Resolution
by the Federal Joint Committee
on an amendment to the Pharmaceutical Directive (AM-RL):
Appendix XII – Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a
Alipogene tiparvovec

From 21 May 2015

In its session on 21 May 2015, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 16 April 2015 (Federal Gazette, AT 28.05.2015 B1), as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient alipogene tiparvovec:

Alipogene tiparvovec

Therapeutic indication:

Alipogene tiparvovec (Glybera®) is indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein. Glybera should only be administered to patients with an LPL protein mass of at least 5% of normal.

1. Extent of additional benefit of the pharmaceutical

   Alipogene tiparvovec is authorized as a pharmaceutical for the treatment of a rare disease in accordance with EC regulation number 141/2000 of the European Parliament and Council of 16 December 1999 on orphan drugs. In accordance with SGB V section 35a, paragraph 1, sentence 10, the additional medical benefit has been proved through market authorization.

   In accordance with the rules of procedure of the Federal Joint Committee, chapter 5, section 12, paragraph 1, number 1, sentence 2, the Federal Joint Committee determines the extent of the additional benefit for the number of patients and patient groups for whom a therapeutically significant additional benefit exists. This quantification of the additional benefit has been conducted in accordance with the criteria laid out in the rules of procedure, chapter 5, section 5, paragraph 7, numbers 1 to 4.

   Extent of additional benefit:

   Due to the binding statutory regulation in SGB V, section 35a, paragraph 1, sentence 10, clause 1, the G-BA is obliged to assume an additional benefit of alipogene tiparvovec independently of the data and findings available for the assessment, as long as alipogene tiparvovec is legally authorized as a pharmaceutical for the treatment of a rare disease ((EC) regulation 141/2000 of the European Parliament and Council of 16 December 1999); the additional benefit of these pharmaceuticals is considered proved without exception in accordance with the fictional regulation in SGB V, section 35a, paragraph 1, sentence 10, clause 1. The actual existence of the additional benefit assumed under law can be examined only when the revenues generated by the pharmaceutical through statutory health insurance exceed 50 million euros.

   The G-BA classifies the extent of additional benefit of alipogene tiparvovec, which is to be assumed from a legal viewpoint in accordance with SGB V, section 35a, paragraph 1, sentence 10, clause 1, as not quantifiable based on the criteria in the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), section 5, paragraph 7 in consideration of the severity of the disease and the therapeutic goal in treating the disease.

   Study results according to endpoints:

   The data submitted were not sufficiently relevant. The data available at the time this resolution was drafted do not allow a professionally valid statement on an additional benefit or its quantification.

2. Number of patients and criteria for defining patients groups eligible for treatment

   approx. 17 to 35 patients

3. Requirements for quality-assured administration

   The specifications outlined in the product information are to be followed. The European Medicines Agency (EMA), the European regulatory authority, provides the contents of the product information for alipogene tiparvovec (Glybera®) at the following publicly accessible link (last accessed: 11 March 2015):

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002145/WC500135472.pdf

Treatment with alipogene tiparvovec must be initiated and monitored by physicians experienced in treating patients with LPLD and in the administration of gene therapy pharmaceuticals and with the full consent of the patient.

The administration of alipogene tiparvovec must be monitored medically, and suitable medical emergency equipment must always be on hand in case of an anaphylactic reaction.

The market authorization holder shall set up a disease registry to collect information on the epidemiology of the disease and the demographics, safety and effectiveness outcomes of patients with familial LPLD treated with Glybera®. Details of the operation of the registry shall be agreed with the national competent authorities in each member state. All patients treated with Glybera® shall be enrolled in the registry. In addition, patients, who have been treated with Glybera® in a clinical trial shall be enrolled in the registry at the end of the trial. Doctors shall be encouraged also to enrol patients with familial LPLD who are not treated with Glybera®. The market authorization holder shall agree the details of a restricted access programme with the national competent authorities and must implement such programme nationally prior to launch. Glybera® shall only be supplied if the healthcare professionals involved in the treatment of a patient have received the educational pack and if the prescriber confirms that the patient agrees to participate in the registry.

