Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Momelotinib (myelofibrosis)

of 15 August 2024

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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 all reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (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). 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 assessment 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 € 30 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, paragraphs 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. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by 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 turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient momelotinib on 15 February 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1 of the Rules of Procedure (VerfO) of the G-BA. 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 15 February 2024.

Momelotinib for the treatment of disease-related splenomegaly or symptoms in adults with moderate to severe anaemia is approved as a medicinal product for the treatment of rare diseases 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 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 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 15 May 2024 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 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 G24-04) and the statements made in the written statement and oral hearing procedure, as well of the amendment 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 approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of momelotinib.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Momelotinib (Omjjara) in accordance with the product information

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

Therapeutic indication of the resolution (resolution of 15 August 2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

a) Adults with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve; for the 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 the results of the multicentre, randomised, double-blind, phase III SIMPLIFY- 1 study, in which momelotinib was compared with ruxolitinib. The study consists of a 24-week randomised, controlled and blinded treatment phase. This was followed by an open-label treatment phase in which participants from both study arms could receive momelotinib at the end of the 24-week treatment phase. The 24-week blinded treatment phase was used for the benefit assessment.

The study population of the SIMPLIFY-1 study comprises non-pretreated adults with myelofibrosis and splenomegaly. A total of 432 subjects were enrolled in the study and randomised in a 1:1 ratio according to transfusion dependence (yes/ no) and platelet count ($< 100 \times 10^9$/l / $\geq 100 \times 10^9$/l and $\leq 200 \times 10^9$/l / $> 200 \times 10^9$/l) (intention-to-treat (ITT) population). The ITT population comprises 215 subjects in the momelotinib arm and 217 subjects in the ruxolitinib arm.

In order to limit the study population to the therapeutic indication, which includes subjects with moderate or severe anaemia, a modified intention to treat (mITT) population, which represents subjects with a haemoglobin (Hb) value < 10 g/dl and is used for the benefit assessment, was defined post hoc.

The mITT population comprises 181 subjects (momelotinib arm N = 86; ruxolitinib arm N = 95).

The primary endpoint of the study was the reduction in spleen volume by ≥ 35%. The study, which was completed in May 2019, was conducted in 131 study sites across North America, Europe, Asia and Australia.

For the study, a total of three data cut-offs were performed:

- 1 July 2019 (final data cut-off)
- 12 September 2016 (end of the double-blind treatment phase; interim analysis week 24)
- 12 September 2017

For the benefit assessment of momelotinib, the data cut-off from 1 July 2019 was used.

Mortality

In the SIMPLIFY-1 study, the endpoint of overall survival was operationalised as the time span (in months) from the first dose in the blinded treatment phase to death, regardless of the cause of death. Overall survival was only collected up to 30 days after the last dose of the 24-week treatment phase.

There was no statistically significant difference between the treatment arms.

Morbidity

Spleen response using MRI/CT

In the SIMPLIFY-1 study, spleen response was the primary endpoint. The spleen response rate was defined as the percentage of subjects with a spleen volume reduction by ≥ 35% measured by magnetic resonance imaging (MRI) or computed tomography (CT) at week 24 compared to baseline.

A long-lasting reduction of the pathologically elevated spleen volume combined with a noticeable decrease of impairing disease symptoms for the patients is considered to be patient-relevant. In the present case, the spleen response was collected exclusively by means of imaging procedures. There was no statistically significant difference between the treatment arms in this regard. There were also no statistically significant differences in the present endpoints on disease symptomatology.

As this is the primary endpoint, it is presented additionally.

Leukaemic transformation

In the SIMPLIFY-1 study, leukaemic transformation is operationalised as the time from randomisation to the occurrence of leukaemic transformation, defined as an increase in the blast count in the bone marrow by ≥ 20% or a blast count in the peripheral blood of ≥ 20% in conjunction with an absolute blast count of ≥ 1×10^9/l that persists for ≥ 2 weeks.

The transformation of myelofibrosis into acute myeloid leukaemia is a poor prognostic factor for overall survival and is considered to be patient-relevant.

The results of the SIMPLIFY-1 study show no statistically significant difference between the treatment arms with only one event observed overall.

Transfusion independence

The endpoint of transfusion independence was operationalised in the SIMPLIFY-1 study as:

– Percentage of subjects who have not received any RBC transfusions for at least 24 weeks (transfusion independence).

- Percentage of subjects who have not received RBC transfusions for at least 24 weeks and did not have an Hb value < 8 g/dl.
- Percentage of subjects who had achieved 12-week transfusion independence at week 24 with an Hb that was not allowed to be below 8 g/dl (cases associated with clinically manifest bleeding are excluded).
- Percentage of subjects who had achieved 12-week transfusion independence at week 24 with an Hb that was not allowed to be below 8 g/dl during this period and showed transfusion dependence at baseline (cases associated with clinically manifest bleeding are excluded).
- Event time for the median time to (first) 12-week transfusion independence with an Hb that was not allowed to be below 8 g/dl.

