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 – Vandetanib

of 5 September 2013

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. 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 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.

According to Section 35a, paragraph 5b SGB V, pharmaceutical companies can at any time apply for a new benefit assessment for a resolution according to Section 35a, paragraph 3 SGB V published until 31 December 2012, in deviation from paragraph 5 if the additional benefit is considered not proven because the required evidence was not submitted in full.

2. Key points of the resolution

In its resolution of 6 September 2012, as the result of the benefit assessment of the medicinal product Caprelsa® with the active ingredient vandetanib (hereinafter vandetanib) according to Section 35a, paragraph 1, sentence 5 SGB V, the G-BA established that an additional benefit for vandetanib is considered not proven because the pharmaceutical company did not submit with the dossier of 14 March 2012 proof of the additional benefit of vandetanib in relation to the appropriate comparator therapy determined by the G-BA in the approved therapeutic indication as required under Section 35a, paragraph 1, sentence 3 No. 3 SGB V. This resolution was published before 6 September 2012.

The application of the pharmaceutical company for a renewed benefit assessment according to Section 35a SGB V was received by the office of the G-BA on 14 November 2012. At its

session on 6 December 2012, the G-BA decided to grant the application of the pharmaceutical company for a renewed benefit assessment according to Section 35a, paragraph 5b SGB V, which was received on 14 November 2012.

On 8 March 2013, the pharmaceutical company submitted the final dossier to the G-BA for a renewed benefit assessment according to Section 35a SGB V for the active ingredient vandetanib.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 17 June 2013 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

In the course of the written statement procedure, the pharmaceutical company submitted further data. In a letter dated 23 July 2013, the G-BA commissioned the IQWiG to supplement the benefit assessment of the data available in the dossier as well as the data submitted later in the written statement procedure. The addendum to the benefit assessment of the IQWiG was submitted to the G-BA on 8 August 2013.

The G-BA came to a resolution on whether an additional benefit of vandetanib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment (A13-09) prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment (A13-26) prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 of the Rules of Procedure of the G-BA (VerfO). The methodology proposed by IQWiG in Annex A of the dossier assessment for ticagrelor (dossier assessment A11-02, pages 86 to 92) was not used in the benefit assessment of vandetanib.

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:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Approved therapeutic indication of vandetanib (Caprelsa ®) in accordance with the product information

Caprelsa® is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

For patients in whom *Rearranged during Transfection* (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see sections 4.4 and 5.1 of the product information).

Appropriate comparator therapy:

The appropriate comparator therapy for vandetanib for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease is best supportive care.

Best supportive care is defined as the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve quality of life (e.g. bisphosphonates for painful bone metastases, external radiotherapy).

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.
5. If there are several alternatives, the more economical therapy should be chosen, preferably a therapy for which a fixed reimbursement rate applies.
   After the amendments in Section 6 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) by Article 4 No. 2 of the Act on the Amendment of Drug Law and other Regulations came into force on 13 August 2013 (cf Federal Law Gazette I p. 3108 ff.), this criterion is not considered when determining the appropriate comparator therapy.

<u>Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:</u>

On 1. No other active ingredients are approved for the treatment of medullary thyroid carcinoma.

On 2. Resection is generally considered as a non-medicinal treatment for medullary thyroid carcinoma. Patients for whom resection with a curative objective is indicated are not considered in the context of this study. Non-medicinal treatment is therefore not considered an appropriate comparator therapy. Furthermore, all non-medicinal palliative measures that can be summarised within the framework of best supportive care are considered.

On 3. No corresponding resolutions have been passed.

On 4. The generally accepted state of medical knowledge was illustrated by a guideline search and an evidence search. Based on the evidence available, best supportive care is determined as the current therapy standard in relation to the therapeutic indication. Best supportive care refers to all measures that guarantee the best possible patient-individual optimised supportive treatment to alleviate symptoms and improve quality of life but do not pursue a primarily curative treatment goal.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

Probability and extent of the additional benefit

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

For patients with aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease, there is a hint for a minor additional benefit compared with the appropriate comparator therapy.

Justification:

The G-BA classifies the extent of the additional benefit of vandetanib as minor 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. Compared with the appropriate comparator therapy “Best supportive care”, in accordance with § Section 5, paragraph 7 in conjunction with Section 2, paragraph 3 AM-NutzenV, this is a moderate and not only minor improvement of the therapy-relevant benefit that has not yet been achieved.

Probability of additional benefit

The results of the pivotal study D4200C00058 (hereinafter Study 58) are available for the assessment of the additional benefit. This is a randomised, placebo-controlled, two-armed, double-blind Phase III study. This ongoing study is being conducted in 63 study centres in 24 countries worldwide with a total of 331 patients randomised at a ratio of 2:1. Patients in the test arm (231) received 300 mg vandetanib once daily; patients in the control arm (100), received placebo once daily. Patients in both the vandetanib arm and the placebo arm received concomitant treatment classified as best supportive care. The total study population consists of patients in whom medullary thyroid carcinoma (MTC) is in a non-resectable and locally advanced or metastatic stage but whose disease progression was not necessarily aggressive and symptomatic. Because the marketing authorisation of vandetanib is limited to patients with aggressive and symptomatic MTC, only this patient group represents the target population to be considered in answering this question. According to the European Public Assessment Report (EPAR), the proportion of the target population in the total study population is up to 56%. Therefore, of the 331 patients in the total study population, the target population includes only 186 patients: 126 in the vandetanib arm and 60 in the placebo arm.

The study medication was continued in accordance with protocol until the occurrence of progression. When progression occurred, patients stopped randomised treatment with the study drug and, after unblinding, had the option to switch to open treatment with vandetanib (crossover or continued treatment). In the target population, 38 of the 43 patients with progression in the placebo arm and 26 of the 69 patients with progression in the vandetanib arm received this treatment.

Two analyses were planned for the study: an interim analysis and a final evaluation. The interim analysis (data cut-off of 31 July 2009) was planned based on the primary endpoint PFS; the final analysis was planned based on overall survival. The final evaluation is still pending.

The reliability of data (probability of additional benefit) is classified in the “hint” category. This classification takes into account uncertainties in the data basis on the additional benefit. At the study level, the risk of bias is assessed as high. An important aspect is the possibility for patients to switch to open treatment with vandetanib and subsequent completion of the double-blind randomised treatment phase after disease progression.
A survival time analysis was performed for various endpoints, such as mortality, morbidity (time

to worsening of pain), and side effects. Informative censoring can be assumed here. The risk of bias at the endpoint level is therefore considered high.

The reliability of data (probability of additional benefit) can therefore not be classified as an "indication" but rather as a "hint".

Extent of the additional benefit

Mortality

In Study 58, the endpoint "overall survival" was evaluated as the only endpoint of the benefit assessment according to the intention-to-treat (ITT) principle included over the entire period up to the data cut-off for the primary analysis on 13 July 2009. For overall survival, there is no statistically significant difference between the vandetanib arm and the control arm. In both treatment groups, 21 (16.7%) (vandetanib + BSC) and 10 (16.7%) (placebo + BSC) patients died in the relevant sub-population. A representation of the median survival time or the 25% quantile of the time to death is therefore not possible. An additional benefit of vandetanib compared with the appropriate comparator therapy is therefore not proven for overall survival.

Morbidity

Time to worsening of pain (TWP)

In Study 58, the endpoint "Time to worsening of pain (*TWP*)" was surveyed as a combined endpoint derived from the assessment for the most severe pain based on the validated BPI-SF (*Brief Pain Inventory-Short Form*) Pain Questionnaire as well as the patient's response regarding the use of opioid analgesics. The BPI-SF uses numerical rating scales from 0 to 10, where 0 corresponds to "no pain" and 10 to "worst pain imaginable". The combined endpoint for the TWP was met if the patient achieved progression of "strongest pain", which is defined as an increase of at least 2 points on the rating scale in the scale of strongest pain from baseline, or the use or dose increase of opioid analgesics without pain relief within the following 14 days (also measured by the use of pain medication and the BPI-SF).

In the dossier of the pharmaceutical company, there was no evaluation of the severity of pain for patients in the relevant sub-population with pain progression. As part of the written statement procedure, the pharmaceutical company submitted an evaluation of the mean strongest pain in patients with pain progression. They can be found in the written statement procedure of the pharmaceutical company and the addendum of the IQWiG.

Patients who showed pain progression during the course of the study had a mean pain intensity of 3 to 4 points on the scale at the start of study. At the time of pain progression, a mean pain of about 6 points was documented. For the endpoint "time to worsening of pain", there is a statistical advantage for vandetanib with a prolongation of TWP compared with placebo (hazard ratio of 0.62, 95% confidence interval (CI): [0.39; 0.99], p value: 0.045). The median time to worsening of pain was approx. 11 months in the vandetanib group and approx. 3 months in the placebo group; this represents an improvement of approx. 8 months. The prevention or reduction of moderate pain is patient-relevant. For the characteristic age, there was an indication of an effect modification (interaction test: $p = 0.198$). Regarding the individual subgroups, in younger patients (< 65 years), there was a statistically significant difference between the treatment groups in favour of vandetanib + BSC. For the older patients (≥ 65 years), the result was not statistically significant. However, an age-specific difference does not seem biologically plausible or medically justified against the background of previous

experience in the treatment of patients with MTC. The assessment of the endpoint TWP is therefore not separated by age group.

For the endpoint "time to worsening of pain", the G-BA assesses the extent of additional benefit for vandetanib as considerable because compared with the appropriate comparator therapy, best supportive care, a delay in the onset of a serious disease symptom is achieved. This is not a long-term freedom from serious symptoms. A classification as a major additional benefit is therefore not justified.

Objective response rate, duration of objective response, disease control rate

The endpoints "objective response rate (ORR)", "duration of objective response (DOR)", and "disease control rate (DCR)" were not used for the present evaluation because no patient-relevant operationalisation was used, and these endpoints were assessed exclusively using imaging techniques.

Progression-free survival (PFS)

The endpoint "progression-free survival" shows a statistically significant prolongation of progression-free survival in favour of vandetanib. This endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The morbidity component "time to the onset of first objective disease progression" was not assessed on the basis of symptoms but exclusively by means of imaging techniques, which is not sufficient for classification as a patient-relevant endpoint. Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the endpoint "Progression-free survival". Because of the consistent direction of effects for the patient-relevant endpoint "time to worsening of pain" and the endpoint "progression-free survival", the endpoint PFS, which is not directly patient-relevant in the present case, supports the result on the additional benefit, although this does not change the result.

Quality of life

In Study 58, data on quality of life were collected using the FACT-G, *Functional Assessment of Cancer Therapy General Scale*. This endpoint was determined on a purely exploratory basis. No usable data on quality of life were provided. Therefore, no valid statements can be derived on the extent of the additional benefit for the endpoint "quality of life".

Side effects

The positive effects of vandetanib are offset by adverse events (AE).

In order to address the imbalance in treatment duration between the two treatment groups (median treatment duration approximately 88 weeks in the vandetanib arm vs approximately 37 weeks in the placebo arm), survival analyses were submitted as part of the written statement procedure. The hazard ratio (HR) takes into account the individual observation time of each patient (in the case of premature end of observation, by means of censoring). Because of the informative censoring, these analyses are highly biased. Recalculations of individual incidence densities were also submitted. The Incidence Density Ratio (IDR) is the ratio of the number of patients who suffer one event per 1,000 patient years. However, this measure makes sense only if the risk of suffering an event is similar over the entire observation period. This can be the case with rare events, for example. The IDR is therefore an appropriate

measure only in exceptional cases. For the severe adverse events “Prolongation of QTc time”, operationalised according to Standardised MedDRA Query (SMQ) Torsade de pointes/QTc prolongation, and for the serious adverse events “Diarrhoea”, operationalised based on the preferred term (PT), no information on survival time analysis was available. The IDR calculations were thus considered for these two endpoints.

The relative risks (RR) for the endpoints on side effects, which are estimated over naïve proportions in the dossier of the pharmaceutical company, must also be considered highly biased. However, they are taken into account in the present case.

Total rate of AE

The total rate of adverse events cannot be calculated for the time-adjusted evaluation; when the non-time-adjusted results are considered, the overall rate of side effects is high (vandetanib arm: 100% of patients, placebo arm: 94.9% of patients). There was no statistically significant difference between the treatment groups. For this endpoint, lesser or greater harm from vandetanib + BSC is not proven.

Serious adverse events (SAE)

The comparison of the time-adjusted results in the vandetanib arm and the placebo arm did not reveal a statistically significant difference for serious adverse events (SAE). When considering the non-time adjusted results (RR), a statistically significant result was found to the detriment of vandetanib + BSC. For this endpoint, there is no proof of greater or lesser harm from vandetanib + BSC when considering the time-adjusted analysis; however, when considering the relative risks, there is greater harm from vandetanib + BSC compared with placebo + BSC.

Severe AE

In the vandetanib arm, the time-adjusted score for the endpoint “Severe adverse events (CTCAE grade ≥ 3)” showed a statistically significant result in favour of vandetanib + BSC compared with the control arm. For this endpoint, significantly different event rates were observed when considering the non-time adjusted analysis (RR) to the detriment of vandetanib + BSC (vandetanib arm: 61.1% vs placebo arm: 23.7% of patients with an event, RR and CI not calculated). For this endpoint, there is proof of greater harm from vandetanib + BSC.

Therapy discontinuations because of AE

In the vandetanib arm, the time-adjusted analysis for the endpoint “therapy discontinuations because of AE” did not show a statistically significant result between treatment groups compared with the control arm. For this endpoint, no significant result is available even when considering the non-time adjusted evaluation (RR). (Vandetanib arm: 11.9% vs placebo arm: 1.7 % of patients with one event, RR: 7.02 and 95% CI [0.95; 51.93]). For this endpoint, there is no proof of greater or lesser harm from vandetanib + BSC.

Frequent AE or AE of special interest

For the endpoint “Skin rashes”, the time-adjusted analysis showed a statistically significant result between treatment groups to the detriment of vandetanib + BSC. For this endpoint, when

considering the non-time adjusted analysis (RR) significantly different event rates were also observed to the detriment of vandetanib + BSC (vandetanib arm: 49.2% vs placebo arm: 13.6% of patients with an event, RR and CI not calculated). For this endpoint, there is proof of greater harm from vandetanib + BSC.

No time-adjusted evaluations were available for the endpoint “diarrhoea”. For this endpoint, when considering the non-time adjusted analysis (RR) significantly different event rates were also observed to the detriment of vandetanib + BSC (vandetanib arm: 52.4% vs placebo arm: 22.0% of patients with an event, RR and CI not calculated). The G-BA therefore sees a disadvantage for vandetanib + BSC with regard to the endpoint “diarrhoea”. However, the calculation of the incidence density ratio for the endpoint diarrhoea (SAE) showed no statistically significant difference between the treatment arms. For this endpoint, there is no proof of greater or lesser harm from vandetanib + BSC.

For the endpoint “QTc prolongation”, the time-adjusted analysis showed a statistically significant result between treatment groups to the detriment of vandetanib + BSC. For this endpoint, when considering the non-time adjusted analysis (RR) significantly different event rates were observed to the detriment of vandetanib + BSC (vandetanib arm: 15.9% vs placebo arm: 1.7% of patients with an event, RR and CI not calculated). For the endpoint “QTc prolongation (CTCAE ≥ 3)” higher event rates were also observed for vandetanib + BSC (vandetanib arm: 7.9% vs placebo arm: 0% of patients with an event, RR and CI not calculated). For the endpoint “QTc prolongation (CTCAE ≥ 3)”, the calculation of the incidence density ratio showed no statistically significant difference between treatment arms. However, this result is very imprecise (95% CI [0.4; 115.83]). Therefore, for this endpoint greater, harm from vandetanib + BSC is assumed with high probability. The QTc-related adverse events have also been included by the EMA in the risk management plan for vandetanib.

In terms of side effects, this results in greater harm from vandetanib, thereby justifying a downgrading of the extent of the additional benefit.

In the overall assessment of the results on morbidity, the lack of evaluable data on mortality and quality of life, and the results on side effects, even taking into account the severity of the disease, there is a hint for a minor additional benefit for vandetanib.

Based on these considerations, the information in the dossier, and the results of the benefit assessment as well as the written statements and the results of the addendum to the benefit assessment, the G-BA found a minor additional benefit of vandetanib compared with best supportive care.

Limitation

The period of validity of a conditional marketing authorisation is one year and can be extended annually (*cf* Article 14, paragraph 7 Regulation 726/2004 in conjunction with Article 6, paragraph 1 Regulation 507/2006).

Against the background that the pharmaceutical company is obliged to submit to the EMA further comprehensive clinical data on the harmlessness and efficacy of the medicinal product Caprelsa®, which may be relevant for the assessment of the benefit of the medicinal product in accordance with Section 35a SGB V, the limitation of the resolution is justified. It enables the proof of safety and efficacy to be provided to the approval authority based on the

conditional marketing authorisation to be included promptly in the benefit assessment of the medicinal product in accordance with Section 35a SGB V. A period of three years is considered appropriate for this purpose. With regard to the evidence to be provided, the EMA requires, among other things, that data on efficacy and safety endpoints of studies, including a study on RET mutation status in patients with sporadic medullary thyroid carcinoma, be provided. These data must be submitted to the G-BA for a new referral.

In accordance with Section 3, number 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of vandetanib 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 proving an additional benefit of vandetanib in relation to the appropriate comparator therapy (Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, No. 5 VerfO). Otherwise, the additional benefit is considered not proven.

The possibility of carrying out a benefit assessment for vandetanib at an earlier point in time for other reasons (cf Chapter 5, Section 1 paragraph 2, numbers. 2 – 4 VerfO) remains unaffected by this.

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

Target population in statutory health insurance (SHI): approx. 60 to 1,500 patients

This information on patient numbers refers to the target population in the statutory health insurance.

The G-BA bases its resolution on the patient numbers submitted by the pharmaceutical company in the dossier. 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.

This medicinal product was approved by the EMA under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated, particularly with regard to a benefit of Caprelsa® in patients without *Rearranged during Transfection* (RET) mutation status. A study will be conducted in order to investigate this. The EMA will evaluate new information on this medicinal product at least once per year and, if necessary, the summary of product characteristics will be updated.

Because of the disease- and medicinal-product-specific characteristics, in particular the rarity of the disease, the demarcation of the target population in accordance with the therapeutic indication, and the complexity of the treatment, treatment with Caprelsa® should be initiated and monitored only by specialists experienced in the therapy of patients with this disease. These are: specialists in internal medicine, haematology, and oncology, specialists in internal medicine and endocrinology, and specialists participating in the Oncology Agreement. Or the prescription is made on the recommendation of an interdisciplinary tumour conference. The aforementioned doctors must meet the conditions of the EPAR requirements regarding training material and equipment.

