Gemeinsamer Bundesausschuss

Justification

of 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

Fedratinib (myelofibrosis)

of 2 September 2021

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 German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. 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 in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Instead, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation 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 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 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA 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 relevant date for the first placing on the (German) market of the combination of active ingredient fedratinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 March 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 12 March 2021.

Fedratinib for the treatment of myelofibrosis 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 of the sentence German Social Code, Book Five (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 based on the marketing authorisation 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 15 June 2021 on 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 also held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-10) and the statements made in the written statements and oral hearing process, as well of the addendum drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1,

numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of fedratinib.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of fedratinib (Inrebic) in accordance with the product information

Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

Therapeutic indication of the resolution (resolution from the 2 September 2021):

see approved therapeutic indication

2.1.2 Extend of the additional benefit and significance of the evidence

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

(a) adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, treatment of disease-related splenomegaly or symptoms

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

For the benefit assessment, the pharmaceutical company presented results of the multicentre, globally conducted, randomised, double-blind, three-arm phase III study JAKARTA.

Patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis according to the 2008 WHO and IWG-MRT criteria who had not previously received a JAK2 inhibitor were included in the study. According to the inclusion criteria, only patients with myelofibrosis classified as high-risk or intermediate-risk 2 according to IWG-MRI criteria were included for screening.

Patients were randomised 1:1:1 to the three treatment arms, fedratinib 400 mg/day (N = 96 patients), fedratinib 500 mg a day (N = 97 patients), and placebo (N = 95). The 500 mg/day treatment arm is not relevant for the benefit assessment since the dosage is non-conformant with the product information.

Patients should be treated according to the protocol in all treatment arms for at least six treatment cycles of 28 days each. Patients in the placebo arm could be rerandomised to either fedratinib arm after completion of the six cycles or before completion if disease progression occurred. A total of 71 patients were rerandomised from the placebo arm, with 35 patients assigned to the 400 mg/day arm. Patients in the fedratinib arms underwent treatment discontinuation in the event of progression.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Due to the occurrence of Wernicke's encephalopathies, a *clinical hold* was issued by the FDA in November 2013, and fedratinib treatment was discontinued for all patients enrolled in the JAKARTA study. At this time, all patients had completed the first six cycles of treatment or had already permanently discontinued treatment (in most cases due to adverse events). All patients were subsequently offered thiamine supplementation. Patients could also receive alternative therapy after a two-week washout period following the last fedratinib administration. Thiamine supplementation and follow-up should also be continued in the case of alternative therapy or participation in another clinical study. With the completion of the follow-up visits and the resolution or stabilisation of all serious adverse events and adverse events of special interest, study participation was terminated without further observation. The last fedratinib administration was on 2 December 2013, and the last study visit of a patient was on 25 June 2014.

Results of the data cut-off from 01.05.2013 were presented in the dossier by the pharmaceutical company. On this day, all study participants were unblinded.

At this time, the median duration of observation was 62 weeks in the 400 mg/day fedratinib arm and 24.0 weeks in the placebo arm.

Mortality

The endpoint overall survival was operationalised in the JAKARTA study as time from randomisation to death or censoring.

Due to the premature study discontinuation, the study participants could not be followed up until death from any cause. Furthermore, the a priori planned analyses on the endpoint could not be performed. Thus, for overall survival, only post hoc defined analyses up to the end of treatment cycle 6 are available due to the *clinical hold* and the associated study discontinuation.

Overall, the results on overall survival are of small significance. Statistically, there is no difference.

Morbidity

Spleen response by MRI/CT; symptom response by modified MSAF

In the JAKARTA study, spleen response was the primary endpoint. This was defined as the percentage of patients with a spleen volume reduction of ≥ 35% measured by MRI or CT at the end of cycle 6. Remeasurement by MRI/CT was performed 4 weeks later to confirm the spleen response rate ≥ 35%. During the written statement procedure, clinical experts pointed out that in clinical practice, the spleen response is mainly determined by palpation.

The modified MFSAF (Mylofibrosis Symptom Assessment Form) used to assess symptom response comprises six items on the disease-specific symptoms "night sweats", "itching (pruritus)", "abdominal disorders", "pain under the ribs on the left side", "fullness and bone or muscle pain". The operationalised endpoint was a reduction ≥ 50% in total symptom score (TSS). The MFSAF was already classified in the benefit assessment procedure for ruxolitinib (resolution of 6 November 2014) as a valid instrument for symptom assessment in the present therapeutic indication.

A long-lasting reduction of the pathologically elevated spleen volume combined with a noticeable decrease of impairing disease symptoms and improvement of the quality of life for the patient is considered to be patient-relevant.

In both the analyses of spleen response without reconfirmation at 4 weeks and when reconfirmation at 4 weeks was considered, there was a statistically significant advantage for patients in the fedratinib arm.

At the same time, there was a statistically significant advantage for fedratinib-treated patients in symptom response by modified MFSAF both in symptom response rate operationalised as ≥ 50% reduction in TSS at the end of cycle 6 and in responder analyses operationalised as the time to improvement by ≥ 50% compared with baseline. The responder analyses show this advantage under fedratinib both in terms of the overall symptom score TSS and in all individual components except "muscle/bone pain".

The advantage in spleen response combined with an advantage in symptom response is considered a significant, clinically relevant improvement.

Symptom burden according to MPN-SAF

The pharmaceutical company also assessed the symptom burden using the MPN-SAF. In this regard, analyses were presented on the mean change at the end of treatment cycle 6 compared to baseline. The return rate for all items was below 70%. Uncertainties about validity still persist. The data are therefore not considered for the benefit assessment.

EQ 5D-VAS

Health status was assessed in the JAKARTA study using the visual analogue scale of the EuroQoL-5 dimension (EQ 5D). Higher values indicate a better health status. With the written statement procedure, the pharmaceutical company submitted responder analyses showing an improvement of ≥ 15 mm (15%).

There were no statistically significant differences between the two treatment arms. It should be noted that the return rate in the comparator arm was less than 70% and is therefore subject to uncertainty. Due to the time-to-event analysis provided later and the censoring reasons and frequencies, the responder analysis is used as an appropriate analysis in this case, but with a high risk of bias.

Brief Fatigue Inventory

The patients included in the JAKARTA study were also questioned about the intensity and effects of fatigue using the Brief Fatigue Inventory questionnaire. Analyses of the mean change at the end of treatment cycle 6 from baseline were presented. The return rate for all items was below 70%. The data are therefore not considered for the benefit assessment.

Overall, based on the advantage in spleen volume reduction combined with an associated advantage in symptom response, a clinically relevant advantage can be established in the morbidity category.

Quality of life

No data on health-related quality of life were assessed in the JAKARTA study.

Side effects

Analyses of the safety population were presented, in which adverse events were recorded up to 30 days after the end of cycle 6. Patients after *cross-over* were not included.

Adverse events in total

The results were only presented additionally. At least one adverse event occurred in almost all patients included in the study.

Serious adverse events (SAE)

There was no statistically significant difference in the occurrence of serious adverse events between the two treatment arms.

Severe adverse events CTCAE grade ≥ 3

Treatment with fedratinib resulted in a statistically significant higher incidence of serious side effects events than placebo.

Therapy discontinuation due to AE

There was no statistically significant difference in treatment discontinuation due to AE.

Adverse events of special interest

There was a statistically significant disadvantage in favour of fedratinib in the endpoint "time to first anaemia ("CTCAE grade 3/4")" and a statistically significant advantage in favour of fedratinib in the endpoint "time to first secondary malignancy".

Overall, there is a disadvantage in the category of side effects due to the more frequent occurrence of severe AEs CTCAE grade ≥ 3 to the disadvantage of fedratinib.

Overall assessment / conclusion

Mortality, morbidity, and adverse event results are available from the JAKARTA study for the benefit assessment of fedratinib for treating disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve. The study was discontinued prematurely due to the occurrence of Wernicke's encephalopathy.

For overall survival, only post hoc defined analyses of overall survival to the end of treatment cycle 6 with a short observation period are available due to *clinical hold* and the associated study discontinuation. Overall, the results on overall survival are of small significance. Statistically there is no difference.

A statistically significant advantage can be observed for the endpoints spleen response and symptom burden assessed by modified MFSAF. The advantage in spleen response combined with an advantage in symptom response is considered a significant, clinically relevant improvement.

In the category of side effects, one disadvantage can be identified overall.

The overall assessment of the additional benefit considers that the present JAKARTA study is subject to considerable uncertainties and limitations. A relevant uncertainty exists in particular because the study had to be discontinued prematurely due to Wernicke's encephalopathies. This leads to a shortened observation period overall. Significant data for the endpoint overall survival are not available due to premature study discontinuation.

Another uncertainty regarding the study conducted from 2012 to 2014 is that the comparator used in the study does not reflect the current German standard of care, according to clinical experts.

The extent of the described limitations and uncertainties of the present study results is assessed to be so significant in the overall assessment that it does not permit quantification of the overall additional benefit despite the significant advantage in morbidity.