The educational pack for healthcare professionals must be agreed with the national competent authorities prior to distribution and consist of the following components:

- Product information (summary of product characteristics, patient information leaflet and patient alert card)
- Educational materials for healthcare professionals
- Educational materials for the patients
- Patient's events diary

The market authorization holder must include a patient alert card with every pack of pharmaceuticals.

The pharmaceutical has been authorized under "exceptional circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this summary of product characteristics will be updated as necessary.

4. Costs of treatment

Duration of treatment:

Designation of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Number of treatment days per patient per year
Alipogene tiparvovec	0.5 ml per injection site (intramuscular)	1	1	1

Consumption:

Designation of therapy	Strength (ml)[1]	Quantity per pack (ml/ampoules)[2]	Average annual consumption (ampoules)
Alipogene tiparvovec	0.5	1	26

Costs:

Cost of pharmaceutical:

Designation of therapy	Cost (pharmacy retail price)[3]	Cost after legally mandated rebates
Alipogene tiparvovec	€53,781.59	€50,708.92 [€1.77[4]; €3,070.90[5]]

"Lauer-Taxe", effective: 15 February 2015

[1] Patient-specific pack for the administration of 1 x 10^{12} LPL^{S447X} gc/kg body weight according to product information 0.5 ml per injection site. Calculation according to 2013 microcensus: average body weight 76.3 kg corresponds to 26 vials and 52 syringes of 0.5 ml each, and 52 injection sites.

[2] Largest pack (3 x 10^{12} genome copies/ml injection solution – 1 count).

[3] Largest pack.

[4] Rebate in accordance with SGB V, section 130.

[5] Rebate in accordance with SGB V, section 130a.

Costs for additional, necessary statutory health insurance (SHI) benefits:

Designation of therapy	Type of benefit	Cost after legally mandated rebates per patient per year	Number per patient per year
Alipogene tiparvovec	Immunosuppressive treatment:		
	Ciclosporin[6]	€742.61	87 days[9]
	Mycophenolate mofetil[7]	€535.40	87 days[9]
	Methylprednisolone[8]	€18.17	1
	Overall	€1,296.18	
	Spinal or regional anaesthesia	€214.96[10, 11]	1
	Injection regulated electrophysiologically or by	€427.44[10]	52
	Treatment monitoring by testing for neutralizing antibodies and possible T cell reactivity to AAV1 and LPL^{S447X}	Not a billable fee schedule item[10]	3[12]
	LPL protein mass test	Not a billable fee schedule item[10]	1

Annual treatment costs[13]:

Designation of therapy	Annual treatment costs per patient
Alipogene tiparvovec	€1,318,431.90
Costs for additional, necessary SHI benefits	€1,938.58 plus treatment monitoring by testing for neutralizing antibodies and possible T cell reactivity to AAV1 and LPL^{S447X} and LPL protein mass test

II.

Validity

1. This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 21 May 2014.
2. This resolution remains valid until 1 June 2016.

The justification for this resolution will be published on the websites of the Federal Joint Committee at www.g-ba.de.

Berlin, 21 May 2015

The Federal Joint Committee in
accordance with SGB V,
section 91

The Chair
Prof. Hecken

[6] Reference price group. Daily dosage of 225 mg (2 x 100 mg + 1 x 25 mg per day) used.
[7] Daily dosage used 2 g (4 x 500 mg).
[8] One-time administration of 1 mg/kg as bolus (125 mg dry substance with solvent).
[9] According to product information three days before to 12 weeks after administration.
[10] In accordance with the German Uniform Value Scale (EBM) 2015.
[11] The fee schedule items for the preparation of a spinal anaesthesia (coagulation tests) are not shown.
[12] According to product information before as well as 6 and 12 months after administration.
[13] Alipogene tiparvovec is approved for one-time use only. The treatment shall not be repeated.