Long-term or sustained avoidance of transfusions (transfusion independence) is generally a relevant therapeutic goal. In principle, transfusion independence of ≥ 24 weeks may represent a patient-relevant endpoint.

However, the present therapeutic indication includes both patients who are dependent on regular transfusions and those who do not require any or only occasional supportive red blood cell transfusions for anaemia-related symptoms. In the SIMPLIFY-1 study, 57% of patients in the momelotinib arm and 45.7% in the comparator arm were classified as showing chronic transfusion dependence at baseline. There are uncertainties regarding the operationalisation of transfusion dependence at baseline. In addition, the transfusion burden at baseline is low.

No criteria were pre-specified in the study documents as to when blood transfusions should be given. As a rule, the indication for a blood transfusion is not only based on laboratory values (e.g. haemoglobin), but also takes into account the overall clinical picture. Information on detailed criteria for the administration of transfusions was not presented by the pharmaceutical company. The lack of information results in uncertainty about the extent to which transfusions were administered under comparable conditions in different study sites and whether this corresponds to the German healthcare context.

The significance of an analysis of the total population is limited as only half of the patients in the SIMPLIFY-1 study showed transfusion dependence at baseline.

Due to the relevant uncertainties mentioned above, the results of SIMPLIFY-1 are considered insufficiently robust to derive an additional benefit from them. The results are presented additionally.

Transfusion dependence

The transfusion dependence rate is defined as the percentage of subjects who show transfusion dependence after 24 weeks. In doing so, the transfusion dependence rate in the SIMPLIFY- 1 study is defined as one of the following criteria:

- At least 4 units of RBC transfusions in the previous 8 weeks or
- haemoglobin level < 8 g/dl in the previous 8 weeks.
- Cases associated with clinically manifest bleeding are excluded.
- Last study visit of the treatment phase before day 162 (missing value at week 24)

The present therapeutic indication includes both patients who are dependent on regular transfusions and those who do not require any or only occasional supportive red blood cell transfusions for anaemia-related symptoms.

No criteria were pre-specified in the study documents as to when blood transfusions should be given. As a rule, the indication for a blood transfusion is not only based on laboratory values (e.g. haemoglobin), but also takes into account the overall clinical picture. Information on detailed criteria for the administration of transfusions was not presented by the pharmaceutical company. The lack of information results in uncertainty about the extent to which transfusions were administered under comparable conditions in different study sites and whether this corresponds to the German healthcare context.

A further uncertainty results from the fact that in the operationalisation presented by the pharmaceutical company, subjects were also considered to be showing transfusion dependence due to a short observation period or a low Hb value, even if they had not received any transfusions.

Against this background, the endpoint is not considered patient-relevant and not used for the benefit assessment.

Symptomatology using MPN-SAF

Symptomatology was assessed in the SIMPLIFY-1 study using the MPN-SAF at baseline and subsequently in a 4-week cycle.

There was no statistically significant difference between the treatment arms.

Brief Fatigue Inventory

The pharmaceutical company submitted analyses for the improvement and deterioration of the BFI total score and the two subdomains of fatigue score and interference score by ≥ 15% of the scale range at week 24 (≥ 1.5 points).

There were no differences between the treatment arms.

PGIC

The pharmaceutical company submitted responder analyses at week 24. In this respect, positive responders are defined as subjects with any improvement in symptoms, i.e. "very significantly improved", "significantly improved" or "slightly improved".

There was no statistically significant difference between the treatment arms.

EQ 5D-VAS

Health status was assessed in the SIMPLIFY-1 study using the visual analogue scale (VAS) of the EuroQoL-5 dimension (EQ 5D).

There was no statistically significant difference between the two treatment arms.

Quality of life

Quality of life was collected in the SIMPLIFY-1 study using the SF-36. For the benefit assessment, responder analyses with a 15% response criterion at week 24 were presented.

With regard to quality of life, there was no difference between the treatment arms.

Side effects

In the SIMPLIFY-1 study, the collection and monitoring of adverse events (AEs) began with the first study medication and continued during the blinded 24-week treatment phase until the first study medication with momelotinib in the open-label treatment phase or until 30 days after the last administration of the study treatment.

Adverse events (AEs) in total

AEs occurred in almost all study participants. The results were only presented additionally.

Serious AEs (SAE) and severe AEs (CTCAE grade ≥ 3)

For SAEs and severe AEs (CTCAE grade ≥ 3), there were no statistically significant differences between the treatment arms.