In the overall assessment, a non-quantifiable additional benefit is identified for fedratinib for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, because the scientific evidence base does not allow quantification.

Significance of the evidence

The benefit assessment is based on data from the randomised, double-blind JAKARTA study.

There is a lack of data on quality of life. About patient-reported outcomes, there were high proportions of censoring. Further limitations are that a higher proportion of patients in the placebo arm had high-risk myelofibrosis and poorer general condition. In addition, the median time since diagnosis was significantly longer for patients in the placebo arm than for patients in the fedratinib arm.

In the overall review the result is a hint for an additional benefit with regard to the significance of the evidence.

(b) adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib, treatment of disease-related splenomegaly or symptoms

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

The pharmaceutical company submitted data for this patient population from the multicentre, open-label, single-arm, Phase II JAKARTA-2 study. The JAKARTA-2 study included patients with a diagnosis of primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis according to WHO 2008 and IWG-MRI criteria. Patients whose myelofibrosis was classified as intermediate risk-1 with symptoms or intermediate risk-2 or high risk according to the Dynamic International Prognostic Scoring System (DIPSS) were included. Patients were required to have received prior therapy with ruxolitinib given for at least 14 days (unless intolerance or allergy to ruxolitinib was present) and be resistant or intolerant to ruxolitinib as judged by medical investigators. However, according to the product information of ruxolitinib, treatment should be stopped after six months if there is no response.

A total of 97 patients were included in the study. According to the study protocol, a dosage of 400 mg fedratinib should be administered. The fedratinib administration was scheduled for at least 6 cycles of 28 days each. In the event of an inadequate response, the dose could be increased up to 600 mg. In 33 of the 97 patients, such a dose increase, which does not conform to the requirements in the product information, was carried out.

As was true for the JAKARTA study, due to the *clinical hold* issued by the FDA following the occurrence of Wernicke's encephalopathy, fedratinib administration was discontinued for all patients in December 2013 and patients were offered thiamine supplementation. From the start of thiamine supplementation, patients were followed for another 90 ± 3 days for safety.

The last study visit of a patient took place on 7 May 2014. The data cut-off submitted by the pharmaceutical company was carried out on this date.

Mortality

The endpoint overall survival was defined as an exploratory endpoint in the JAKARTA-2 study alone and operationalised as time from the first dose to death or censoring.

Due to the premature study discontinuation, the study participants could not be followed up until death from any cause. Furthermore, the a priori planned analyses on the endpoint could not be performed. The pharmaceutical company submitted additional analyses for the benefit assessment.

Due to the single-arm study design and the uncertainties in the analysis caused by the premature study discontinuation, no conclusions on the extent of additional benefit in the mortality category can be derived from the results of the JAKARTA-2 study.

Morbidity

Spleen response by MRI/CT; symptom response by modified MSAF

In the JAKARTA-2 study, spleen response was the primary endpoint. This was defined as the percentage of patients with a spleen volume reduction of ≥ 35% measured by MRI or CT.

The modified MFSAF (Mylofibrosis Symptom Assessment Form) used to assess symptom response comprises six items on the disease-specific symptoms "night sweats", "itching (pruritus)", "abdominal disorders", "pain under the ribs on the left side", "fullness and bone or muscle pain". The operationalised endpoint was a reduction ≥ 50% in total symptom score (TSS).

A long-lasting reduction of the pathologically elevated spleen volume combined with a noticeable decrease of impairing disease symptoms and improvement of the quality of life for the patient is considered to be patient-relevant.

The high percentage of patients with a dosage non-compliant with marketing authorisation must be taken into account.

EORTC QLQ-C30

In the JAKARTA-2 study, the symptomatology was also assessed using EORTC QLQ-C30 symptom scales ("fatigue", "nausea and vomiting", "pain", "dyspnoea", "insomnia", "appetite loss", "constipation", "diarrhoea"). Higher values correspond to severe symptomatology. The endpoint was operationalised as the time to improvement by ≥ 10 points.

Symptom burden according to MPN-SAF

The pharmaceutical company also assessed the symptom burden using the MPN-SAF. In this regard, analyses were presented on the mean change at the end of treatment cycle 6 compared to baseline. The return rate for all items was below 70%. Uncertainties about validity still persist. The data are therefore not considered for the benefit assessment.

Brief Fatigue Inventory

The patients included in the JAKARTA-2 study were also questioned about the intensity and effects of fatigue using the Brief Fatigue Inventory questionnaire. Analyses of the mean change at the end of treatment cycle 6 from baseline were presented. The return rate for all items was below 70%. The data are therefore not considered for the benefit assessment.

