Justification

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V- Ataluren (expiry of the deadline)

of 1 December 2016

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 10, 1st half-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 10, 2nd half-sentence SGB V). Section 35a, paragraph 1, sentence 10, 1st half-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. Only the extent of the additional benefit has to be proven.

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, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 11 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 10 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.

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 11 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

Ataluren as the active ingredient of the medicinal product Translarna was first marketed on 1 December 2014. At its session on 15 June 2015, the G-BA decided on the benefit assessment of ataluren in accordance with Section 35a SGB V. The period of validity of this resolution was limited to 1 June 2016.

On 1 June 2016, the pharmaceutical company submitted a dossier for the benefit assessment of ataluren to the G-BA in due time in accordance with Chapter 5 Section 8 Number 5 of the Rules of Procedure of the G-BA, according to which the required evidence must be submitted no later than the day on which the deadline expires.

Ataluren for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene (nMDMD), in ambulatory patients aged 5 years and older is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 10, 1st half-sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit is assessed on the basis of the approval 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 1 September 2016 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 has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G16-05) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

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 ataluren.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product

Extent of the additional benefit

In summary, the extent of the additional benefit of ataluren is assessed as follows:

[1] General Methods, version 4.2 from 22.04.2015. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

For ambulatory patients aged 5 years and older with nMDMD, there is minor additional benefit.

Justification:

The renewed benefit assessment after the expiry of the deadline is based on the data of the phase III study PTC124-GD-020-DMD (020 study) and the phase II study PTC124-GD-007-DMD (007 study) submitted by the pharmaceutical company.

In the multicentre, randomised, placebo-controlled, double-blind 020 study, patients were enrolled, stratified by the factors of age, duration of corticosteroid use and walking distance in the 6-minute walk test (6MWT) at baseline, and treated for 48 weeks. Inclusion criteria included 6MWT of ≥ 150 m and ≤ 80% of standard value for age and height and stable systemic corticosteroid therapy for 3 months prior to enrolment in the study. The study population comprised a sub-population of the therapeutic indication.

In the intervention arm, a total daily dose of 40 mg/kg body weight (BW) of ataluren, divided into three doses, was used according to the marketing authorisation.

The efficacy endpoints were improvement 6MWT, time to 10% deterioration 6MWT, proximal muscle function measured as change in Timed Function Tests (TFT) 10 m run/ walk, climbing 4 steps up/down, physical functioning, health-related quality of life (HRQoL), activities of daily living (ADL), and side effects.

Subgroup analyses were pre-specified for the following endpoints, among others: 6MWT at randomisation (≥ 350 m/ < 350 m), 6MWT at baseline (< 300 m, ≥ 300 to < 400 m, ≥ 400 m), duration of corticosteroid treatment before baseline (≥ 6 months to < 12 months/ ≥ 12 months) and age group (< 9/ ≥ 9 years).

In addition, the results of the 007 study are used for the benefit assessment. In this multicentre, three-arm, randomised, placebo-controlled, double-blind study, patients were enrolled, stratified by the factors of age, corticosteroid use and 6MWT at baseline, and treated for 48 weeks.

Inclusion criteria included 6MWT of ≥ 75 m, exclusion criteria included initiation or non-adaptive (e.g. dose adjustment due to growth or weight gain) change in corticosteroid treatment.

In the relevant intervention arm, a total daily dose of 40 mg/kg body weight (BW) of ataluren, divided into three doses, was used according to the marketing authorisation.

Efficacy endpoints included improvement in 6MWT, time to 10% deterioration 6MWT, TFTs, health-related quality of life (HRQOL), and side effects.

Subgroup analyses were pre-specified for the following endpoints, among others: Age (< 9 / ≥ 9 years), 6MWT (≥ 350/ < 350 m), corticosteroids at baseline (yes/ no) and age distribution (5-6, 7-8, 9-11, ≥ 12 years).

Subgroup analyses for the endpoint 6MWT to baseline (< 300 m, ≥ 300 to < 400 m, ≥ 400 m) are not available.

The risk of bias is estimated to be low for the 007 and 020 studies.

In the dossier of the pharmaceutical company, additional meta-analyses of the two studies were presented. Although these meta-analyses were based on patient-individual data, they

are only of limited use for assessing the extent of additional benefit, as it is questionable whether the two study populations are sufficiently similar. In the 007 study, only some of the patients enrolled are in the phase of rapidly progressive loss of walking ability, the so-called "ambulatory decline phase" (ADP). However, the population of the 020 study includes only patients in ADP due to its inclusion criteria. Thus, as the percentage of patients in the ADP differs between the two studies, these studies cannot be evaluated in their entirety in a meta-analysis.

In the dossier, the pharmaceutical company presented a meta-analytic evaluation for, among others, the subgroup of patients with ≥ 300 to < 400 m 6MWT (at baseline). This subgroup is a sub-population of the whole therapeutic indication (in the 007 study, it was 39.6% at baseline and 43.4% in the 020 study). Therefore, this meta-analysis for this sub-population can be used to support the assessment of the additional benefit.