Therapy discontinuation due to AEs

For the endpoint of therapy discontinuation due to AEs, there was a statistically significant difference to the disadvantage of momelotinib compared to ruxolitinib.

Specific AEs

In detail, the results for severe AEs (CTCAE grade ≥ 3) showed a statistically significant effect in favour of momelotinib over ruxolitinib for the PT "Anaemia".

Conclusion on side effects

The overall analysis results in a disadvantage of momelotinib in the endpoint of therapy discontinuation due to AEs with regard to the endpoint category of side effects. In detail, there was a single relevant difference in the specific AEs in the PT "Anaemia" with an effect in favour of momelotinib compared to ruxolitinib.

Overall assessment

For the benefit assessment of momelotinib for the treatment of disease-related splenomegaly or symptoms in adults with moderate or severe anaemia with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythemia myelofibrosis, who are Janus Kinase (JAK) inhibitor naïve, results on mortality, morbidity, quality of life and adverse events are available from the SIMPLIFY-1 study.

For the endpoint overall survival, no statistically significant difference was detected between the treatment groups.

In the morbidity endpoint category, there were no relevant differences with regard to leukaemic transformation, with only 1 event observed overall. There were also no relevant differences in the endpoints on symptomatology (MPN-SAF, BFI), severity of symptoms (PGIC) and health status (EQ-5D VAS).

No relevant difference was found with regard to quality of life which was surveyed using the SF-36.

Based on the results on side effects, there was a disadvantage of momelotinib in the endpoint of therapy discontinuation due to AEs. In detail, there was a single relevant difference in the specific AEs in the PT "Anaemia" with an effect in favour of momelotinib compared to ruxolitinib.

In the overall assessment, a non-quantifiable additional benefit was identified for momelotinib compared to ruxolitinib for the JAK inhibitor naïve patient group since the scientific data does not allow quantification.

Significance of the evidence

The data from the randomised, double-blind SIMPLIFY-1 study are available for the benefit assessment.

The results from the SIMPLIFY-1 study are based on a sub-population defined post hoc with a haemoglobin (Hb) value < 10 g/dl (mITT). The subsequent exclusion of subjects resulted in differences in the distribution of potentially relevant prognostic factors. There were differences > 10% in the baseline characteristics of disease type, JAK2V617F mutation and transfusion independence.

The risk of bias at study level and endpoint level is rated as high overall.

In the overall assessment, the result is a hint for the identified additional benefit with regard to significance of the evidence.

b) Adults with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who have been treated with ruxolitinib; for the treatment of disease-related splenomegaly or symptoms

Hint for a minor additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company presented the results of the SIMPLIFY-2 study and the MOMENTUM study.

SIMPLIFY-2 study

The SIMPLIFY-2 study is a multicentre, randomised, open-label, phase III study which compared momelotinib with the best available therapy (BAT). The study consists of a 24-week randomised treatment phase. This was followed by an extended treatment phase in which participants from both study arms could receive momelotinib at the end of the 24-week treatment phase. The 24-week treatment phase was used for the benefit assessment. BAT was administered in the comparator arm at the discretion of the investigators and could be adjusted during the treatment phase. Frequently used active ingredients in the context of BAT were ruxolitinib (89.7%), hydroxyurea (15.4%) and prednisolone (10.3%).

The study population of the SIMPLIFY-2 study comprises adults with myelofibrosis and splenomegaly who have been pretreated with the JAK inhibitor ruxolitinib and whose previous treatment was associated with the necessity for red blood cell transfusion and/or thrombocytopenia or anaemia or bleeding. A total of 156 subjects were enrolled in the study and randomised in a 2:1 ratio according to transfusion dependence (yes/ no) and baseline TSS value (< 18 / ≥ 18) (ITT population). The ITT population comprises 104 subjects in the momelotinib arm and 52 subjects in the control arm.

In order to limit the study population to the therapeutic indication that includes patients with moderate or severe anaemia, a population was defined post hoc that represents subjects with a haemoglobin (Hb) value < 10 g/dl (mITT population) and is used for the benefit assessment.

The population relevant for the benefit assessment comprises 105 subjects (momelotinib arm N = 66; control arm N = 39).

The primary endpoint of the study was the reduction in spleen volume by ≥ 35%. The study, which was completed in April 2019, was conducted in 55 study sites in North America and Europe.

For the study, a total of three data cut-offs were performed:

- 25 June 2019 (final data cut-off)
- 28 July 2016 (end of the randomised treatment phase; interim analysis week 24)
- 12 September 2017

For the benefit assessment of momelotinib, the data cut-off from 25 June 2019 was used.