Due to the single-arm study design, no conclusions on the extent of additional benefit in the morbidity category can be derived from the results of the JAKARTA-2 study.

Quality of life

EORTC QLQ-C30 functional scales

Quality of life was assessed in the JAKARTA-2 study using EORTC QLQ-C30 functional scales. These include the scales "Global health status", "Physical functioning", "Role functioning", "Emotional functioning", "Cognitive functioning" and "Social functioning". The endpoint was operationalised as the time to the improvement of ≥ 10 points, with higher scores representing better quality of life.

Due to the single-arm study design, no conclusions on the extent of additional benefit in the quality of life category can be derived from the results of the JAKARTA-2 study.

Side effects

Adverse events in total

An adverse event (AE) occurred in almost all patients. The results were only presented additionally.

Serious adverse events (SAE)

26.8 % of the patients had at least one serious adverse event (SAE).

Severe adverse events CTCAE grade ≥ 3

Severe adverse events (CTCAE grade ≥ 3) were experienced by 60.8% of patients.

Therapy discontinuation due to AE

13.4% of patients discontinued therapy due to an AEs.

Adverse events of special interest

The most common AEs of special interest were "Potential Wernicke's encephalopathy," "SMQ bleeding (narrow definition)," "SMQ bleeding (broad definition)," "cardiac insufficiency/cardiomyopathy," "anaemia, CTCAE grade 3 or 4," and "thrombocytopenia."

Due to the single-arm study design, no conclusions on the extent of additional benefit in the category of side effects can be derived from the results of the JAKARTA-2 study.

Overall assessment / conclusion

The assessment of the additional benefit of fedratinib for treating disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis treated with ruxolitinib is based on the single-arm JAKARTA-2 study.

Results for the patient-relevant endpoints of the categories mortality, morbidity, quality of life and adverse events are available.

Due to the single-arm design of this study, a comparative assessment is not possible.

Therefore, a quantitative assessment of the extent of the effect and quantification of the additional benefit based on the data presented is not possible.

In the overall assessment, a non-quantifiable additional benefit is identified for fedratinib for the treatment of disease-related splenomegaly or symptoms in adult patients with primary

myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib because the scientific evidence base does not allow quantification.

Significance of the evidence

The benefit assessment is based on data from the single-arm JAKARTA-2 study.

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

In addition, the JAKARTA-2 study was discontinued prematurely. This resulted in overall short observation times. In addition, because of this, only post hoc defined analyses of overall survival are available.

The overall result regarding the significance of the evidence is a hint of non-quantifiable additional benefit.

2.1.3 Limitation of the period of validity of the resolution

The period of validity of the statements made in the resolution on the patient population b) "adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis treated with ruxolitinib" finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G35-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

The present benefit assessment in patient population b) is based on the results of the single-arm JAKARTA-2 study. Due to the occurrence of Wernicke's encephalopathies and the associated clinical hold in 2013, the JAKARTA-2 study was discontinued early, which resulted in a short observation period. Overall, there is a lack of significant data on the patient-relevant endpoints in the categories of mortality, morbidity, health-related quality of life and side effects for the benefit assessment.

In view of the fact that data comparing fedratinib with the *best available therapy* are expected from the currently ongoing clinical FREEDOM2 study, which may be relevant for the assessment of the additional benefit, it is justified to time-limit the decision until further scientific evidence is available for the assessment of the extent of the additional benefit of fedratinib.

For this purpose, the G-BA considers a limitation for the resolution until 1 March 2025 to be appropriate.

Conditions for the limitation:

For the renewed benefit assessment after the expiry of the deadline, the dossier should contain significant results for the patients in the therapeutic indication that is the subject of the assessment from the currently ongoing FREEDOM2 study on all patient-relevant endpoints that are used to evaluate the additional benefit.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of fedratinib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of fedratinib (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO).

The possibility that a benefit assessment for fedratinib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 – 6 VerfO) remains unaffected hereof.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Inrebic with the active ingredient fedratinib.

Fedratinib was approved as an orphan drug.

In the therapeutic indication considered, 2 patient populations were differentiated:

(a) adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, treatment of disease-related splenomegaly or symptoms

(b) adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who have been treated with ruxolitinib, treatment of disease-related splenomegaly or symptoms .

a)

Data from the RCT JAKARTA (fedratinib vs placebo) are available for the categories mortality, morbidity and side effects.

Due to the *clinical hold* and the associated premature study termination, only post hoc defined analyses with a short observation period are available for mortality. Overall, the results on overall survival are of small significance. Statistically, there is no difference.

In the morbidity category, fedratinib treatment resulted in a benefit for the endpoint spleen response, which, combined with the benefit in symptom response (by MFSAF), is considered a significant, clinically relevant improvement.