The analyses subsequently submitted in the written statement procedure do not add any data suitable for assessing the adequacy of the meta-analysis.

Mortality

No deaths occurred in the 020 study or the 007 study. Due to mortality, no statement on the extent of the additional benefit is possible.

Morbidity

Change in 6MWT

The 6-minute walk test examines in a standardised way the walking distance that patients can cover within 6 minutes. The endpoint 6MWT is patient-relevant in Duchenne muscular dystrophy. The operationalisation of the measurement of walking distance is considered valid in the available studies. The validity of the relevance threshold of 30 m chosen in the dossier cannot be conclusively assessed.

In the 020 study, only the subgroup of patients with a walking distance of ≥ 300 to < 400 metres at baseline showed a statistically significant lower deterioration in walking distance; the difference between the placebo and ataluren groups was 42.89 metres (95% CI 11.75 m to 74.03 m; p = 0.007). The lower confidence interval was thus below the relevance threshold of 30 metres specified in the dossier.

In the 007 study, there is no statistically significant difference in 6MWT for the total population. No separate evaluation was available for the sub-population of patients with a walking distance of ≥ 300 to < 400 metres at baseline.

In the meta-analysis of the sub-population of patients with a 6MWT of ≥ 300 to < 400 metres at baseline, a statistically significant lower decrease was found over the study period.

In the 020 study, only the subgroup of patients with 6MWT of < 300 metres at baseline showed a statistically significant lower deterioration of the "time to at least 10% deterioration 6MWT". Median duration was 56 days in the placebo group and 164 days in the intervention group (HR 0.48 [95% CI 0.24 m to 0.93 m] p = 0.031).

In the 007 study, there was a statistically significant difference between the groups. (HR 0.52 [95% CI 0.28 to 0.966] p = 0.039), but not for the time to 10% improvement in 6MWT, which was also collected.

The percentage of patients with ≥ 10% deterioration of 6MWT was significantly higher for ataluren in the 007 study (43.9%) than for placebo (26.3%); in the 020 study, these percentages differed only slightly and not significantly, at 45.6% and 43.0%, respectively. For the percentage of patients with ≥ 10% improvement measured only in the 007 study, the difference of 10.5% for placebo and 21.1% for ataluren was insignificant.

In the meta-analysis of the sub-population of patients with 6MWT of ≥ 300 to < 400 metres at baseline, no statistically significant difference was found for the endpoint of time to at least 10% deterioration.

Timed Function Test (TFT)

The following endpoints were collected for assessing a change in proximal muscle function (timed function test = TFT) at week 48:

Required time to run/ walk 10 m

In the 007 and 020 studies, no statistically significant change in the time needed to run/ walk 10 m was found.

In the meta-analysis of the 007 and 020 studies, a statistically significant lower deterioration of time required to run/ walk 10 m was found in the 6MWT subgroup ≥ 300 to < 400 metres at baseline for ataluren.

Time to climb 4 steps up

Neither in the 020 study nor in the 007 study was a statistically significant lower change in the time needed to climb 4 steps up found for ataluren.

In the meta-analysis of the 007 and 020 studies, a statistically significantly lower deterioration in the time needed to climb 4 steps up was found in the 6MWT subgroup ≥ 300 to < 400 metres at baseline for ataluren.

Time to climb 4 steps down

In the 020 study, but not in the 007 study, a statistically significant lower deterioration in the time needed to climb 4 steps down was found for ataluren.

In the meta-analysis of the 007 and 020 studies, a statistically significantly lower deterioration in the time needed to climb 4 steps down was found in the 6MWT subgroup ≥ 300 to < 400 metres at baseline for ataluren.

There were no consistent statistically significant results for any morbidity endpoint for the total population in either study; furthermore, the results of the endpoint "standing up from the supine position", which was only collected in the 007 study were insignificant. Based on the available results on morbidity, the extent of the additional benefit is assessed as low.

Quality of life

In the 020 study, quality of life was assessed with the Paediatric Outcomes Data Collection Instrument (PODCI). No significant differences could be shown.

For the 007 study, no results are available for the measurement of quality of life with the PODCI; the measurements collected there with the Paediatric Quality of Life Inventory (PedsQL) showed no significant differences.

Based on the available results on quality of life, no statement on the extent of the additional benefit is possible.

Side effects

Adverse events (AEs) and serious adverse events (SAEs) were collected according to the Medical Dictionary for Regulatory Activities (MedDRA) using the system organ class (SOC) and preferred term (PT).

In the 020 study, the side effect profile was comparable between the ataluren and placebo groups. The percentage of patients with SAEs and the percentage with severe and life-threatening AEs differed only slightly between the ataluren and placebo groups. Therapy discontinuations due to AEs did not occur, there were no deaths. The most frequent AE classified by SOC/ PT for the placebo and ataluren groups, respectively, were infections (43.5% vs 54.8%) or involved the gastrointestinal tract (41.7% vs 45.2%). The frequency of side effects differed only slightly between the groups.