MOMENTUM study

The MOMENTUM study is a multicentre, randomised, double-blind, phase III study, which compared momelotinib to danazol. The study consists of a 24-week randomised, controlled and blinded treatment phase. This was followed by an open-label treatment phase in which participants from the intervention arm could continue to receive momelotinib at the end of the 24-week treatment phase. Participants in the danazol arm could receive either momelotinib or up to 48 weeks of danazol after completion of the 24-week treatment phase. The 24-week blinded treatment phase was used for the benefit assessment.

The study population of the MOMENTUM study comprises adults with symptomatic myelofibrosis and splenomegaly who have been pretreated with the JAK inhibitors ruxolitinib or fedratinib. The participants had anaemia (Hb < 10 g/dl) and needed transfusion or grade 3-4 AEs (thrombocytopenia, anaemia or bleeding) with previous treatment with a JAK inhibitor. A total of 195 subjects were enrolled in the study and randomised in a 2:1 ratio.

The primary endpoint of the study was the MFSAF-TSS response rate at week 24. The study, which was completed in December 2022, was conducted in 107 study sites across America, Europe, Asia and Australia.

For the study, the following data cut-offs were performed:

- 17 January 2023 (data cut-off for closing the database)
- 3 December 2021 (end of the double-blind treatment phase)

For the benefit assessment of momelotinib, the data cut-off from 3 December 2021 was used. For the endpoint of spleen response, the data cut-off from 17 January 2023 was used.

Mortality

In the SIMPLIFY-2 study, the endpoint of overall survival was operationalised as the time span (in months) from the first dose in the blinded treatment phase to death, regardless of the cause of death. Overall survival was only collected up to 30 days after the last dose of the 24-week treatment phase. In the MOMENTUM study, overall survival was defined as the time span from the first dosage or the time of randomisation of subjects who did not receive treatment until death, regardless of the cause of death. Overall survival was collected up to 7 years after the first dose of study medication.

There was no statistically significant difference between the treatment arms in either of the SIMPLIFY-2 and MOMENTUM studies.

Morbidity

Spleen response using CT/MRI

In the SIMPLIFY-2 study, spleen response was the primary endpoint. In the MOMENTUM study, this was defined as a secondary endpoint.

The spleen response rate was defined in both studies as the percentage of subjects with a spleen volume reduction by ≥ 35% measured by MRI or CT at week 24 compared to baseline. Subjects who had a missing baseline examination or a missing examination after 24 weeks (baseline vs after 24 weeks) or whose examinations were carried out with different imaging procedures were considered non-responders.

A long-lasting reduction of the pathologically elevated spleen volume combined with a noticeable decrease of impairing disease symptoms for the patients is considered to be patient-relevant. In the present case, the spleen response was collected exclusively by means of imaging procedures.

In the SIMPLIFY-2 study, there was no statistically significant difference between the treatment arms in this regard. As this is the primary endpoint, it is presented additionally.

The MOMENTUM study showed a statistically significant advantage of momelotinib compared to danazol. In conjunction with the advantage in symptom response (MFSAF), this advantage is rated as a patient-relevant effect with a clinically relevant improvement.

Leukaemic transformation

In the SIMPLIFY-2 study, leukaemic transformation is operationalised as the time from randomisation to the occurrence of leukaemic transformation, defined as an increase in the blast count in the bone marrow by ≥ 20% or a blast count in the peripheral blood of ≥ 20% in conjunction with an absolute blast count of ≥ 1×10^9/l that persists for ≥ 2 weeks.

The transformation of myelofibrosis into acute myeloid leukaemia is a poor prognostic factor for overall survival and is considered to be patient-relevant.

The results of the SIMPLIFY-2 study showed no statistically significant difference between the treatment arms with only 3 events observed overall.

Transfusion independence

The endpoint of transfusion independence was operationalised in the SIMPLIFY-2 study as:

- Percentage of subjects who have not received any RBC transfusions for at least 24 weeks (transfusion independence).
- Percentage of subjects who have not received RBC transfusions for at least 24 weeks and did not have an Hb value < 8 g/dl.
- Percentage of subjects who had achieved 12-week transfusion independence at week 24 with an Hb that was not allowed to be below 8 g/dl (cases associated with clinically manifest bleeding are excluded).
- Percentage of subjects who had achieved 12-week transfusion independence at week 24 with an Hb that was not allowed to be below 8 g/dl during this period and showed

transfusion dependence at baseline (cases associated with clinically manifest bleeding are excluded).

- Event time for the median time to (first) 12-week transfusion independence with an Hb that was not allowed to be below 8 g/dl.

In the MOMENTUM study, the endpoint of transfusion independence was operationalised as:

- Percentage of subjects who have not received any RBC transfusions for at least 24 weeks (transfusion independence).
- Percentage of subjects who had achieved 12-week transfusion independence at week 24 with an Hb that was not allowed to be below 8 g/dl (cases associated with clinically manifest bleeding are excluded).
- Percentage of subjects who had achieved 12-week transfusion independence at week 24 with an Hb that was not allowed to be below 8 g/dl during this period and showed transfusion dependence at baseline (cases associated with clinically manifest bleeding are excluded).

Long-term or sustained avoidance of transfusions (transfusion independence) is generally a relevant therapeutic goal. In principle, transfusion independence of ≥ 24 weeks may represent a patient-relevant endpoint.

However, the present therapeutic indication includes both patients who are dependent on regular transfusions and those who do not require any or only occasional supportive red blood cell transfusions for anaemia-related symptoms. In the SIMPLIFY-2 study, 78.8% of patients in the momelotinib arm and 64.1% in the comparator arm were classified as showing chronic transfusion dependence at baseline. In the MOMENTUM study, it was 48.5% of patients in the momelotinib arm and 52.3% of patients in the comparator arm. In addition, the MOMENTUM study showed a low transfusion burden at baseline.

No criteria were pre-specified in the study documents as to when blood transfusions should be given. As a rule, the indication for a blood transfusion is not only based on laboratory values (e.g. haemoglobin), but also takes into account the overall clinical picture. Information on detailed criteria for the administration of transfusions was not presented by the pharmaceutical company. The lack of information results in uncertainty about the extent to which transfusions were administered under comparable conditions in different study sites and whether this corresponds to the German healthcare context.

The significance of an analysis of the total population is limited as only half of the patients in the MOMENTUM study showed transfusion dependence at baseline. Due to the relevant uncertainties mentioned above, the results of the MOMENTUM study are considered insufficiently robust to derive an additional benefit from them. The results are presented additionally.

Transfusion dependence

The transfusion dependence rate is defined as the percentage of subjects who show transfusion dependence after 24 weeks. In doing so, the endpoint in the SIMPLIFY- 2 study is defined as one of the following criteria:

- At least 4 units of RBC transfusions in the previous 8 weeks or
- haemoglobin level < 8 g/dl in the previous 8 weeks.

- Cases associated with clinically manifest bleeding are excluded.
- Last study visit of the treatment phase before day 162 (missing value at week 24)

In the MOMENTUM study, transfusion dependence is defined as one of the following criteria:

- Requirement of ≥ 4 units of RBC or whole blood transfusions in the 8 weeks prior to first dosing or randomisation.
- Associated with a haemoglobin level ≤ 9.5 g/dl
- Cases associated with clinically manifest bleeding are excluded.

The present therapeutic indication includes both patients who are dependent on regular transfusions and those who do not require any or only occasional supportive red blood cell transfusions for anaemia-related symptoms.

No criteria were pre-specified in the study documents as to when blood transfusions should be given. As a rule, the indication for a blood transfusion is not only based on laboratory values (e.g. haemoglobin), but also takes into account the overall clinical picture. Information on detailed criteria for the administration of transfusions was not presented by the pharmaceutical company. The lack of information results in uncertainty about the extent to which transfusions were administered under comparable conditions in different study sites and whether this corresponds to the German healthcare context.

A further uncertainty results from the fact that in the operationalisation of the SIMPLIFY-2 study presented by the pharmaceutical company, subjects were also considered to be showing transfusion dependence due to a short observation period or a low Hb value, even if they had not received any transfusions.

Against this background, the endpoint is not considered patient-relevant and not used for the benefit assessment.

MFSAF

Symptomatology was collected in the MOMENTUM study using the MFSAF v.4.0 questionnaire.

In its written statement, the pharmaceutical company submitted responder analyses with a response criterion of 15% at week 24.

There was a statistically significant advantage of momelotinib compared to danazol.

Brief Fatigue Inventory

For the benefit assessment, there are analyses for the improvement and deterioration of the BFI total score and the two subdomains of fatigue score and interference score by ≥ 15% of the scale range at week 24 (≥ 1.5 points). In the MOMENTUM study, the fatigue symptom was already evaluated using MFSAF v4.0 TSS and is therefore not considered here.

Due to low return rates, which are already evident at week 4 (momelotinib 68.2% and BAT: 66.6%) and continue to deteriorate up to week 24, especially in the intervention arm (momelotinib: 40.9%; BAT: 58.9%), there are no usable data for the SIMPLIFY-2 study. In addition, there are large differences in the return rate (≥ 15%) between the treatment arms.

Patient Global Impression of Severity (PGIS)

The PGIS was collected in the MOMENTUM study. There is no information on how missing values at baseline and/or week 24 were handled.

Momelotinib showed positive effects for the items of severity of symptoms and severity of fatigue. It cannot be deduced from the Hedges' g that there is a clinically relevant effect.