In terms of side effects, one disadvantage is noted with fedratinib.

Due to relevant uncertainties and limitations, in particular, due to the premature discontinuation of the study and the associated short observation periods, as well as due to the comparator in the JAKARTA study, which does not reflect the current German standard of care, no overall quantification of the additional benefit can be made despite the significant benefit in morbidity.

The reliability of data is assessed with a hint.

b)

Data from the single-arm study JAKARTA-2 are available for the categories mortality, morbidity, quality of life and side effects.

Due to premature study discontinuation, only post hoc defined analyses are available on mortality. Overall, the observation times are shortened due to the discontinuation.

Due to the single-arm design of this study, a comparative assessment is not possible.

The data are therefore not suitable for quantifying the extent of the additional benefit.

Thus, the overall conclusion is that there is a non-quantifiable additional benefit.

The reliability of data is rated as a hint because only a single-arm study is available.

The validity of the resolution is limited to 1 March 2025. At this date, data from the ongoing FREEDOM2 (fedratinib vs *best available therapy*) study relevant to the benefit assessment have to be presented.

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 is based on the information from the dossier of the pharmaceutical company. The calculation procedure of the pharmaceutical company to determine patient numbers is comprehensible but is subject to uncertainties.

On the one hand, these concern the starting point resulting from a health services research analysis concerning, among other things, the (non-)consideration of ICD codes, a possible parallel registration of inpatients and outpatients, a possible selection bias in the selection of treatment centres. In addition, the range of the percentage of patients with disease-related splenomegaly is not considered adequate. Furthermore, there are uncertainties regarding the proportion of patients with a platelet count ≥ 50 x 10^{9}/l who should not be treated with fedratinib, and the restriction regarding platelet count was not considered at the same time. The percentage of patients with ruxolitinib treatment is based on data from 2013 and is therefore also subject to limitations. Despite the limitations listed, the number of patients calculated here is considered to be more precise than that from the benefit assessment procedure for ruxolitinib (resolution of 6 November 2014).

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 Inrebic (active ingredient: fedratinib) at the following publicly accessible link (last access: 29 July 2021):
https://www.ema.europa.eu/documents/product-information/inrebic-epar-product-information_de.pdf

Initiation and monitoring of treatment with fedratinib should be performed only by specialists in internal medicine and haematology and oncology experienced in the therapy of patients with myelofibrosis.

Given the risk of occurrence of (Wernicke's) encephalopathies, patients' thiamine levels should be assessed prior to initiation and at regular intervals during treatment (e.g., monthly for the first 3 months and every 3 months thereafter) and as clinically indicated.

2.4 Treatment costs

The treatment costs are based on the product information as well as the information in the LAUER-TAXE® (last revised: 15 August 2021).

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 patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the doses of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Fedratinib	continuously, 1 x daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Fedratinib	400 mg	400 mg	4 x 100 mg	365	1,460 x 100 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 130a 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. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging 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					
Fedratinib 100 mg	120 HC	€ 5,664.96	€ 1.77	€ 320.25	€ 5342.94

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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 evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be considered 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.

Additionally, required SHI services for the medicinal product application to be evaluated according to the product information and patient information leaflet are given by the necessity of determining the thiamine level prior to therapy initiation. According to the product information, thiamine levels should be assessed at baseline and at regular intervals thereafter, e.g. monthly for the first 3 months and every 3 months thereafter (and as clinically indicated). Accordingly, 7 determinations per year are assumed.

Designation of the therapy	Designation of the service	Costs/ unit	Number/ patient/ year	Costs / patient / year
Fedratinib	Quantitative chromatographic determination(s) of one or more substance(s) - Vitamins GOP 32306	€ 22.30	7	€ 156.10

3. Bureaucratic costs calculation

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 12 March 2021, the pharmaceutical company submitted a dossier for the benefit assessment of fedratinib 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 15 June 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 6 July 2021.

The oral hearing was held on 26 July 2021.

An amendment to the benefit assessment with a supplementary assessment (here only if aspects actually submitted in SN were reassessed: from data submitted in the written statement procedure) was submitted on 13 August 2021.

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 the 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 24 August 2021, and the draft resolution was approved.

At its session on 2 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	8.06.2021	Information of the benefit assessment of the G-BA
Working group Section 35a	1.07.2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	26.07.2021	Conduct of the oral hearing
Working group Section 35a	4.08.2021 18.08.2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal product	24.08.2021	Concluding consultation of the draft resolution
Plenum	2.09.2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 September 2021

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

Prof. Hecken