Justification

Gemeinsamer Bundesausschuss

to 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 in According to Section 35a SGB V Mexiletine

of 1 August 2019

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. According to Section 35a, paragraph 6 SGB V, the G-BA may also arrange for a benefit assessment according to Section 35a, paragraph 1 SGB V for reimbursable medicinal products containing an active ingredient that is not a new active ingredient within the meaning of Section 35a, paragraph 1 SGB V if a new marketing authorisation with new data protection is granted for the medicinal product.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is deemed to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medicinal benefit in relation to the appropriate comparator therapy need not 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 evaluation of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V in conjunction with the Chapter 5, Sections 5 et seq. of the Rules of Procedure, G-BA (VerfO) has not been carried out. Only the extent of the additional benefit has to be demonstrated.

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 retail prices 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, subsection 1–6 VerfO, in particular regarding the additional medicinal 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is evaluated exclusively on the basis of the approval studies.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate given to the IQWiG in its 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 in such a way that, in the case of orphan drugs, IQWiG is only commissioned to carry out a benefit assessment in case of a previously defined comparator therapy when the sales volume of the drug 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 shall pass a resolution 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 market of the active ingredient mexiletine for the symptomatic treatment of non-dystrophic myotonic disorders in accordance with Chapter 5, Section 8, paragraph 1, number 7 of the Rules of Procedure of the G-BA (VerfO) is 1 February 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 7 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1 number 7 VerfO on 31 January 2019.

Mexiletine for symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders is authorised as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be already proven by 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 2 May 2019 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G19-03) 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 marketing authorisation 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 through 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of mexiletine.

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

2.1.1 Approved therapeutic indication of mexiletine (Namuscla®) in accordance with the product information

Namuscla® is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

2.1.2 Extent of the additional benefit

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

Non-quantifiable

1 General methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

Justification:

The benefit assessment is based on the multi-centre, randomised, double-blind and placebo-controlled cross-over Phase III *MYOMEX* study, which was conducted exclusively in study centres in France. Included were patients with myotonia congenita and patients with paramyotonia congenita aged 18 to 65 years. In total, the study lasted 31.8 months.

The cross-over study included two treatment periods of 18–22 days each. Study participants received mexiletine in one treatment period and placebo in the other treatment period. Randomisation (ratio 1:1) was used to determine which treatment (mexiletine or placebo) was started. In the 2nd treatment period, the participants then received the other intervention. To prevent carry-over effects, the two treatment periods were separated by a 4- to 8-day washout period during which no intervention was performed. The median duration of the treatment periods was 19 days (minimum: 10 days, maximum: 21 day) for mexiletine and 18 days (minimum: 17 days, maximum: 22 days) for placebo. On the last day of each treatment period, one study visit was made.

26 persons were included in the study. However, one patient was excluded from the study before receiving the first dose of the study medication. Therefore only 25 patients were included in the assessment. The median age of the study population is 45 years, and the majority is male (68% men, 32% women). 13 study participants (52%) suffered from myotonia congenita and 12 study participants (48%) suffered from paramyotonia congenita. 56% of the study participants had already taken mexiletine before the start of study; 44% were taking mexiletine at the time of screening. For these individuals, a 4- to 8-day washout period took place prior to taking the study intervention.

The primary endpoint of the study was the severity of muscle stiffness, which was assessed using a visual analogue scale. Secondary endpoints included physical functionality, health-related quality of life and adverse events.

Mortality

No deaths occurred in the *MYOMEX* study.

Morbidity

VAS severity of muscle stiffness

The severity of muscle stiffness was measured using a visual analogue scale (VAS). The VAS consisted of a 10 cm straight horizontal line continuously representing the degree of muscle stiffness from “no stiffness” (VAS value 0) to “worst possible stiffness” (VAS value 100). Patients assessed the degree of muscle stiffness within the last three days by marking the line. The survey was conducted on the first and last day of each treatment period (Days 1, 18, 22, and 39).

The VAS on muscle stiffness is considered a patient-relevant endpoint. However, there are no validated response thresholds.

In the combined analysis of treatment effects across both treatment sequences, a statistically significant and very distinct treatment effect in favour of mexiletine compared with placebo was observed. Patient-reported muscle stiffness decreased by 41.7 mm on the VAS under treatment with mexiletine; however, the decrease on the VAS was only 9.0 mm under treatment with placebo.
Because there are no effect estimators for the combined analysis that take into account the intra-individual dependency of the data according to the cross-over design of the study, the p values from a linear mixed model were used for the assessment; these are considered valid.
In the endpoint VAS severity of muscle stiffness, based on Hedges’ g calculations, a statistically significant and clinically relevant difference in favour of mexiletine therapy

compared with placebo is also found when the two treatment periods are considered separately.