Patient Global Impression of Change (PGIC)

With regard to PGIC, the pharmaceutical company presented responder analyses at week 24 from the SIMPLIFY-2 and MOMENTUM studies.

For the same question, the PGIS provides more significant results than the PGIC, which is why the analyses of the PGIS were used for the MOMENTUM study.

The SIMPLIFY-2 study showed a statistically significant advantage of momelotinib compared to BAT.

EQ 5D-VAS

Health status was assessed in the SIMPLIFY-2 study using the visual analogue scale (VAS) of the EuroQoL-5 dimension (EQ 5D).

There was no statistically significant difference between the treatment arms.

EORTC-QLQ-C30

The EORTC QLQ-C30 was surveyed in the MOMENTUM study at baseline, week 12 and week 24. Due to low return rates, only the results from week 12 were used for the benefit assessment.

There were positive effects of momelotinib for the endpoints of fatigue and pain. It cannot be deduced from the Hedges' g that there is a clinically relevant effect.

<u>Quality of life</u>

SF36

Quality of life was collected in the SIMPLIFY-2 study using the SF-36. For the benefit assessment, responder analyses with a 15% response criterion at week 24 were presented.

Due to low return rates, which are already evident at week 4 (momelotinib and BAT: 66.7% each) and continue to deteriorate up to week 24, especially in the intervention arm (momelotinib: 39.4%; BAT: 59.0%), there are no usable data for the SF-36 questionnaire. In addition, there are large differences in the return rate (≥ 15%) between the treatment arms.

EORTC-QLQ-C30

The EORTC QLQ-C30 was surveyed in the MOMENTUM study at baseline, week 12 and week 24. Due to low return rates, only the results from week 12 were used for the benefit assessment.

There were no statistically significant differences between the treatment arms.

Side effects

In the SIMPLIFY-2 study, the collection and monitoring of AEs begins with the first study medication during the 24-week treatment phase. In the momelotinib treatment group, AEs will be monitored until 30 days after the last administration of study medication or the first study medication during the extended treatment phase (whichever occurred earlier). In the BAT treatment group, observation will continue until 28 weeks after randomisation, until 30 days after the last administration of study medication or the last dose during the 24-week treatment phase or the first study medication during the extended treatment phase (whichever occurred earlier).

In the MOMENTUM study, the collection and monitoring of AEs begins with the first study medication momelotinib or danazol during the blinded 24-week treatment phase.

All AEs occurring after enrolment in the study, prior to treatment, during treatment or within 30 days after the end of treatment are collected here.

Adverse events (AEs) in total

AEs occurred in almost all study participants in the SIMPLIFY-2 and MOMENTUM studies. The results were only presented additionally.

Serious AEs (SAE) and severe AEs (CTCAE grade ≥ 3)

There were no statistically significant differences between the treatment arms for SAEs and severe AEs (CTCAE grade ≥ 3) in either the SIMPLIFY-2 study or the MOMENTUM study.

Therapy discontinuation due to AEs

In the SIMPLIFY-2 study, there was no statistically significant difference to the disadvantage of momelotinib for the endpoint of therapy discontinuation due to AEs.

In the MOMENTUM study, there were no statistically significant differences between the treatment arms.

Specific AEs

With regard to serious adverse events with an incidence ≥ 5% of patients, there was a statistically significant difference in favour of momelotinib for pneumonia (PT) in the MOMENTUM study.

With regard to severe adverse events with CTCAE grade ≥ 3 with an incidence ≥ 5% of patients, there was a statistically significant difference in favour of momelotinib for renal and urinary disorders (SOC) and pneumonia (PT) in the MOMENTUM study.

Conclusion on side effects

The overall analysis results in a disadvantage of momelotinib compared to BAT in the endpoint of therapy discontinuation due to AEs with regard to the endpoint category of side effects in the SIMPLIFY-2 study. In detail, there are advantages for some specific AEs.

Overall assessment

The benefit assessment of momelotinib for the treatment of disease-related splenomegaly or symptoms in adults with moderate or severe anaemia with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythemia myelofibrosis treated

with ruxolitinib is based on the randomised phase III SIMPLIFY-2 and MOMENTUM studies. In the SIMPLIFY-2 study, momelotinib was compared with best available therapy (BAT) and in the MOMENTUM study, momelotinib was compared with danazol.

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms in both studies.

There was no statistically significant difference with regard to the endpoint of spleen response in the SIMPLIFY-2 study. The MOMENTUM study showed a statistically significant advantage of momelotinib, which, in combination with the advantage of momelotinib in symptom response (MFSAF), is considered a patient-relevant effect with a clinically relevant improvement. With regard to leukaemic transformation, which was surveyed in the SIMPLIFY-2 study, there was no statistically significant difference with only 3 observed events overall.

