Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ponatinib (Reassessment after the Deadline: Acute Lymphoblastic Leukaemia)

of 20 November 2020

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 a rare disease (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 SGB V. Evidence of the medical benefit and the additional medical 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 assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, Nos. 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 during the last twelve 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 in accordance with Chapter 5, Section 5, paragraphs 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 solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided 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 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 of 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 pharmaceutical company first submitted a dossier for the benefit assessment of the active ingredient ponatinib (Iclusig) on 29 July 2013. The resolution of 23 January 2014 passed by the G-BA in this procedure was limited until 1 December 2015. The limitation was prolonged until 1 June 2020 at the request of the pharmaceutical company.

For the benefit assessment after the deadline, on 29 May 2020, the pharmaceutical company submitted the dossier to the G-BA in due time (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, No. 5 VerfO).

Ponatinib for the treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation is approved 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.

In accordance with Section 35a, paragraph 1, sentence 11, 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 and the significance of the evidence are assessed by the G-BA on the basis of the approval studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess 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 2020 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 G20-09) 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 assessed 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 - 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not set aside in the benefit assessment of ponatinib.

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

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.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of ponatinib (Iclusig) in accordance with the product information

Iclusig is indicated in adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

2.1.2 Extent of the additional benefit and significance of the evidence

Adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

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

Hint for a non-quantifiable additional benefit because the scientific data does not permit quantification.

Justification:

The pivotal study AP24534-10-201 (PACE) will be used for the benefit assessment of ponatinib in the therapeutic indication Philadelphia-chromosome positive acute lymphocytic leukaemia (Ph+ ALL).

The PACE study is a single-arm, multi-centre, open-label phase II study to assess the efficacy and safety of ponatinib in patients with chronic phase (CP), accelerated phase (AP), or blast phase CML or Ph+ ALL who

- were either resistant or intolerant (R/I) to previous therapy with dasatinib or nilotinib or
- had developed a T315I mutation following TKI therapy.

32 patients with Ph+ ALL were included in the study and treated with ponatinib 45 mg/day. The study was conducted at 66 study sites in Australia, Belgium, Germany, France, Great Britain, Italy, Canada, the Netherlands, Sweden, Singapore, Spain, South Korea, and the United States. The final analysis was performed on the data cut-off of 6 February 2017. The primary endpoint for patients with Ph+ ALL upon study inclusion was major haematological response within 6 months. Other endpoints include major molecular response (MMR), overall survival (OS), and side effects. Data on health-related quality of life were not surveyed in the PACE study.

Overall, for the benefit assessment of ponatinib in the therapeutic indication Philadelphia chromosome positive acute lymphocytic leukaemia (Ph+ ALL), only data from the single-arm PACE study are available; these do not allow a comparison. The data are therefore not suitable for making statements about the extent of the additional benefit.

Mortality

In the PACE study, 78.1% of patients with Ph+ ALL (R/I cohort) died between the first dose of ponatinib and the end of the study: 80%; TKI cohort: 77.3%). At the time of analysis, the median OS was 33.1 weeks (R/I cohort: 56.5 weeks; T315I cohort: 28.4 weeks).

In the absence of comparative data, it is not possible to draw conclusions about the extent of the additional benefit based on these results.

Morbidity

No relevant data are available.

Quality of life

In the PACE study, the quality of life was not surveyed. There are therefore no data from the PACE study to assess the additional benefit for ponatinib in terms of quality of life.

Side effects

In the Ph+ ALL populations, all patients experienced at least one adverse event.

25 out of 32 patients with Ph+ ALL (78.1%) experienced at least one serious adverse event (SAE) (R/I cohort: 80.0%; T315I cohort: 77.3%). The most frequent SAE (≥ 5%) corresponding to PT were febrile neutropoenia (21.9%), atrial fibrillation and tumour progression (12.5% each), and sepsis, septic shock, and dehydration (6.3% each).

In 28 of 32 patients with Ph+ ALL (87.5%), at least one severe AE with CTCAE grade ≥ 3 occurred (R/I cohort: 90%; T315I cohort: 86.4%). The most frequent AE with a severity of ≥ 3 were febrile neutropoenia (25.0%), neutropoenia (21.9%) and decreased thrombocyte count, and anaemia (18.8%).

The occurrence of an AE resulted in 3 of 32 patients with Ph+ ALL (9.4%) definitively discontinuing the study medication (R/I cohort: 10%; T315I cohort: 9.1%).

The most frequent AE of special interest were skin and subcutaneous tissue disorders (59.4%), infections and infestations (71.9%), and myelosuppression (59.4%).

Statements on the extent of the additional benefit with regard to adverse events cannot be made because of the lack of a control group.

Overall assessment/conclusion

For the benefit assessment of ponatinib for the treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation, there are results for the endpoint categories mortality and side effects from the uncontrolled PACE study.

Because of the single-arm study design, a comparative overall assessment of the study results is not possible.

Thus, a quantitative assessment of the extent of the effect and a quantification of the additional benefit on the basis of the data submitted is not possible.

As a result, the G-BA classifies the extent of the additional benefit of ponatinib in the present indication as non-quantifiable because of the limited data basis based on the criteria in Section 5, paragraph 7 of the AM-NutzenV, taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. According to Section 35a, paragraph 1,

sentence 11, 1st half of sentence SGB V, there is an additional benefit; however, this is non-quantifiable because the scientific data basis does not allow this.

On the T315I mutation

According to the commentators, patients with a T315I mutation have a particularly poor prognosis because the point mutation T315I leads to resistance to all previously approved tyrosine kinase inhibitors (TKI) except for ponatinib. Ponatinib is the only TKI also explicitly approved in the presence of a T315I mutation.

Significance of the evidence

The reliability of data is assessed as a hint because only a single-arm, uncontrolled study is available, and a comparative assessment is not possible.

In the overall view, there is a hint for a non-quantifiable additional benefit in terms of the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is a renewed benefit assessment of the active ingredient ponatinib because of the expiry of the limitation of the resolution of 23 January 2014.

Iclusig® was approved as an orphan drug.

This assessment refers to the use of ponatinib for the treatment of Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in the following patient population:

Adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

For this patient group, the pharmaceutical company presents results from the one-armed, uncontrolled PACE study.

Thus, for patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), only data from a single-arm study are available; these do not allow a comparison. The data are therefore not suitable to be able to quantify the extent of the additional benefit.

The reliability of data is assessed as a hint because only a single-arm, uncontrolled study is available, and a comparative assessment is not possible.

In the overall view, for ponatinib for the treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation, there are results for the endpoint categories mortality and side effects from the uncontrolled PACE study, a hint for a non-quantifiable additional benefit is identified because the scientific data basis does not allow quantification.

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 resolution will be based on the information from the dossier of the pharmaceutical company regarding the number of patients. In determining the number of patients in the SHI target population, the pharmaceutical company uses the resolution of the G-BA in the 1st

procedure on ponatinib from 2014. Because the pharmaceutical company does not expect any significant increase in the target population, the range of 25 to 195 patients from this resolution is estimated as the SHI target population. These figures are plausible; however there are uncertainties because of the limited data basis.

For example, in the procedure on ponatinib from 2014, it was restrictively pointed out that both the calculation of the range and the demographic structure of the underlying data set could not be reconstructed.

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 Iclusig (active ingredient: ponatinib) at the following publicly accessible link (last access: 3 September 2020):

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

Treatment with ponatinib should be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL).

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide information for healthcare professionals on ponatinib in a suitable form, in particular on the importance of the risk assessment of patients before starting treatment with ponatinib; on data on the relationship between dosage and the risk of vascular occlusion; on recommendations for close monitoring when a dose reduction is applied; on recommendations to discontinue treatment if no complete haematological response has occurred within 3 months of treatment; on major side effects for which monitoring and/or dose adjustment is recommended (according to SmPC: pancreatitis, increased amylase and lipase levels, myelosuppression, abnormalities in liver function tests, bleeding, cardiac disorders/left ventricular dysfunction, vascular occlusion, hypertension); on instructions for side effect management based on monitoring and dose modification or treatment discontinuation.

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: 1 November 2020).

Treatment duration:

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 different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and 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				
Ponatinib	continuously, 1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/application	Dose/patient/treatment day	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Ponatinib	45 mg	45 mg	1 × 45 mg	365	365 × 45 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 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 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 product:

Designation of the therapy	Package 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					
Ponatinib 45 mg	30 FCT	€ 6,525.03	€ 1.77	€ 379.01	€ 6,144.25
Abbreviations: FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 November 2020

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 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 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

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 29 May 2020, the pharmaceutical company submitted a dossier for the benefit assessment of ponatinib 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 2020 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 22 September 2020.

The oral hearing was held on 5 October 2020.

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 were discussed at the session of the subcommittee on 10 November 2020, and the proposed resolution was approved.

At its session on 20 November 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	25 August 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	29 September 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	5 October 2020	Conduct of the oral hearing
Working group Section 35a	13 October 2020 3 November 2020	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 on Medicinal Products	10 November 2020	Concluding discussion of the draft resolution
Plenum	20 November 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 November 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken