2 March 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Givlaari (givirosan)
Treatment of acute hepatic porphyria
EU/3/16/1731
Sponsor: Alnylam Netherlands B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substances at the time of orphan designation	Synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA, covalently linked to a ligand containing three N-acetylgalactosamine residues
Other name(s)	ALN-AS1
International Non-Proprietary Name	Givosiran
Tradename	Givlaari
Orphan condition	Treatment of acute hepatic porphyria
Sponsor's details:	Alnylam Netherlands B.V. Strawinskylaan 3051 1077 ZX Amsterdam Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Alnylam UK Limited
COMP opinion date	13 July 2016
EC decision date	29 August 2016
EC registration number	EU/3/16/1731
Post-designation procedural history	
Transfer of sponsorship	Transfer from Alnylam UK Limited to Alnylam Netherlands B.V. – EC decision of 18 December 2018
Marketing authorisation	
Rapporteur / Co-rapporteur	P.B. van Hennik / F. Ventura
Applicant	Alnylam Netherlands B.V.
Application submission date	28 June 2019
Procedure start date	18 July 2019
Procedure number	EMA/H/C/004775
Invented name	Givlaari
Proposed therapeutic indication	Treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older Further information on Givlaari can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/givlaari
CHMP opinion date	30 January 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	E.J. Rook / A. Magrelli
Sponsor's report submission date	25 July 2019
COMP discussion	3-5 December 2019
COMP opinion date	3 February 2020

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2016 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on preclinical data demonstrating a significant reduction of levels of aminolevulinic acid (ALA) and porphobilinogen (PBG) in the serum;
- the condition is life-threatening due to paralysis and respiratory arrest during an attack and chronically debilitating due to attacks, which are causing pain, nausea, seizures and skin blistering;
- the condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA covalently linked to a ligand containing three N-acetylgalactosamine residues will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate a faster downregulation of the neurotoxic intermediate metabolites, aminolevulinic acid and porphobilinogen, in the serum as compared to the authorised product. Additionally, a single administration of the product resulted in a lasting response, which is not achievable by the use of the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor did not report any change to the classification of the condition or changes in diagnostic criteria. The condition remains acceptable as it was at the time of the initial orphan designation.

The approved therapeutic indication "'Treatment of Acute Hepatic Porphyria (AHP) in adults and adolescents aged 12 years and older" falls within the scope of the designated orphan condition "treatment of acute hepatic porphyria".

Acute hepatic porphyria (AHP) is a family of rare, serious, and severely debilitating genetic disorders of liver heme synthesis. Symptoms are due to the accumulation of the neurotoxic heme formation products aminolevulinic acid (ALA) and porphobilinogen (PBG), caused by increased expression of the delta-aminolevulinate synthase 1 (ALAS1) enzyme.

There are 4 AHP subtypes, each involving a defect in a distinct heme pathway enzyme: acute intermittent porphyria (AIP) caused by mutations in hydroxymethylbilane synthase gene (HMBS; also known as PBG deaminase), hereditary coproporphyria (HCP) caused by mutations in coproporphyrinogen oxidase gene, variegate porphyria (VP) caused by mutations in protoporphyrinogen oxidase gene, and ALA dehydratase (ALAD) deficient porphyria (ADP) caused by mutations in ALA dehydratase gene (Anderson, Bloomer et al. 2005) (Bissell and Wang 2015). AIP is the most common AHP subtype, occurring in approximately 80% of cases.

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP (see EPAR).

Chronically debilitating and/or life-threatening nature

There have been no changes to the life-threatening and chronically debilitating nature of the condition since the orphan drug designation in 2016. There have there been no newly approved therapies since that time.

Acute porphyria attacks typically require urgent medical attention in a healthcare setting, and some attacks with progressive motor weakness, paralysis, or respiratory failure require prolonged hospitalization and rehabilitation, and neurologic damage can be permanent. An attack is often serious, and carries potential for permanent disability, and where specific treatment is delayed or not available, attacks can be life-threatening. Up to 65% of AHP patients suffer impaired physical functioning and ongoing symptoms between attacks, of which chronic pain is the most common one.