The other endpoints on symptomatology (EORTC-QLQ-C30, BFI) show no relevant difference. With regard to the endpoints on severity of symptoms (PGIC), the SIMPLIFY-2 study showed an advantage of momelotinib compared to BAT. There were no relevant differences for the endpoint of health status (EQ-5D VAS).

No relevant difference was found with regard to quality of life, which was collected using the SF-36 and the EORTC-QLQ-C30 questionnaires.

Based on the results on side effects, there was a disadvantage of momelotinib in the endpoint of therapy discontinuation due to AEs in the SIMPLIFY-2 study. In detail, there was an advantage of momelotinib in the specific AEs compared to danazol in some specific AEs.

In the overall assessment, a minor additional benefit was identified due to the positive effects of momelotinib on the spleen response in conjunction with an improvement of symptomatology and an improvement in the severity of symptoms for the group of patients treated with ruxolitinib.

Significance of the evidence

The data from the randomised SIMPLIFY-2 and MOMENTUM studies are available for the benefit assessment.

These results from the SIMPLIFY-2 study are based on a post hoc sub-population with a haemoglobin (Hb) value < 10 g/dl (mITT). The subsequent exclusion of subjects resulted in differences in the distribution of potentially relevant prognostic factors. There were differences > 10% between the study arms in the percentage of excluded subjects. There were also differences > 10% in the baseline characteristics of sex, region, cytogenetic assessment, transfusion dependence, transfusions, dose adjustments and anaemia of CTCAE grade ≥ 3 during ruxolitinib pretreatment. SIMPLIFY-2 is an open-label study; due to the lack of blinding, the risk of bias, particularly for subjectively assessed endpoints, is considered to be high.

Overall, the results of the MOMENTUM study have a high risk of bias due to imbalances in the baseline characteristics of disease type and DIPSS.

The comparator danazol used in the MOMENTUM study has no known effect on spleen volume due to its mode of action, in contrast to the active ingredient ruxolitinib used as part of the BAT in the SIMPLIFY-2 study.

The risk of bias at study level and endpoint level is rated as high for both studies overall.

In the overall assessment, the result is a hint for the identified additional benefit with regard to significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Omjjara with the active ingredient momelotinib.

Momelotinib was approved as an orphan drug for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

The benefit assessment is based on the SIMPLIFY-1, SIMPLIFY-2 and MOMENTUM studies and differentiates between two patient groups who are Janus Kinase (JAK) inhibitor naïve or who have already received JAK inhibitors:

a) Adults with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve; for the treatment of disease-related splenomegaly or symptoms

b) Adults with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who have been treated with ruxolitinib; for the treatment of disease-related splenomegaly or symptoms

On patient group a)

The benefit assessment of momelotinib is based on the multicentre, randomised, double-blind, phase III SIMPLIFY-1 study, which compared momelotinib with ruxolitinib.

For the endpoint overall survival, no statistically significant difference was detected between the treatment groups.

With regard to the morbidity endpoint category, there were neither positive nor negative effects of momelotinib.

No relevant difference for the benefit assessment was derived with regard to the endpoint category of quality of life.

Based on the results on side effects, there was a disadvantage of momelotinib in the endpoint of therapy discontinuation due to AEs. In detail, there was a statistically significant effect in favour of momelotinib in some specific AEs.

In the overall assessment, a non-quantifiable additional benefit is identified for momelotinib since the scientific data basis does not allow quantification.

Relevant uncertainties arise from the segregation of the mITT population relevant for the benefit assessment. There were differences > 10% in the baseline characteristics of disease type, JAK2V617F mutation and transfusion independence. The risk of bias at study level and endpoint level is rated as high for the study overall.

Overall, the reliability of data of the additional benefit identified is classified as a "hint".

About patient group b)

The benefit assessment of momelotinib is based on the randomised, phase III SIMPLIFY-2 and MOMENTUM studies. In the SIMPLIFY-2 study, momelotinib was compared with best available therapy (BAT). Frequently used active ingredients in the context of BAT were ruxolitinib (89.7%), hydroxyurea (15.4%) and prednisolone (10.3%). In the MOMENTUM study, momelotinib was compared with danazol.

For the endpoint overall survival, no statistically significant difference was detected between the treatment groups.

With regard to the endpoint category of morbidity, the endpoint of spleen response resulted in a statistically significant advantage of momelotinib, which, in combination with the advantage of momelotinib in symptom response (MFSAF), is considered a patient-relevant effect with a clinically relevant improvement. In addition, there was an improvement in the severity of symptoms (PGIC).

No relevant difference for the benefit assessment was derived with regard to the endpoint category of quality of life.