Symptoms based on the INQoL

Another efficacy endpoint used for the benefit assessment is the presence of the symptoms muscle weakness, muscle block, pain, and fatigue at the end of each treatment period as measured by the Individualised Neuromuscular Quality of Life Questionnaire (INQoL). This endpoint is presented in addition to the results reported under "Quality of life" of the INQoL. The results presented under morbidity describe the presence of disease symptoms regardless of their severity. The absence of the common symptoms of muscle weakness, muscle block, pain, and fatigue in non-dystrophic myotonies is seen as the best treatment outcome. Because of a lack of adequate statistical modelling of the study results for the binary endpoints, the results on symptomatology are presented only descriptively.

Of the 25 study participants, 24 patients (96%) reported muscle weakness and muscle blocks, 17 patients (68%) reported pain, and 20 patients (80%) reported fatigue. Muscle weakness was reported in 20 patients (80%) after treatment with mexiletine and in 23 patients (92%) after treatment with placebo. Muscle blocks occurred in 24 patients (96%) after treatment with mexiletine and in 23 patients (92%) after treatment with placebo. Pain was reported in 8 patients (32 %) after treatment with mexiletine and in 18 patients (72 %) after treatment with placebo. Fatigue was reported in 13 patients (52 %) after treatment with mexiletine and in 20 patients (80 %) after treatment with placebo.

Quality of life

INQoL

The health-related quality of life was assessed using the Individualised Neuromuscular Quality of Life Questionnaire (INQoL). The questionnaire consists of the three domains: symptomology, quality of life, and treatment effect. The symptoms domain consists of four sub-domains: muscle weakness, muscle block, pain, and fatigue. The quality of life domain consists of five sub-domains: activity (physical component), independence and social relationships (social components), and emotions and body perception (psychological components). In the treatment effect domain, the perceived and expected treatment effect is queried.
When determining the scores for the sub-domains for symptoms, the extent of difficulties because the symptoms and their importance for the affected persons are in the foreground. Therefore, the scores calculated for the symptomatic domain are also assigned to the endpoint category quality of life. Higher values represent a greater limitation of quality of life. The treatment effect domain does not reflect morbidity or quality of life and is therefore not considered in the benefit assessment.

In the combined analysis of both treatment sequences, a statistically significant treatment effect in favour of mexiletine compared with placebo was observed for the domain symptoms in the sub-domains muscle weakness, muscle block, pain, and fatigue.

The combined analysis of both treatment sequences also shows a statistically significant treatment effect for mexiletine compared with placebo in the domain quality of life, both in the overall quality of life and in the sub-domains activity, independence, social relationship, emotions, and body perception, which form the basis of the overall quality of life.

Because there are no effect estimators for the combined analysis that take into account the intra-individual dependency of the data according to the cross-over design of the study, the p values from a linear mixed model were used; these are considered valid.

For treatment period 1, Hedges' g calculations for the domain symptoms reveal clinically relevant differences for three of the four symptoms surveyed (muscle block, pain, and fatigue). For the domain quality of life, based on Hedges' g calculations, four of the five sub-

domains (activity, independence, social relationships, and emotions) show clinically relevant improvements in favour of mexiletine.

No adequate analyses are available for treatment period 2 because the pharmaceutical company reported baseline values that were not collected according to the study protocol and study report. Separate results and effect estimates are therefore not presented for this period.

Side effects

Adverse events were recorded on the last treatment day of each treatment period. Within the study, adverse events occurred in 15 patients (60%) treated with mexiletine and in 9 patients (36%) treated with placebo. Serious adverse events were not observed. A severe AE in the mexiletine arm caused one participant to withdraw from the study. Unwanted events of any severity with a frequency ≥ 10% under treatment with mexiletine were gastrointestinal disorders, infections and infestations, psychiatric disorders, nervous system disorders, and musculoskeletal and connective tissue disorders.
However, because of the low number of events and the short duration of the *MYOMEX* study, no reliable statements can be derived on the damage potential.

Overall assessment

The benefit assessment was based on the randomised, double-blind and placebo-controlled cross-over Phase III *MYOMEX* study in which mexiletine was investigated in adult patients with myotonia congenita or paramyotonia congenita.

The morbidity endpoint muscle stiffness shows a statistically significant and clinically relevant advantage in favour of mexiletine compared with placebo.

In the endpoint category of health-related quality of life, a statistically significant treatment effect in favour of mexiletine versus placebo was observed for the domain symptoms in the sub-domains muscle weakness, muscle block, pain, and fatigue. In three of the four sub-domains (muscle block, pain, and fatigue), the differences are clinically relevant according to Hedges' g calculations. In the quality of life domain, statistically significant treatment effects in favour of mexiletine compared with placebo are also found in all sub-domains. According to Hedges' g calculations, the differences in four of the five sub-domains (activity, independence, social relationships, and emotions) are clinically relevant.

