

Since givosiran is registered in the Netherlands for treatment of acute hepatic porphyria for adults and adolescents from 12 years and older, its use in patients younger than 12 years of age is off-label.

Indication committee
The Erasmus MC has set up an indication committee. All patients who might benefit from treatment with Givosiran will be discussed in this committee. The indication committee decides on:

- the initiation of treatment for each individual patient, based on the eligibility criteria in this protocol.
- the continuation of treatment for each individual patient based on the efficacy of Givosiran in individual patients and the stop criteria described in this protocol. Information on the treatment efficacy will be presented to the committee at set time points (6 month after initiation, one year after initiation, two after initiation and thereafter each 5 years).
- dose reductions in patients in complete remission for the duration of a year (see dosing)
- delegation of drug administration to another center / hospital / services for home care.

The indication committee will discuss all patients on Givosiran treatment at least twice a year, focusing on treatment response. In individual cases, interim analysis

[1] Treatment of patients already on givosiran treatment via the early access program will be continued.

will be performed on request by the indication committee (e.g. in case of adverse events, deterioration at an earlier stage etc.). Evaluation of this protocol will be performed every 2 years.

The committee will exists of at least three persons:
1 At least 1 metabolic internist from the Porphyria Expertcenter Rotterdam
2 Independent chair
3 At least 1 independent outside member (participation via Teams or life). Either external, but involved in acute porphyria patient care of in metabolic care. Or involved but independent in the Erasmus MC

Optional participants include (invited and preferable present): Nurse or specialist nurse involved in metabolic patients, Medical ethics representative, Administration.

Dr Langendonk or substitute will coordinate these meetings. The composition of the committee will be revised yearly and changed upon requirements and new insights. The committee meetings will be scheduled at least 4 times a year, and in the first year, each patient will be discussed at least twice a year, after the first year each patient will be discussed at least once a year.

Dosing
The starting dose of givosiran is 2,5 mg/kg/month. This dose is rounded down by max 10% to fit to the available content of 1 vial. For example, if the starting dose for a patient results in 1,08 ml givosiran, this dose will be rounded down to 1 ml to match the content of 1 vial (1 vial is 1 ml). There is no evidence for reduced effectiveness within this 10% margin. Safety will be monitored and in patients with insufficient effectiveness, the dose will be increased in logical steps up to the maximum registered dose.

After the first year, a dose reduction is indicated for patients in complete remission – complete remissions defined as no heme use during this year, and a reduction in d-ALA in urine by at least 50%. The indication committee will be informed on dose reduction. Dose reduction will be performed by prolonging the time intervals between the injections. In those with recurrence of symptoms, dosing interval will return to monthly.

Optimal use of vials
We will optimize the use of vials, in order to reduce waste of vials and thereby saving costs.
- By rounding down doses (max 10%) to match the content of a vial (see dosing)
- By using the remaining of a vial used for one patient to treat another patient, this can be optimized by pooling patient's visits
- The expiration date was optimized for incidental use the next day

Follow-up investigations
At least 4 times a year, patients need to attend outpatient appointments for assessment, of which at least twice a year in the Erasmus MC. Because of the importance of the follow-up appointments, missing two or more sequential appointments can result in discontinuation of treatment (see stop criteria). The indication committee decides on treatment (dis)continuation using the stop criteria (see next paragraph).

Follow-up assessment
First year baseline and thereafter every 6 months (see also data-collection)

- History, adverse events/side effects of injections
- Vital signs, neurological and pain evaluation (including pain medication)
- Number of attacks: patient reported and/or biochemically proven
- Routine chemistry and haematology; glucose, electrolytes (Sodium, Potassium, Calcium, and more on indication), creatinine, liver enzymes and function (ASAT, GGT, INR, Albumin, and more on indication), screening TSH (thyroid hormone on indication), homocysteine, haemoglobin, leucocytes and thrombocytes counts.
- Serum and urine sample for d-ALA and PBG
- on a voluntary basis over a period of 5 years, every 6 months for 1,5 years and then every year; Physical tests: eye-hand movement coordination, activity and sleep quality measurement for 3 weeks (activity watch; Actiwatch®), hair cortisol or other additional testing.

All tests will be age-appropriate.