Based on the results on side effects, there was a disadvantage of momelotinib in the endpoint of therapy discontinuation due to AEs. In detail, there was an advantage of momelotinib in the specific AEs compared to danazol in some specific AEs.

In the overall assessment, a minor additional benefit of momelotinib is identified.

Due to relevant uncertainties arising, among other things, from the segregation of the mITT population relevant for the benefit assessment and imbalances in the baseline characteristics, the significance of the evidence is classified in the "hint" category.

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).

In the dossier submitted by the pharmaceutical company, there were uncertainties regarding the patient numbers due to the lack of consideration of potential diagnostic codes and a lack of consideration of some of the symptomatic patients. In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of fedratinib (resolution of 2 September 2021). Based on the percentage values for anaemia from the dossier of the pharmaceutical company, which are subject to uncertainties (the percentage values could possibly be higher), omitting the limitation to the platelet count ≥ 50 x 10^9/l carried out in the procedure for fedratinib, the following patient numbers result: For patient group a) patients who are Janus Kinase (JAK) inhibitor naïve, approx. 460 to 1,470 patients and for patient group b) patients who were treated with ruxolitinib approx. 210 to 1,160 patients.

The resolution on fedratinib (resolution of 2 September 2021) includes a more valid derivation of the patient numbers in the SHI target population, which can be used despite existing uncertainties.

Based on the derivation of the patient numbers from the procedure for fedratinib (resolution of 2 September 2021) with the changes described above, the following patient numbers result:

Baseline (procedure D-650 fedratinib): Prevalence of myelofibrosis in Germany in 2021 (6,629)

1. Patients with disease-related splenomegaly or symptoms 53.0% to 73.8% (3,513 to 4,895)
2. Application of the SHI share 87.8%; sub-population of insured persons with disease (3,084 to 4,298)

3a. Patients with myelofibrosis and treatment with ruxolitinib (1,694)

3b. Patients with myelofibrosis and discontinuation of treatment with ruxolitinib 37.4% (633)

3. Patient group b): Patients who were fully or partially treated with ruxolitinib (633 to 1,694)
4. Patient group a): therapy-naïve patients (sub-population of insured persons with disease minus patient group b) (1,390 to 3,665)

   Consideration of patients with anaemia (percentage values from information provided by the pharmaceutical company for momelotinib):

5a. Patient group a); 33 to 40% with moderate to severe anaemia (459 to 1,466)

5b. Patient group b); 33 to 68.18% with moderate to severe anaemia (209 to 1,155)

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 Omjjara (active ingredient: momelotinib) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 23 July 2024):

https://www.ema.europa.eu/en/documents/product-information/omjjara-epar-product-information_en.pdf

Treatment with momelotinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with myelofibrosis.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2024).

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 varies from patient to patient 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 dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

a) Adults with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve; for the treatment of disease-related splenomegaly or symptoms

and

b) Adults with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who have been treated with ruxolitinib; for the treatment of disease-related splenomegaly or symptoms

Treatment period:

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

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Momelotinib	200 mg	200 mg	1 x 200 mg	365	365 x 200 mg

Costs:

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					
Momelotinib	30 FCT	€ 5,936.41	€ 2.00	€ 335.74	€ 5,598.67
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 15 July 2024

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 taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section

35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for

example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and

pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve; for the treatment of disease-related splenomegaly or symptoms

   No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

   References:
   Product information for momelotinib (Omjjara); Omjjara film-coated tablets; last revised: January 2024

b) Adults with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who have been treated with ruxolitinib; for the treatment of disease-related splenomegaly or symptoms

   No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

   References:
   Product information for momelotinib (Omjjara); Omjjara film-coated tablets; last revised: January 2024

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 15 February 2024, the pharmaceutical company submitted a dossier for the benefit assessment of momelotinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1 VerfO.

The benefit assessment of the G-BA was published on 15 May 2024 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 statements was 5 June 2024.

The oral hearing was held on 24 June 2024.

An amendment to the benefit assessment with a supplementary assessment was submitted on 27 June 2024.

A new version of the G-BA's dossier assessment was prepared on 10 July 2024. This version 1.1 of 10 July 2024 replaces version 1.0 of the dossier assessment of 15 May 2024 and was brought to the attention of the Subcommittee on Medicinal Products at its session on 9 July 2024. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 was discussed at the session of the subcommittee on 6 June 2024, and the proposed resolution was approved.

At its session on 15 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 June 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	19 June 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	24 June 2024	Conduct of the oral hearing
Working group Section 35a	2 July 2024 30 July 2024	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 products	6 August 2024	Concluding discussion of the draft resolution
Plenum	15 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 August 2024

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

Prof. Hecken