In the endpoint category of side effects, no reliable statements can be derived on the damage potential of mexiletine because of the low number of events and the short duration of the *MYOMEX* study.

Thus, the positive and considerable effects in favour of mexiletine are shown in the improvement of muscle stiffness and health-related quality of life. However, because the patients in the *MYOMEX* study were treated with mexiletine for only 19 days (median) and placebo for 18 days (median), the duration of treatment is too short to be able to make any statements about the sustainability of the effects observed in this study, which are considerable in magnitude. In the course of the written statement procedure, it was demonstrated that because of the clinically applied off-label use, there are many years of experience using mexiletine for the therapy of myotonia. However, based on the data presented in the *MYOMEX* study, the damage potential of mexiletine cannot be assessed because the short duration of the study. The overall value added can therefore not be quantified based on the data provided.

In the overall view, mexiletine thus has a non-quantifiable additional benefit compared with placebo.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Namuscla® with the active ingredient mexiletine. Namuscla® has been approved as an orphan drug and is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

For the benefit assessment, the pharmaceutical company presents the randomised and double-blind cross-over Phase III *MYOMEX* study in which mexiletine was compared with placebo.

The morbidity category muscle stiffness shows a statistically significant and clinically relevant advantage in favour of mexiletine compared with placebo. Also in the endpoint category of health-related quality of life, there are statistically significant and distinct advantages in favour of mexiletine over placebo. On the other hand, the damage potential of mexiletine cannot be assessed because of the low number of events and the short duration of the *MYOMEX* study.

The effects in favour of mexiletine are thus positive and considerable compared with placebo. However, the duration of treatment in the study was too short to be able to make statements about the sustainability of the effects observed. The damage potential cannot be assessed based on the data provided. In the overall view, there is a non-quantifiable additional benefit of mexiletine over placebo.

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.

The information on the number of patients corresponds to the information provided by the pharmaceutical company in the benefit assessment dossier. To determine the number of individuals in the total population of Germany, the pharmaceutical company uses projections for the year 2019 made by the statistisches Bundesamt [German Federal Office for statistics]. Further calculations are based on a prevalence rate of non-dystrophic myotonia (1:100,000), which was determined for England in 2011. The estimated proportion of adult patients with non-dystrophic myotonia (82%) is based on an expert assumption. To illustrate the uncertainty, the pharmaceutical company finally estimates a proportion of ±10%.

The information provided by the pharmaceutical company is subject to uncertainties overall. It is unclear to what extent a prevalence rate reported for England in 2011 is transferable to the German health care context. References in the literature indicate that the prevalence rate depends largely on the region. Furthermore, there are no references to the proportion of adult patients or to the proportion of uncertainties for which the pharmaceutical company does not provide a justification.

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 Namuscla® (active ingredient: mexiletine) at the following publicly accessible link (last access: 29 April 2019):

https://www.ema.europa.eu/en/documents/product-information/namuscla-epar-product-information_de.pdf

Treatment with mexiletine should only be initiated and monitored by specialists who are experienced in the treatment of patients with myotonia.

In accordance with the requirements of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide a training manual for doctors or a patient passport for all medical personnel and all patients.

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 July 2019).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration varies from patient to patient and/or is shorter on average.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Mexiletine	continuous, 1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	annual average consumption by potency
Medicinal product to be assessed					
Mexiletine	167 mg - 500mg	167 mg - 500mg	1 × 167 mg - 3 × 167 mg	365	365 × 167 mg - 1,095 × 167 mg

Costs:

To facilitate comparability, the pharmaceutical costs were approximated both on the basis of the pharmacy sales price level and also the price less statutory rebates in accordance with Sections 130 and 130 a 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 pharmaceutical costs were then calculated on the basis of the costs per pack less the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy selling price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Mexiletine	100 hard capsules	€ 3,967.31	€ 1.77	€ 223.30	€ 3,742.24

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2019

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 costs in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed in accordance with the product information, the costs incurred for this 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 usual expenditure in the course of the treatment are not shown.

There are no additionally required SHI services.

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 31 January 2019, the pharmaceutical company submitted a dossier for the benefit assessment of mexiletine 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 2 May 2019 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 23 May 2019.

The oral hearing was held on 11 June 2019.

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 statements received and the oral hearing were discussed at the session of the subcommittee on 23 July 2019, and the proposed resolution was approved.

At its session on 1 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 April 2019	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	5 June 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 June 2019	Conduct of the oral hearing
Working group Section 35a	19 June 2019 2 July 2019 16 July 2019	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal products	23 July 2019	Concluding discussion of the proposed resolution
Plenum	1 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 August 2019

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

Prof Hecken