Long-term complications and comorbidities of AHP include chronic kidney disease, depression, anxiety, hypertension, irreversible neuropathy sometimes leading to quadriplegia, and liver disease. More than 50% of AHP patients have hypertension and chronic kidney disease.

AHP continues to be a chronically debilitating and potentially life-threatening condition.

Number of people affected or at risk

The sponsor performed a literature search and identified a number of publications reporting the incidence of AHP and also referred to patient registries, which are a source of prevalence estimates.

Table 1. The Calculated Prevalence of Patients with Current or Past Symptoms of AIP, VP, or HCP in European Countries

Country	Population (millions)	Prevalence (cases per million inhabitants)a		
		AIP	**VP**	**HCP**
Finland	5.4	5.9	2.4	0.0
France	62.2	5.5	4.8	0.4
Republic of Ireland	4.2	N/A	6.4	0.0
Northern Italy	27.0	5.0	N/A	1.0
Italy	58.1	N/A	2.4	N/A
Netherlands	16.7	8.1	2.4	0.8
Norway	4.7	6.3	2.8	0.0
Poland	38.5	7.2	0.4	0.0
Spain	40.5	6.3	1.6	1.6
Sweden	9.1	23.0	4.4	0.0
Switzerland	7.6	9.9	10.4	1.8
UK	61.1	7.2	3.2	1.7
All Countries above	308.1	5.9	3.2	0.8

Abbreviations: AIP=acute intermittent porphyria; HCP=hereditary coproporphyria; N/A=not applicable; UK=United Kingdom; VP=variegate porphyria.
Adapted from Elder et al. 2013 which reports data from the European registry for porphyria
[a]Prevalence calculated by multiplying the incidence by a multiplier. Per Elder et al., 45 was used as the multiplier for AIP and 40 for VP; multiplier of 40 assumed for HCP. Overall prevalence described above is calculated from 'all countries above' for AIP, VP and HCP and is converted to incidence per 100,000.

Based on the calculated prevalence of 0.101 per 10,000, and the most recent EU population estimate (January 2015) of 508.2 million people, the estimated number of patients with AHP is 5,133. This confirms that the prevalence of AHP has not changed since the initial designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Anderson et. al. (2005) lay down recommendations for the diagnosis and treatment of the acute porphyria, which were based on the clinical experience of the experts on acute porphyria and their review of the literature.

In patients experiencing acute attacks or those patients who fail to respond to supportive measures, treatment with IV hemin (3-4 mg/kg/day × 3-5 days) is recommended. Hemin therapy is approved as Normosang® (Normosang SmPC 2017) (heme arginate) in the EU. Hemin is a blood-derived product that has been marketed since 1999 in the EU. Normosang is indicated for the treatment of acute attacks of hepatic porphyria (AIP, HCP, and VP).

While hemin is currently only approved for the use during acute attacks, in some patients with a history of severe or recurrent attacks, it is administered prophylactically (e.g., given every 1 to 2 weeks) off-label by some specialists, as an attempt to prevent attacks. However, prospective confirmatory studies regarding the use of hemin as prophylaxis are lacking. Data from a prospective, international, observational study in 112 patients with Acute Hepatic Porphyria with Recurrent Attacks (EXPLORE study), showed that 46% still suffered from attacks despite the chronic treatment with hemin prophylaxis.

Significant benefit

Alnylam received advice from the COMP on demonstrating significant benefit in the study program. COMP agreed that a single pivotal placebo-controlled Phase 3 study (ALN-AS1-003; ENVISION) could be sufficient to establish significant benefit for the purpose of orphan drug maintenance, specifically the final advice letter noted:

"In case the CHMP decides that the benefit/risk assessment is in favour for givosiran and if the Applicant can demonstrate a patient relevant/clinically significant reduction in acute severe attacks as well as a good safety profile, the data of the proposed single pivotal Phase 3 study could be sufficient to maintain orphan status."