No studies are available in patients with renal or hepatic functional impairment. Since ataluren is excreted via these organs, the accumulation of active ingredient and metabolites may occur if corresponding functional impairments are present. For renal or hepatic functional impairments, there was a higher percentage for the ataluren group (13.0% for ataluren vs 7.8% for placebo)

In the 007 study, the percentage of patients with SAEs differed only slightly between the ataluren and placebo groups. Therapy discontinuations due to AEs did not occur, there were no deaths. The most common AEs for the placebo and ataluren groups, respectively, were vomiting (38.6% vs 56.1%), headache (24.6% vs 38.6%) and diarrhoea (24.6% vs 19.3%). The frequency of side effects differed only slightly between the groups.

Based on the available results on the side effects, it is not possible to make a statement on the extent of the additional benefit.

Conclusion

The G-BA classifies the extent of the additional benefit of ataluren on the basis of the criteria in Section 5 paragraph 7 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as low, taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. According to Section 5 paragraph 7 in conjunction with Section 2 paragraph 3 AM-NutzenV, it is a moderate improvement of the therapy-relevant benefit, since, in addition to the positive results of the already assessed 007 study, a slight improvement in the "time to climb 4 steps down" and for one subgroup each in the "walking distance in the 6MWT" as well as "*time to 10% deterioration of the* 6MWT*"* could be achieved in the study submitted after the expiry of the deadline. The results on quality of life and side effects do not allow a statement on the quantification of the additional benefit.

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

The data are based on the incidence of DMD, determined on the basis of data from newborn screening programmes in several countries (including Austria, Great Britain) and the age

distribution of DMD patients. The percentage of ambulatory patients over 5 years of age was determined based on study results of patients with or without corticosteroid treatment. Together with the percentage of nMDMD in all DMD genotypes derived from registry studies and the percentage of SHI patients, this results in a target population of approximately 30 to 40 patients. These figures differ from those of the resolution of 21 May 2015 due to the change in the methodology of the calculation and the underlying factors (prevalence, percentage of ambulatory patients, age distribution of DMD patients).

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 Translarna™ (active ingredient: ataluren) at the following publicly accessible link (last access: 13 October 2016; http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002720/WC500171813.pdf

Treatment with ataluren should only be initiated and monitored by specialists who are experienced in the treatment of patients with Duchenne/Becker muscular dystrophy.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

In principle, the treatment costs are based on the requirements in the product information and the LAUER-TAXE®.

However, the cost calculation cannot rely on the LAUER-TAXE® data at this point in time, as the pharmaceutical company discontinued the proprietary medicinal product Translarna™ (active ingredient ataluren) from the market on 1 April 2016. A reimbursement amount for Ataluren was set by the Joint Arbitration Board under Section 130b paragraph 5 SGB V pursuant to Section 130b paragraph 4 SGB V. Pursuant to Section 23 paragraph 1 of the Rules of Procedure of the Joint Arbitration Board under Section 130b paragraph 5 SGB V, the decisions pursuant to Section 130b paragraphs 4, 7 and 9 may be inspected at the office of the Arbitration Board.

As no price is publicly available at this point in time, the derivation of the costs is presented here, but without specifying a price.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Treatment days per patient per year
Ataluren	Continuously, 3 x daily	Continuously	365	365

Consumption:

For the determination of body weight: the pharmaceutical company did not present robust evidence for an average lower body weight of boys with nMDMD compared to healthy boys in the corresponding age range, neither in the dossier nor in the literature of the statement. Therefore, general body weight data is used to determine consumption.

Designation of the therapy	Potency (mg)	Quantity per pack (sachet)	Annual average consumption (tablets)
Ataluren	125 mg	30	1,095 (sachets each 125 mg) + 1,460 (sachets each 250 mg)[2]
Ataluren	250 mg	30	

Costs:

Costs of the medicinal products:

Designation of the therapy	Costs (Pharmacy sales price according to potency and pack size)	Costs after deduction of statutory rebates
Ataluren 125 mg	No data available	No data available
Ataluren 250 mg	No data available	No data available

Costs for additionally required SHI services: not applicable

3. Bureaucratic costs

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 1 June 2016, the pharmaceutical company submitted a dossier for the benefit assessment of ataluren to the G-BA in due time in accordance with Chapter 5 Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 September 2016 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

[2] Consumption for body weight (BW) 33.12 kg, according to the dosage table in the product information for 32 - 35 kg/BW:.BW. Average of the male population in the respective age group from 5 to 16 years (federal health reporting) weighted by the percentage of ambulatory patients in the respective age group.

statements was 22 September 2016.

The oral hearing was held on 10 October 2016.

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 22 November 2016, and the proposed resolution was approved.

At its session on 1 December 2016, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 September 2016	Information of the benefit assessment of the G-BA
Working group Section 35a	5 October 2016	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 October 2016	Conduct of the oral hearing
Working group Section 35a	18 October 2016 1 November 2016 16 November 2016	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	22 November 2016	Concluding discussion of the draft resolution
Plenum	1 December 2016	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 December 2016

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

Prof. Hecken