After two years of uncomplicated treatment, the indication committee can decide to delegate drug administration to another center / hospital / services for home care. The Porphyria Expertcenter Rotterdam is part of the center for lysosomal and metabolic disease (CLMZ). This CLMZ has extensive experience in supervising and coordinating delegated care. The Erasmus MC will remain the principle treating center for acute porphyria, and will remain responsible for the treatment with givosiran even if the care is delegated, the other center will support. The patient is required to attend the Erasmus MC outpatient clinic with additional tests in order to remain on this treatment.

Stop criteria
Givosiran treatment will be stopped, based on assessment of all data by the indication committee, if any of the following apply[2]:

- The patient is unable to tolerate injections due to injection related severe adverse events that cannot be resolved.
- Limited reduction in recurrent attack frequency (less than 25% reduction after one year).
- Ongoing heme prophylaxes (< 25-50% reduction of heme dosages after one year). Heme will not be continued by the porphyria center, but incidentally patients receive additional treatment in another center.
- The patient is non-compliant with assessments (non-compliance is defined as no attendances or no testing for assessments in the expert centre in Erasmus MC during any year).

Monitoring of patients taken off treatment will continue for disease course and patient will be supported with other clinical measures when possible. These patients should continue to be assessed in the Erasmus MC, to allow gathering of important information.

[2] These criteria will also apply to patients started with givosiran during early access program.

Data collection and reporting

Data collection

Data will be collected as part of routine clinical care and recorded in an electronic file. Both treated and untreated patients will be followed. Data will be collected according to good clinical practice guidelines (GCP) (patients give their informed consent for participation in the local Dutch data acquisition). A more detailed flow-chart of follow-up parameters is present.

Data will be collected in our local Registry, a new register was set up in Castor and stored in the Erasmus MC. Access is only granted to members of the team.

Data	*Year 1*	*Year 2*	*Year 3+*	*Frequency per year*
History	1x	check	check	Once a year
Adverse events	x	x	X	As often as reported
Side effects	x	x	X	As often as reported
Vital signs	x	x	X	Once a year
Neurological exam †	X	x	x	On indication
Pain evaluation	x	X	x	Once a year
*Attacks**	x	x	x	As often as reported
Chemistry and haematology	4x	2x	1x	Variable
Porphyria markers	4x	2x	1x	On indication more often
Neurological test: eye-hand movement coordination	2x	1x	1x	
Physical activity and sleep quality measurement for 3 weeks (Actiwatch)	2x	1x	1x	
Stress level (hair cortisol)	2x	1x	1x	

* Attacks; defined as biochemically proven acute porphyric attacks.
† only on indication, in those with ongoing or new neurological symptoms.
X always indicated to check and make notes.

Reporting

The center of expertise will perform an analysis of data on efficacy and safety (i.e. data obtained from treated and untreated Dutch patients, as well as from available peer-reviewed publications). The results will be used for reporting and to further improve the appropriate use of givosiran. The depth of data collection and the extend of reporting will depend on the availability of additional research funds to cover the costs of these additional activities - the National Health Care Institute did not provide additional financial support as part of this managed access and appropriate use document.

In the same frequency - yearly, or every two years – the center of expertise will report its findings to the National Health Care Institute (Zorginstituut). In this report, the following topics will be addressed:

- Number of patients submitted to the indication committee for givosiran treatment and number of patients with a positive committee decision to initiate treatment
- Number of patients receiving (continued) treatment with givosiran
- Number of patients that receive a reduced dose
- Number of patients for whom treatment was ceased, and reason for cessation
- Notable findings or points of discussion with respect to

  - treatment initiation
  - treatment dosing, including rounding down and dose reduction
  - treatment effectiveness
  - occurrence of serious side effects
  - optimal use of vials
  - follow-up investigation
  - stop criteria
  - data collection
  - the managed access and appropriate use protocol in general
- Frequency of indication committee meetings and notable practical considerations with respect to the indication committee

Reports will be send in March, so that its insights can be used in a yearly Monitor focusing on appropriate use of (expensive) medicines, published in December by the National Health Care Institute. If information from these reports is used to draw lessons or conclusions, stakeholders will be consulted and invited to comment prior to publication.