The primary endpoint was a composite endpoint AAR (annualised attack rate, including non-overlapping porphyria attacks requiring either hospitalization, or requiring urgent healthcare visit, or porphyria attacks requiring IV hemin administration at home in AIP patients over the 6-month treatment period.

Pivotal Study 003 met its primary endpoint, demonstrating that 2.5 mg/kg once monthly givosiran treatment led to statistically significant and clinically meaningful reduction of 74% in the AAR (Annualized Attack Rate of the composite primary endpoint) compared to placebo in AIP patients (rate ratio=0.26, p<0.0001). Further, givosiran resulted in a 73% reduction in AAR compared to placebo in the overall AHP patient population (rate ratio=0.27, p=1.356×10-8), a secondary endpoint (Table 2).

Table 2. Annualized Attack Rate of Composite Attacks in Patients with AIP and AHP During the 6-Month DB Period (FAS)

	AIP Patients		**AHP Patients**	
	Placebo (N=43)	**Givosiran (N=46)**	**Placebo (N=46)**	**Givosiran (N=48)**
Total number of attacks	284	83	297	90
Mean AAR (per patient-year) (95% CI)	12.52 (9.35, 16.76)	3.22 (2.25, 4.59)	12.26 (9.22, 16.29)	3.35 (2.37, 4.74)
Rate ratio (95% CI) (givosiran vs placebo)	0.26 (0.16, 0.41)		0.27 (0.17, 0.43)	
p-value	$6.040x10^{-9}$		$1.356x10^{-8}$	
Median AAR (per patient-year) (Q1,Q3)	10.68 (2.24, 26.09)	1.04 (0.00, 6.23)	10.65 (2.24, 25.93)	1.04 (0.00, 6.35)
Number (%) of patients with 0 attacks	7 (16.3%)	23 (50.0%)	8 (17.4%)	24 (50.0%)

Abbreviations: AAR=annualized attack rate; AHP=Acute Hepatic Porphyria; AIP=acute intermittent porphyria; CI=confidence interval; FAS=full analysis set; IV=intravenous; Q1=first quartile; Q3= third quartile; SC=subcutaneous; vs=versus
Composite attacks comprise attacks requiring hospitalization, urgent health care visits, or IV hemin treatment.
Note: Median AAR was calculated from the individual patient's AAR. The mean AAR, rate ratio, the corresponding 95% CI and p-value for comparing 2.5 mg/kg givosiran versus placebo are derived using the negative binomial regression model with treatment group, stratification factors (prior hemin prophylaxis status and historical attack rates; for AIP patients only), and the logarithm of the follow-up time as an offset variable. A rate ratio <1 represents a favourable outcome for 2.5 mg/kg givosiran.

Table 3. Component Analysis of Annualised Rate of Composite Attacks During the 6-month Double-Blind Period in AIP Patients and AHP Patients (FAS)

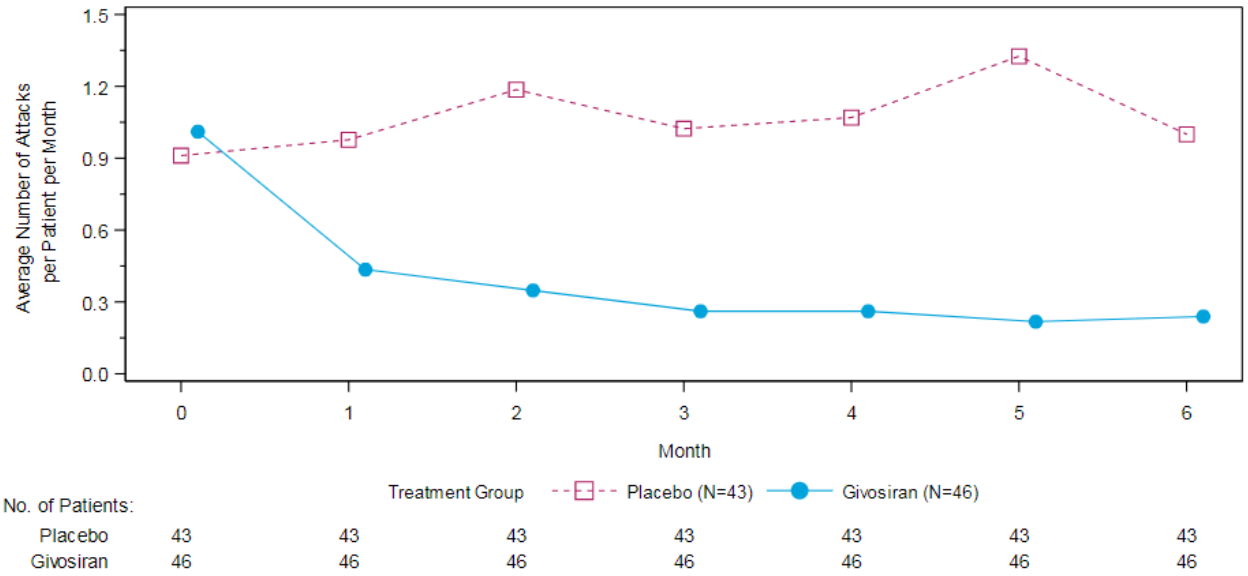
	AIP Patients		AHP Patients	
	Placebo (N=43)	**Givosiran (N=46)**	**Placebo (N=46)**	**Givosiran (N=48)**
Total follow-up time (years)	19.9	21.5	21.2	22.4
Attacks requiring hospitalization				
Total number of attacks	68	43	69	50
Mean AAR (95% CI)	3.21 (1.98, 5.20)	1.65 (0.98, 2.78)	3.06 (1.90, 4.94)	1.74 (1.04, 2.92)
Rate ratio (95% CI) (givosiran vs placebo)		0.51 (0.25, 1.04)		0.57 (0.28, 1.15)
Attacks requiring urgent healthcare visit				
Total number of attacks	184	37	196	37
Mean AAR (95% CI)	7.53 (5.13, 11.05)	1.22 (0.73, 2.05)	7.51 (5.21, 10.83)	1.19 (0.72, 1.97)
Rate ratio (95% CI) (givosiran vs placebo)		0.16 (0.09, 0.31)		0.16 (0.08, 0.30)
Attacks requiring IV hemin administration at home[a]				
Total number of attacks	32	3	32	3

Abbreviations: AAR=annualized attack rate; AIP=acute intermittent porphyria; CI=confidence interval; FAS=Full Analysis Set; IV=intravenous; N=Number of patients in treatment group.
[a]Negative binomial regression analysis was not performed for this component because <10 patients had this type of attack.
Note: Composite attacks were attacks that required hospitalization, urgent healthcare visit, or IV hemin administration at home. The mean AAR, rate ratio, and the corresponding 95% CI for comparing 2.5 mg/kg givosiran versus placebo were calculated if ≥10 patients had an attack using the negative binomial regression model with treatment group and stratification factors (prior hemin prophylaxis status and historical attack rates) as fixed effects and the logarithm of the follow-up time as an offset variable. A rate ratio <1 represents a favorable outcome for 2.5 mg/kg givosiran.

In AIP patients who had at least 1 composite attack, the median composite AAR was significantly lower in the givosiran treatment arm, than in the placebo arm.

During the 6-month DB period, patients with AIP treated with givosiran had a rapid and sustained decrease in attacks, as defined by the composite primary endpoint, after the first dose compared to placebo. For placebo patients, the attack rate remained stable over time.

Figure 1. Mean Number of Attacks per Patient per Month During the 6-month DB in AIP Patients



Abbreviations: AAR=annualized attack rate; AIP=Acute intermittent porphyria; FAS_{AIP}=AIP patients in full analysis set.
Note: Month 0 represents 6 months prior to randomization, and the estimate is calculated as total number of attacks/total duration in months. Month 1 and beyond were categorized relative to the first dose of study drug, and the estimate was calculated as total number of attacks/total number of patients reached that month. One month = 28 days was used in categorization.

Givosiran also demonstrated a statistically significant reduction on secondary endpoints such as biomarker ALA (aminolevulinic acid) and PBG (porphobilinogen) levels, and hemin use, and daily worst pain (Table 4), supporting the clinical relevance of the treatment effect.

Table 4. Summary of Additional Clinical Efficacy Measures in Patients with AIP During the 6-Month DB Period

		Placebo (N=43)	**Givosiran (N=46)**
Urinary ALA Levels (mmol/mol Cr); Secondary Endpoint			
At 3 Months	Median (Q1, Q3)	15.65 (7.51, 28.86)	0.78 (0.48, 1.70)
	Treatment difference[a] (95% CI)[b]	-14.65 (-17.97, -9.63)	
	p-value[c]	1.574×10^{-13}	
At 6 Months	Median (Q1, Q3)	16.15 (7.97, 22.97)	1.29 (0.89, 4.56)
	Treatment difference[a] (95% CI)[b]	-12.80 (-16.10, -7.81)	
	p-value[c]	3.94×10^{-10}	
Urinary PBG Levels (mmol/mol Cr); Secondary Endpoint			
At 6 Months	Median (Q1, Q3)	35.10 (25.57, 50.00)	4.42 (1.55, 15.27)
	Treatment difference[a] (95% CI)[b]	-27.48 (-34.04, -20.99)	
	p-value[c]	5.92×10^{-10}	
Hemin Use[d]; Secondary Endpoint			
Mean annualized days of hemin use (95% CI)		29.7 (18.4, 47.94)	6.77 (4.20, 10.92)
Ratio of annualized days of hemin use[e] (95% CI)		0.23 (0.11, 0.45)	

		Placebo (N=43)	Givosiran (N=46)
p-value		2.36×10^{-05}	
Daily Worst Pain; Secondary Endpoint			
AUC of change from baseline	Median (Q1, Q3)	5.29 (-23.05, 11.15)	-11.51 (-29.18, 3.04)
	Treatment difference[a] (95% CI)[b]	-10.07 (-22.83, 0.94)	
	p-value[f]	0.046	
Daily Worst Fatigue[g]; Secondary Endpoint			
AUC of change from baseline	LS Mean (95% CI)	-4.21 (-13.53, 5.12)	-11.15 (-20.10, -2.20)
	Difference in LS mean[e] (95% CI)	-6.94 (-19.84, 5.96)	
	p-value	0.288[g]	
Daily Worst Nausea[g]; Secondary Endpoint			
AUC of change from baseline	LS Mean (95% CI)	-4.01 (-10.88, 2.86)	1.48 (-5.10, 8.06)
	Difference in LS mean[e] (95% CI)	5.49 (-4.00, 14.98)	
	p-value	0.253[h]	
Change from Baseline in PCS of SF-12[i]; Secondary Endpoint			
At 6 months	LS Mean (95% CI)	1.43 (-1.00, 3.86)	5.37 (3.05, 7.69)
	Difference in LS mean[e] (95% CI)	3.94 (0.59, 7.29)	
	p-value	0.022[h]	

Abbreviations: AHP=acute hepatic porphyria; AIP=acute intermittent porphyria; ALA=aminolevulinic acid; ANCOVA=analysis of covariance; AUC=area under the curve; CI=confidence interval; DB=double-blind; MMRM=mixed-effect model with repeated measurements; PBG=porphobilinogen; PCS of SF-12=physical component summary of the 12-item Short-Form Health Survey.

[a] Median treatment difference of givosiran compared to placebo

[b] Estimated using Hodges-Lehmann method.

[c] Based on Wilcoxon rank sum test.

[d] The mean annualized days, rate ratio, the corresponding 95% CI and p-value for comparing 2.5 mg/kg givosiran versus placebo were derived using the negative binomial regression model with treatment group and stratification factors (prior hemin prophylaxis status and historical attack rates) as fixed effects and the logarithm of the follow-up time as an offset variable. A rate ratio <1 represents a favourable outcome for 2.5 mg/kg givosiran.

[e] for givosiran compared to placebo

[f] Estimated from stratified Wilcoxon test with stratification factors, prior hemin prophylaxis status and historical attack rates.

[g] The LS Means, treatment difference in LS Mean, their corresponding SEMs and 95% CIs and p-value for comparing 2.5 mg/kg givosiran versus placebo were derived using the ANCOVA model with treatment and stratification factors (prior hemin prophylaxis status and historical attack rates) as fixed effects, and the corresponding weekly mean score at baseline as a covariate. A difference < 0 represents lower cumulative symptoms for 2.5 mg/kg givosiran compared to placebo. The 6-month AUC was calculated based on change from baseline in weekly mean scores.

[h] Nominal p-value.

[i] The LS Means, treatment difference in LS Mean, their corresponding SEMs and 95% CIs and p-value for comparing 2.5 mg/kg givosiran versus placebo are derived using the MMRM model with the corresponding value at baseline as a continuous fixed covariate, stratification factors (prior hemin prophylaxis status and historical attack rates; for AIP patients only), visit, treatment, and treatment-by-visit interaction as fixed effects, and patient as a random effect. A difference <0 represents a favourable outcome for 2.5 mg/kg givosiran.

Finally, of relevance for the discussion of significant benefit, the reduction in the annualised attack rate (AAR) also led to a consequential reduction in annualised days of hemin use compared to placebo in AHP patients (Table 5).

Table 5. Annualised Days of Hemin Use During the 6-month DB Period, Negative Binominal Regression; all AHP Patients (FAS)

Statistic	**Placebo (N=46)**	**Givosiran (N=48)**
Total number of days of hemin use	587	227
Total follow-up time (years)	21.2	22.4
Number of patients with 0 days of hemin use, n (%)	12 (26.1)	26 (54.2)
Median annualized days of hemin use (Q1, Q3)	14.98 (0.00, 45.39)	0.00 (0.00, 11.77)
Mean annualized days of hemin use (95% CI)	28.37 (17.43, 46.18)	7.37 (4.53, 12.02)
Ratio of annualized days of hemin use (95% CI) (givosiran vs placebo)		0.26 (0.13, 0.52)
p-value		0.0002[(i)]

AHP=Acute hepatic porphyria; CI=Confidence interval; FAS=full analysis set; n=Number of patients in analysis; N=Number of patients in treatment group.
Note: Median annualized days of hemin use was calculated from the individual patient's annualized days of hemin use. The mean annualized days, rate ratio, the corresponding 95% CI and p-value for comparing 2.5 mg/kg givosiran versus placebo were derived using the negative binomial regression model with treatment group and stratification factors (prior hemin prophylaxis status and historical attack rates) as fixed effects and the logarithm of the follow-up time as an offset variable. A rate ratio <1 represents a favourable outcome for 2.5 mg/kg givosiran.
[a] - Nominal p-value.

In conclusion, the data obtained with the use of givosiran in prevention of attacks, which cannot be achieved with hemin, and the significant reductions in annualised attack rate and reduced use of hemin, supports the claim of significant benefit over current treatment options.

4. COMP list of issues

Not applicable

5. COMP position adopted on 3 February 2020

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of acute hepatic porphyria (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to paralysis and respiratory arrest during an attack and chronically debilitating due to attacks, which are causing pain, nausea, seizures and sometimes skin blistering;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Givlaari may be of potential significant benefit to those affected by the orphan condition does hold. The sponsor demonstrated in the pivotal clinical trial in patients that Givlaari significantly reduced the rate of severe attacks and consequently reduced the need for the use of hemin. The committee considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Givlaari, synthetic double-stranded siRNA oligonucleotide directed against delta-aminolevulinic acid synthase 1 mRNA, covalently linked to a ligand containing three N-acetylgalactosamine residues, givosiran for treatment of acute hepatic porphyria (EU/3/16/1731) is not removed from the Community Register of Orphan Medicinal Products.