The training material provided by the marketing authorisation holder shall include the following:

- Summary of product characteristics (product information) and package leaflet

- Training material for doctors
- Patient passport (wording as agreed with the CHMP)

The training material for doctors should contain the following key messages:

- Vandetanib extends the QTc interval and can trigger torsade de pointes and sudden cardiac death
- Vandetanib should not be used in patients:
    - whose QTc interval in the ECG is greater than 480 ms
    - who have a congenital long QTc syndrome
    - who had torsade de pointes in the past unless all risk factors that contributed to the torsade de pointes were corrected
- The need for ECG and measurements of potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) levels as well as the frequency and occasions on which they should be taken.
- Patients whose corrected QTc interval in the ECG increases once to at least 500 ms should discontinue vandetanib. Administration can be resumed at reduced dosage after the QTc interval in the ECG has demonstrably returned to the same status as before treatment and the electrolytes are balanced.
- If the QTc interval increases significantly but remains below 500 ms, a cardiologist should be consulted.
- Information on medications for which concomitant administration of vandetanib is contraindicated or not recommended.
- That vandetanib may cause posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS)
- PRES should be considered in patients who experience seizures, headaches, visual disturbances, confusion, or a change in mental function. An MRI of the brain should be performed on any patient with seizures, confusion or altered mental function.
- The need to advise patients on the risks of QTc interval prolongation and PRES as well as the symptoms and signs to be considered and the appropriate measures to take
- The meaning and use of the patient passport

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 August 2013).

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. Vandetanib is taken continuously once a day in accordance with the product information.

Costs of the medicinal product:

The therapeutic measures that are carried out within the framework of the best supportive care vary from patient to patient depending on the symptomatology. Module 3 Section 3.2.2 in the dossier of the pharmaceutical company lists the measures used in the care routine. These include thyroid hormone substitution, painkillers, tranquilizers/sleeping pills, bisphosphonates, and palliative radiotherapy. However, the therapeutic measures of the best supportive care to be carried out concomitantly to the therapy with vandetanib do not regularly differ from the best supportive care to be applied within the framework of the appropriate comparator therapy. A detailed presentation of the therapy costs for treatment costs is therefore not necessary.

Costs for additionally required SHI services:

If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product or package information, the costs incurred for this must be taken into account as costs for additionally required SHI services. Only costs directly related to the use of the medicinal product are taken into account. Medical treatment costs as well as hospital costs incurred for application of the medicinal product (e.g. infusion vials, infusion equipment), for monitoring the success of the treatment or the course of the disease, for routine investigations (e.g. standard laboratory services such as blood counts that do not exceed standard expenditure over the course of oncological treatment), and for medical fee-based services are not shown.

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

In a letter dated 13 November 2012, received on 14 November 2012, the pharmaceutical company submitted an application for a renewed benefit assessment according to Section 35a, paragraph 5 SGB V.

At its session on 6 December 2012, the G-BA decided to grant the application of the pharmaceutical company for a renewed benefit assessment according to Section 35a, paragraph 5b SGB V, which was received on 14 November 2012.

The pharmaceutical company submitted a dossier on 12 February 2013. A formal preliminary examination of the completeness of the dossier was carried out by the Secretariat of the G-BA in accordance with Chapter 5, Section 11, paragraph 2 of the VerfO. The final dossier was submitted on 8 March 2013. The start of the assessment was 15 March 2013.

By letter dated 11 March 2013 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient vandetanib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 June 2013, and the written statement procedure was initiated with publication on the website of the G-BA on 17 June 2013. The deadline for submitting written statements was 8 July 2013.

The oral hearing was held on 23 July 2013.

In a letter dated 23 July 2013, the G-BA commissioned the IQWiG to evaluate the assessment submitted in the written statement procedure by the pharmaceutical company, in particular on pain symptomatology and side effects.

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 27 August 2013, and the proposed resolution was approved.

At its session on 5 September 2013, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 November 2012	Consultation on the application for a renewed benefit assessment according to Section 35a, paragraph 5b SGB V
Plenum	6 December 2012	Resolution on the application for a renewed benefit assessment according to Section 35a, paragraph 5b SGB V
Working group Section 35a	16 July 2013	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 July 2013	Conduct of the oral hearing and decision on the supplementary commission of IQWiG
Working group Section 35a	30 July 2013 13 August 2013 20 August 2013	Consultation on the dossier assessment of the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	27 August 2013	Consultation and consensus on the draft resolution
Plenum	5 September 2013	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 5 September 2013

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

Hecken