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 According to Section 35a SGB V – Ponatinib

of 23 January 2014

Contents

1. Legal basis

According to Section 35a, paragraph 1 of the 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 10, 1st half sentence SGB V. 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 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, 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 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, subsection 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 10 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 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 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 ponatinib in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO is 1 August 2013. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, No. 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 1 VerfO on 29 July 2013.

Ponatinib for the treatment of chronic myeloid leukaemia and Philadelphia chromosome positive acute lymphoblastic leukaemia 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 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 November 2013 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 evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G13-02) 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 Nos. 1 through 4 VerfO. The methodology proposed by IQWiG in Annex A of the dossier evaluation for ticagrelor (dossier evaluation A11-02, pages 86 to 92) was not used in the benefit assessment of ponatinib.

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

2.1 Additional benefit of the medicinal product

Extent of the additional benefit

To answer the question on the extent of the additional benefit, the results of registration study AP24534-10-201 and Phase I dose-finding study AP24534-07-101 supporting the marketing authorisation are available. The assessment of the extent of the additional benefit of ponatinib is based on study AP24534-10-201. This study is a multi-centre, single-arm, open-label Phase II study. This study has not yet been completed. The study included 449 patients with CML in chronic phase, accelerated phase, and blast crisis as well as patients with Ph+ ALL. These patients were either resistant or intolerant to dasatinib or nilotinib (in

Ph+ ALL, only to dasatinib) and were not eligible for treatment with imatinib (hereinafter R/I) or had a T315I mutation of the BCR-ABL gene product (hereinafter T315I). A total of 444 patients were assigned to six study cohorts, taking into account disease phase, resistance/intolerance to previous medication, or T315I mutation status. Five patients could not be assigned to a cohort because despite documented positive T315I history, no T315I mutation could be detected in the study. The cohorts defined in the study protocol and evaluated in the clinical study report included patients with BC-CML and patients with Ph+ ALL. Following the marketing authorisation procedure, the patient populations with CML and with Ph+ ALL were presented separately in the dossier and in the resolution. Therefore, eight cohorts are considered. The evaluation presented at the time of marketing authorisation and in the dossier of pharmaceutical company is based on the data cut-off of 27 April 2012, which was used for the present assessment of the resolution. The median follow-up period was 9.9 months.

The point mutation T315I is of particular clinical relevance. Patients with a T315I mutation did not respond to the therapy options available so far. There was therefore no treatment option available for this patient population. However, the data basis does not allow any conclusions to be drawn as to whether these patients, who are generally not transplantable, are eligible for (potentially curative) allogeneic stem cell transplantation in the course of therapy with ponatinib, as well as what the long-term results are. Because of the missing control group and blinding as well as the short follow-up period, there is a high risk of bias for the effects shown in study AP24534-10-201. Thus, a valid and meaningful assessment of the results to quantify the additional benefit is not possible.

a) Adult patients with CML:

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

For adult patients with chronic myeloid leukaemia in chronic phase, accelerated phase, or blast crisis who are resistant to treatment with dasatinib or nilotinib, do not tolerate dasatinib or nilotinib and are not clinically suitable for subsequent treatment with imatinib, or have a T315I mutation, there is a non-quantifiable additional benefit.

Justification:

The G-BA classifies the extent of the additional benefit of ponatinib as non-quantifiable 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. An additional benefit exists but is non-quantifiable because the scientific data basis does not permit this. The short follow-up period of 9.9 months, the missing control group in the study, and the methodologically inadequate historical comparison presented in the dossier are relevant for the decision in the present case constellation and indication. Because of the unsystematic conduct of the literature search and the considerable limitations in the comparability of the relevant characteristics (in particular the patient population) of the historical studies and the AP24534-10-201 study, this historical comparison is not suitable for quantifying the extent of the additional benefit.

Thus, on the basis of the data submitted, it is not possible to quantitatively assess the extent of the effect or the additional benefit into one of the three categories “low”, “considerable”, or “substantial”.

Mortality

Until the data cut-off of 27 April 2012, median overall survival was not achieved in CP-CML and AP-CML. For BC-CML, the median overall survival was 29.9 weeks.
For CP-CML, the survival rate at 12 months was 93.5% (R/I cohort: 94.4%; T315I cohort: 90.2%); for AP-CML, it was 82.2% (R/I cohort: 83.9%; T315I cohort: 72.2%); for BC-CML, it was 29.5% (R/I cohort: 35.1 %; T315I cohort: 16.0%).
There is no control group. In addition, the historical comparison is methodologically inadequate.
The scientific evidence therefore does not allow a quantification of the extent of the additional benefit of ponatinib from the point of view of mortality.

Morbidity

The following endpoints on cytogenetic, molecular, and haematological response are presented in addition to the patient-relevant endpoint “overall survival”.

Haematologic response (HR)

The rate of major haematologic response (MaHR) is the primary endpoint for patients in advanced stages of CML (AP-CML and BC-CML). It is defined as the proportion of patients who achieved complete haematologic response (CHR) or no evidence of leukaemia (NEL) after the start of study and who continued to meet CHR or NEL criteria in a re-assessment of response rate 28 days after the initial assessment. MaHR was reported for AP-CML and BC-CML; for CP-CML, only the CHR was determined. A total of 48 out of 83 patients in the AP-CML (57.8%) achieved an MaHR. When the R/I and T315I cohorts were considered separately, this was 39 of 65 patients (60.0 %) and 9 of 18 patients (50 %), respectively. For BC-CML, a total of 19 out of 62 patients (30.6%) achieved an MaHR. When the R/I and T315I cohorts were considered separately, this was 12 of 38 patients (31.6%) and 7 of 24 patients (29.2%), respectively. Especially because of the methodologically inadequate historical comparison, but also the missing control group, a statement on the extent of the additional benefit is not possible.

Cytogenetic response (CyR)

For patients in the chronic phase of CML, the primary endpoint of the study is major cytogenetic response (MCyR). MCyR is defined as the proportion of patients who received at least one dose of the study medication and who achieved complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR) after the start of study during the observation period. 144 of the 267 patients (53.9%) in the CP-CML achieved an MCyR on ponatinib; of these, 118 (44.2%) achieved a CCyR. When the R/I and T315I cohorts were considered separately, 99 of 203 patients (48.8%) in the R/I cohort achieved an MCyR; of these, 76 (37.4%) patients achieved a CCyR. In the T315I cohort, 45 of 64 patients (70.3%) achieved an MCyR; of these, 42 (65.6%) achieved a CCyR. Especially because of the methodologically inadequate historical comparison, but also the missing control group, a statement on the extent of the additional benefit is not possible.

Molecular Response (MR)

In the dossier, major molecular response (MMR) is reported. This is defined as the percentage of patients who met the criteria of MMR (ratio of ≤ 0.1% of BCR-ABL to ABL transcripts on the international scale) at least once after the start of study. A total of 79 out of

267 patients (29.6%) in the CP-CML achieved an MMR. When the R/I and T315I cohorts were considered separately, 47 of 203 patients (23.2%) in the R/I cohort achieved an MMR; 32 of 64 patients (50%) in the T315I cohort achieved an MMR. In the AP-CML, this was 9 of 83 patients (10.8%), including 6 with R/I and 3 with T315I. In the BC-CML, this was 8 of 62 patients (12.9%), including 7 with R/I and 1 with T315I. Especially because of the lack of a control group, a statement on the extent of the additional benefit is not possible.

Progression-free survival (PFS)

The endpoint PFS is a combined endpoint composed of endpoints of the mortality and morbidity categories. PFS is defined as the time from the first application of therapy to the progression of the disease or death of any cause. The criteria for progression were defined differently depending on the stage of the CML disease. In CP-CML, the criteria of progression are: death; development of AP-CML or BC-CML; loss of a CHR (in the absence of cytogenetic response) confirmed by two differential blood counts determined at least four weeks apart; loss of a MCyR; increasing number of white blood cells without CHR defined by doubling white blood cells to > 20 K in two blood samples determined at least four weeks apart (after the first four weeks of therapy). In the advanced stages of CML, unlike CP-CML, the loss of MCyR or CHR in AP-CML, the loss of any response in BC-CML, and the increase in white blood cell counts in AP and BC-CML are not considered progression. It is possible that the exclusion of the above criteria has led to a bias in the PFS results for patients with AP-CML or BC-CML. Furthermore, there is no control group. The individual components of the PFS were not considered separately. The endpoint PFS thus cannot be clearly assessed with respect to patient relevance because it is composed of different endpoint categories with different relevance and severity.
Overall, no statement can be made on the basis of the endpoint PFS to quantify the patient-relevant additional benefit.

Quality of life

In the AP24534-10-201 study, the quality of life was not surveyed. There are therefore no data to assess the additional benefit for ponatinib in terms of quality of life.

Side effects

The desired effects of ponatinib are offset by adverse events (AE).

In total, 99.3% of the 417 CML patients experienced at least one adverse event. In the CP-CML, 99.3% of patients had at least one AE. For CP-CML, the most common were thrombocytopaenia (42.2%), skin rash (40.7%) and abdominal pain (38.1%) In the AP-CML, 98.8 % of patients had at least one AE. The most common AE were thrombocytopaenia (47.1%), neutropaenia (31.8%), and abdominal pain (30.6%). For BC-CML, all patients had at least one AE; the most common were skin rash (33.9%), thrombocytopaenia (33.9%), and neutropaenia (33.9%).

204 out of 417 patients with CML (48.9%) had at least one serious adverse event (SAE). In the CP-CML, 39.6% of patients had at least one AE. Pancreatitis (6.3%), abdominal pain (3.3%), and pneumonia (2.6%) were the most common. For AP-CML, the most common SAE were pneumonia (7.1%), neoplastic progression (7.1%), and thrombocytopaenia (5.9%). For BC-CML, the most common SAE were neoplastic progression (24.2%), pneumonia (11.3%), and anaemia (8.1%)

In the CP-CML population, the most frequent AEs with a severity ≥ 3 were thrombocytopaenia (33%), neutropaenia (15.7%), and elevated lipase levels (11.2%). In the AP-CML population, the most common AE with a severity grade ≥ 3 were thrombocytopaenia (38.6%), neutropaenia (32.5%), and anaemia (14.5%). In the BC-CML population, the most common AE with a severity grade ≥ 3 were thrombocytopaenia (32.3%), anaemia (32.3%), and neutropaenia (27.4%).

A total of 49 CML patients (11.8 %) discontinued treatment with ponatinib because of adverse events.

However, valid statements on the extent of the additional benefit with regard to adverse events cannot be made based on the data available because of the lack of long-term data and the limitation of the missing control group. In its evaluation report, the European Medicines Agency (EMA) also addresses the lack of data on long-term safety and has called for further reviews of corresponding data on the safety of therapy with ponatinib.

In the overall assessment of the presents results, based on the marketing authorisation and the desired and undesired effects observed in the aforementioned study, taking into account the written statements received, the oral hearing, and the severity of the disease, the G-BA arrives at the following assessment of the extent of the additional benefit: there is an additional benefit, but is non-quantifiable because the scientific data basis currently does not permit this.

b) Adult patients with Ph+ ALL:

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

For adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib, do not tolerate dasatinib and are not clinically suitable for subsequent treatment with imatinib, or have a T315I mutation, there is a non-quantifiable additional benefit.

Justification:

The G-BA classifies the extent of the additional benefit of ponatinib as non-quantifiable 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. An additional benefit exists but is non-quantifiable because the scientific data basis does not permit this. The short follow-up period of 9.9 months, the low number of cases, the missing control group in the study, and the methodologically inadequate historical comparison presented in the dossier are relevant for the decision in the present case constellation and indication. Because of the unsystematic conduct of the literature search and the considerable limitations in the comparability of the relevant characteristics (in particular the patient population) of the historical studies and the AP24534-10-201 study, this historical comparison is not suitable for quantifying the extent of the additional benefit.

Thus, on the basis of the data submitted, it is not possible to quantitatively assess the extent of the effect or the additional benefit into one of the three categories “low”, “considerable”, or “substantial”.

Mortality

As of the data cut-off of 27 April 2012, median overall survival was 39.3 weeks in the Ph+ ALL population. The survival rate after 12 months was 42.3% (50.0% in the R/I cohort; 39.0%

in the T315I cohort). There is no control group. In addition, the historical comparison is methodologically inadequate.
The scientific evidence therefore does not allow a quantification of the extent of the additional benefit of ponatinib from the point of view of mortality.

Morbidity

The following endpoints on cytogenetic, molecular, and haematological response are presented in addition to the patient-relevant endpoint “overall survival”.

Haematologic response (HR)

The primary endpoint for patients with Ph+ ALL is MaHR. A total of 13 out of 32 patients (40.6%) achieved an MaHR. When the R/I and T315I cohorts were considered separately, this was 5 of 10 patients (50.0 %) and 8 of 22 patients (36.4 %), respectively. Especially because of the methodologically inadequate historical comparison, the low number of cases, and the missing control group, no statement on the extent of the additional benefit can be derived.

Cytogenetic Response (CyR)

Data on the endpoint MCyR are available for patients with Ph+ ALL. 15 of the 32 Ph+ ALL patients (46.9%) achieved a MCyR (6 patients in the R/I, cohort and 9 patients in the T315I cohort); of these, 12 (37.5%) achieved a CCyR. Especially because of the methodologically inadequate historical comparison, the low number of cases, and the missing control group, a statement on the extent of the additional benefit is not possible.

Molecular Response (MR)

A total of 3 out of 32 Ph+ ALL patients (9.4%) achieved an MMR. This corresponds to 2 patients (20%) in the R/I cohort and 1 patient (4.5%) in the T315I cohort. Especially because of the low number of cases and the missing control group, no statement on the extent of the additional benefit can be derived.

Progression-free survival (PFS)

In the indication Ph+ ALL, the definition of progression corresponded to that of BC-CML. Because of the aforementioned limitations, no statement on the quantification of the patient-relevant additional benefit can be made on the basis of the endpoint PFS.

Quality of life

In the AP24534-10-201 study, the quality of life was not surveyed. There are therefore no data to assess the additional benefit for ponatinib in terms of quality of life.

Side effects

The desired effects of ponatinib are offset by adverse events.

In the Ph+ ALL populations all patients had at least one adverse event. Constipation (46.9%), abdominal pain (31.3%), and fatigue (25%) were the most common.

At least one serious adverse event occurred in 23 patients (71.9%). Febrile neutropaenia (21.9%), neoplastic progression (12.5%), and sepsis (9.4%) were the most common. The most frequent AEs with a severity of ≥ 3 were febrile neutropaenia (25%), neutropaenia (21.9%), and anaemia (18.8%).

In total, one ALL patient (3.1%) discontinued treatment with ponatinib because of adverse events.

However, valid statements on the extent of the additional benefit with regard to adverse events cannot be made based on the data available because of the lack of long-term data and the limitation of the missing control group. In its evaluation report, the EMA also addresses the lack of data on long-term safety and has called for further reviews of corresponding data on the safety of therapy with ponatinib.

In the overall assessment of the presents results, based on the marketing authorisation and the desired and undesired effects observed in the aforementioned study, taking into account the written statements received, the oral hearing, and the severity of the disease, the G-BA arrives at the following assessment of the extent of the additional benefit: there is an additional benefit, but is non-quantifiable because the scientific data basis currently does not permit this.

Limitation

In accordance with Article 20 of Regulation (EC) No. 726/2004 of 27 November 2013, the European Commission instructed the EMA to review the data obtained in the field of pharmacovigilance on Iclusig® in the recent past with regard to their influence on the assessment of the risk-benefit balance of this medicinal product and whether they justify the maintenance, restriction, suspension, or revocation of the marketing authorisation of the medicinal product. As part of the review of the risk-benefit ratio, the following in particular should be carried out: “further consideration of the pharmacokinetic and pharmacodynamic profile of Iclusig in order to determine whether there is a need to adjust the optimal dosage, further assessment of the nature, severity, and frequency of all occlusive vascular adverse events (and possible long-term damage) and heart failure requiring treatment, and investigation of the potential mechanisms leading to occlusive vascular events”.

Further data on efficacy and safety endpoints as well as mortality, especially in patients with T315 mutation, are also expected. Furthermore, no data on transplantability and long-term data are available for treatment with ponatinib.

Against this background, the limitation of the duration of the resolution is justified. The limitation to one year will permit timely inclusion of the review of pharmacovigilance data to be carried out by the EMA in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

These data must be submitted to the G-BA for a new referral.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of ponatinib shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of ponatinib (Chapter 5, Section 12, No. 1, sentence 2 VerfO). In principle, an extension of the limitation may be granted if it is justified and clearly demonstrated that the period of the limitation (one year) is not sufficient.

The possibility that a benefit assessment of ponatinib can be carried out at an earlier point in time for other reasons (*cf* Section 35a, paragraph 1, sentence 11 SGB V in conjunction with Chapter 5, Section 12 No. 2 VerfO) remains unaffected by this.

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

a) Adult patients with CML:

Target population: approx. 500 to 940 patients

b) Adult patients with Ph+ ALL:

Target population: approx. 25 to 195 patients

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 number of patients stated in the dossier of the pharmaceutical company. Because of the uncertainty in the data basis, a more precise indication is not possible.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account.

In November 2013, the EMA reported an increased incidence of thrombotic events as part of further evaluations of ongoing clinical studies on ponatinib. In the written statement of the EMA dated 6 December 2013 regarding thrombotic events in connection with treatment with ponatinib, it is stated that a final risk assessment will take place in 2014. The EMA will update the summary of product characteristics as appropriate. Consequently, the status of the product information in particular must be checked to ensure that it is up to date. Any changes must be taken into account.

Because of the disease- and medicinal-product-specific characteristics, in particular the rarity of the disease, the newly initiated risk assessment procedure of the EMA, and the complexity of the treatment, treatment with ponatinib should only be initiated and monitored by specialists experienced in the therapy of patients with CML and Ph+ ALL (specialist in internal medicine and haematology and oncology).

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 January 2014).

Costs of the medicinal product:

The recommended dosage of ponatinib is 45 mg per day according to the product information.

Treatment period:

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 is patient-individual and/or is shorter on average.

Costs for additionally required SHI services:

Because there are no significant regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the therapies applied in the approval study in the comparator arms according to the product information, no costs for additionally required SHI services had to be taken into account. Regular laboratory services such as blood count determinations or medical fees that do not exceed the scope of the usual expenses in the course of oncological treatment will not be taken into account.

3. Bureaucratic costs

The provisions contained in the resolution do not create any information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO. There are thus no bureaucratic costs.

4. Process sequence

A dossier for formal preliminary examination according to Chapter 5, Section 11 VerfO was submitted by the pharmaceutical company on 10 July 2013. On 29 July 2013, the pharmaceutical company submitted the dossier for the benefit assessment to the G-BA in accordance with Section 35a SGB V. The relevant date for the first placing on the market of the active ingredient ponatinib in accordance with Chapter 5, Section 8, No. 1, Sentence 2 VerfO is 1 August 2013.

The benefit assessment of the G-BA was published on 1 November 2013 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 November 2013.

The oral hearing was held on 10 December 2013.

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 14 January 2014, and the proposed resolution was approved.

At its session on 23 January 2014, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	27 August 2013	Information on the results of the completeness check of the dossier
Subcommittee Medicinal product	22 October 2013	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	3 December 2013	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	10 December 2013	Conduct of the oral hearing
Working group Section 35a	17 December 2013 7 January 2014	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal product	14 January 2014	Advice and consensus on the draft resolution
Plenum	23 January 2014	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 23 January 2014

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

Hecken