Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a of the Fifth Book of the German Social Code (SGB V)
Voxelotor (haemolytic anaemia in sickle cell disease, monotherapy or combination with hydroxycarbamide, ≥ 12 years)

of 3 November 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient voxelotor in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA is 15 May 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 13 May 2022.

Voxelotor for the treatment of haemolytic anaemia due to sickle cell disease (SCD) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 August 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G22-20) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of voxelotor.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Voxelotor (Oxbryta) in accordance with the product information

Oxbryta is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Therapeutic indication of the resolution (resolution of 3 November 2022):

- See therapeutic indication according to marketing authorisation.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of voxelotor (with or without hydroxycarbamide) is assessed as follows:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

The pharmaceutical company has submitted data from the pivotal, randomised, double-blind, placebo-controlled phase III HOPE study for benefit assessment. This three-arm study compared treatment with voxelotor at two different doses (900 mg/day and 1500 mg/day) versus treatment with placebo. The benefit assessment is based on the comparison of the study arm with the pivotal voxelotor dose of 1500 mg/day (intervention arm; N = 90) and the placebo study arm (comparator arm; N = 92).

Patients aged between 12 and 65 years with sickle cell disease who had at least one vaso-occlusive crisis (VOC) in the 12 months prior to enrolment in the study and whose haemoglobin (HB) level was between 5.5 g/dl and 10.5 g/dl were enrolled in the study. Patients with more than ten VOC within 12 months and patients who required regular red blood cell transfusions or a red blood cell transfusion during screening were excluded from study participation. Randomisation was in a ratio of 1:1:1 by concomitant treatment with HU (yes/ no), region (North America/ Europe/ other) and age (12 to < 18 years/ 18 to 65 years).

Concomitant treatment with hydroxycarbamide/ hydroxyurea (HU) was allowed, provided stable dosing had been in place for at least 90 days prior to the start of the study. HU therapy at baseline was given to 58 (64%) patients in the intervention arm and 58 (63%) patients in the comparator arm.

Regarding genotypes, about 68% of patients in the intervention arm and about 80% of patients in the comparator arm had an HbSS genotype. In addition, approximately 20% and 8% of patients in the intervention arm had an HbSβ0-thalassemia and HbSβ+-thalassemia genotype, respectively. In the comparator arm, the corresponding percentages are about 12% and 3%, respectively.

The study was divided into three phases (screening, treatment and follow-up), with the treatment phase lasting 72 weeks, followed by a 4-week follow-up.

The primary endpoint of the study was the Hb response rate at week 24, additional endpoints were collected on symptomatology and adverse events. The HOPE study, which was conducted at a total of 60 study sites mainly in the USA, the UK, Egypt and Turkey, ended in 2019.

Mortality

Overall survival was not collected as a separate endpoint in the HOPE study. Deaths were recorded as part of the adverse event assessment, whereby two deaths were descriptively reported in each of the two study arms.

From the available data, there is no relevant difference between the treatment arms.

Morbidity

Vaso-Occlusive Crises (VOC)

Sickle cell disease-associated vaso-occlusive pain crises and other vaso-occlusive complications felt by patients are considered patient-relevant events.

In the HOPE study, the event of a vaso-occlusive pain crisis was defined as:

- moderate to severe pain for a duration of at least two hours
- no cause of pain other than a vaso-occlusive event
- Need to take oral or parenteral opioids, ketorolac or other analgesics as directed or prescribed by a healthcare professional
- Entry in the patient's record that the patient was seen by a doctor within one working day of the event or that the patient contacted the doctor within one working day of the event.

All four criteria had to apply. Acute chest syndrome (ACS) was also assessed as a vaso-occlusive pain crisis in the HOPE study (see also the subsequent comments on this single component).

There is no statistically significant difference between the treatment arms, neither in the analysis of the "annual event rate" nor in the analysis of the "time to 1st VOC" presented additionally.

In agreement with the statements of clinical experts in the written statement procedure, a high priority is attached to the end-organ damage resulting from VOCs in the long term. However, no conclusions on long-term subsequent end-organ damage can be drawn from the available HOPE study data.

ACS or pneumonia

The endpoint "ACS or pneumonia" in the HOPE study was defined as a new pulmonary infiltrate diagnosed by the principal investigator using chest X-ray, associated with fever and/or respiratory symptomatology.

The occurrence of ACS or pneumonia (includes PT "Pneumonia" and PT "Pneumonia due to mycoplasma") was recorded as part of the safety survey.

There is no statistically significant difference between the treatment arms, neither in the analysis of the "annual event rate" nor in the analysis of the "time to 1st ACS or pneumonia" presented additionally.

Erythrocyte transfusion independence

The endpoint "Erythrocyte transfusion independence" was defined in the HOPE study as the percentage of subjects who were not treated with a transfusion of red blood cell concentrates from randomisation until week 72.

In therapeutic indications where patients are dependent on regular red blood cell transfusions, long-term avoidance of such transfusions may represent a patient-relevant endpoint.

However, according to the statements of clinical experts in the written statement procedure, red blood cell transfusion is only indicated in exceptional cases for the treatment of the anaemia associated with sickle cell disease in patients with sickle cell disease. In addition, patients treated with regular red blood cell transfusions (chronic, prophylactic or preventive) were excluded from participation in the HOPE study.

The "erythrocyte transfusion independence" endpoint is therefore not used for the present assessment.

Health status

In the HOPE study, patient-reported health status was assessed using the EQ-5D visual analogue scale.

However, the return rates do not exceed 70% at any of the measurement points, so that the significance of the results is to be considered unreliable. The results on health status are therefore not used to assess the extent of the additional benefit.

In the overall assessment of the results on morbidity, neither an advantage nor a disadvantage of voxelotor (+ hydroxycarbamide, if applicable) compared to placebo (+ hydroxycarbamide, if applicable) can be determined.

Quality of life

No data on health-related quality of life were collected in the HOPE study.

Side effects

With regard to adverse events (AEs), the present assessment is based on the results excluding events related to the underlying disease ("sickle cell anaemia with crisis" (PT), "acute chest syndrome" (PT), "pneumonia" (including "pneumonia due to mycoplasma" (PT)), "priapism" (PT) as well as "osteonecrosis" (PT)).

Adverse events (AEs) in total

AEs occurred in about 90% of patients in the intervention arm and about 90% of patients in the comparator arm. The results were only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs.

Other relevant safety events

In detail, the results on SAEs and severe AEs (CTCAE grade ≥ 3) that occurred with an incidence > 5% in one study arm show a statistically significant difference in favour of voxelotor (+ hydroxycarbamide, if applicable) over placebo (+ hydroxycarbamide, if applicable) for the system organ class (SOC) "General disorders and administration site conditions" alone.

In the overall assessment of the endpoint category of side effects, there are therefore no differences relevant to the assessment between voxelotor (+ hydroxycarbamide, if applicable) and placebo (+ hydroxycarbamide, if applicable).

Overall assessment

The results of the HOPE study are available for the benefit assessment of voxelotor as monotherapy in combination with hydroxycarbamide for the treatment of haemolytic anaemia due to sickle cell disease in patients aged 12 years and older. The study, completed in 2019, compared voxelotor (+ hydroxycarbamide, if applicable) versus placebo (+ hydroxycarbamide, if applicable).

For overall survival, two deaths were descriptively reported in each study arm, which were documented during the assessment of the adverse events (AEs). Effect estimates are not available, so that the available data do not allow a statement on the extent of the additional benefit.

For the endpoint category of morbidity, results are available on the occurrence of vaso-occlusive crises (VOC) and acute chest syndromes (ACS) or pneumonias. There was no statistically significant difference between the treatment arms for VOC, ACS or pneumonia.

With regard to health-related quality of life, no data were collected in the HOPE study.

Also with regard to side effects, there were also no assessment-relevant differences between voxelotor (+ hydroxycarbamide, if applicable) and placebo (+ hydroxycarbamide, if applicable).

In the overall assessment, the G-BA classifies the extent of the additional benefit of voxelotor (+ hydroxycarbamide, if applicable) for the treatment of patients 12 years of age and older with haemolytic anaemia due to sickle cell disease as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The present assessment is based on the results of the randomised, double-blind, placebo-controlled phase III HOPE study.

The overall significance of the results for the observed non-quantifiable additional benefit is low, which is why the significance of the evidence is classified as a "hint".

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Oxbryta with the active ingredient voxelotor. Oxbryta was approved as an orphan drug in the following therapeutic indication:

"Oxbryta is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide."

For the benefit assessment, the pharmaceutical company submitted data from the randomised, double-blind, placebo-controlled phase III HOPE study, in which voxelotor (+ hydroxycarbamide, if applicable) was compared with placebo (+ hydroxycarbamide, if applicable).

For overall survival, two deaths were descriptively reported in each study arm.

For the endpoint category of morbidity, results are available on the occurrence of vaso-occlusive crises (VOC) and acute chest syndromes (ACS) or pneumonias. There was no statistically significant difference between the treatment arms for VOC, ACS or pneumonia.

With regard to health-related quality of life, no data were collected in the HOPE study.

With regard to side effects, there are no assessment-relevant differences between voxelotor (+ hydroxycarbamide, if applicable) and placebo (+ hydroxycarbamide, if applicable).

In the overall assessment, the G-BA classifies the extent of the additional benefit of voxelotor (+ hydroxycarbamide, if applicable) for the treatment of patients 12 years of age and older with haemolytic anaemia due to sickle cell disease as non-quantifiable since the scientific data does not allow quantification. The significance of the evidence is categorised as 'hint'.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The procedure of the pharmaceutical company is mathematically largely comprehensible. The data on the lower limit of patients is considered uncertain due to counteracting effects in the individual calculation steps. The information on the upper limit is assumed to be in a plausible order of magnitude.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Oxbryta (active ingredient: voxelotor) at the following publicly accessible link (last access: 28 September 2022):

https://www.ema.europa.eu/en/documents/product-information/oxbryta-epar-product-information_en.pdf

Treatment with voxelotor should be initiated and monitored by doctors experienced in treating patients with sickle cell disease.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2022).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Voxelotor	continuously, 1 x daily	365	1	365
plus				
Hydroxycarbamide	continuously, 1 x daily	365	1	365

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g., because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The average body measurements were applied for dosages depending on body weight or body surface area (BSA) (average body height of a 12-year-old child: 1,56 m; average body weight: 47.1 kg; average body height of an adult 18 years and over: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.44 m² or 1.90 m² (calculated according to Du Bois 1916)[2]

For hydroxycarbamide, a range of 15 mg/kg BW to 30 mg/kg BW is used. As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Voxelotor	1,500 mg	1,500 mg	3 x 500 mg	365	1,095 x 500 mg
plus					

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Hydroxycarbamide	15 mg/kg = 706.5 mg[3] -	706.5 mg	7 x 100 mg	365	2,555 x 100 mg
	30 mg/kg = 2,310 mg[4]	2,310 mg	2 x 1,000 mg + 3 x 100 mg	365	730 x 1,000 mg + 1,095 x 100 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Voxelotor 500 mg	90 FCT	€ 8,739.65	€ 1.77	€ 495.83	€ 8,242.05
Hydroxycarbamide 1,000 mg	30 FCT	€ 447.48	€ 1.77	€ 24.15	€ 421.56
Hydroxycarbamide 100 mg	60 FCT	€ 98.52	€ 1.77	€ 4.83	€ 91.92
Abbreviations: FCT = film-coated tablets; HC = hard capsules					

LAUER-TAXE® last revised: 15 October 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this

[3] Minimum dosage calculated on the basis of the average body weight of a 12-year-old child.
[4] Maximum dosage calculated on the basis of the average body weight of an adult aged 18 years and over.

must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 13 May 2022, the pharmaceutical company submitted a dossier for the benefit assessment of voxelotor to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 August 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 5 September 2022.

The oral hearing was held on 26 September 2022.

An amendment to the benefit assessment with a supplementary assessment was submitted on 12 October 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 25 October 2022, and the proposed resolution was approved.

At its session on 3 November 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 August 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	20 September 2022	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal products	26 September 2022	Conduct of the oral hearing
Working group Section 35a	4 October 2022 18 October 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	25 October 2022	Concluding discussion of the draft resolution
Plenum	3 November 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 November 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken