Fedratinib (myelofibrosis)

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Requirement of routine data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGBV for the active ingredient fedratinib in the treatment of:

Disease-related splenomegaly or symptoms in adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are not pretreated with a Janus Associated Kinase (JAK) inhibitor and for whom ruxolitinib is the patient-individual appropriate comparator therapy

1. Requirements for routine practice data collection and evaluations

With reference to the justification for the requirement of routine practice data collection for the active ingredient fedratinib for the purpose of the benefit assessment, which forms the basis of the procedure-initiating resolution on the requirement of routine practice data collection of 21 October 2021, the following requirements arise:

1.1 Question according to PICO scheme

Population	Adults with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are pretreated with a Janus Associated Kinase (JAK) inhibitor and for whom ruxolitinib is the patient-individual appropriate comparator therapy
Intervention	▪ Fedratinib The marketing authorisation and the dosage information in the product information of fedratinib (Inrebic®) must be taken into account.
Comparator	▪ Ruxolitinib The marketing authorisation and the dosage information in the product information of ruxolitinib must be taken into account.

Outcome	Mortality ▪ Overall survival Morbidity ▪ Symptomatology, e.g., MFSAF Health-related quality of life Side effects ▪ Serious adverse events (SAE; overall rate) ▪ Severe adverse events (overall rate) ▪ Discontinuation due to adverse events (overall rate) ▪ Specific adverse events (with information on the respective severity)

1.2 Type and methods of data collection

Taking into account the question of the routine practice data collection and the methodological limitations of non-randomised comparisons, the following requirements are placed on the study design and the data source for the present routine practice data collection.

1.2.1 Requirements for the study design

- Non-randomised, prospective comparison of fedratinib with ruxolitinib preferably as a comparative registry study or with lower priority, if a comparative registry study is not feasible, as a comparative study using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection).
- If applicable, endpoint-specific integration of retrospective data, provided that the data also meet the specified data quality requirements in Section 1.2.2.

1.2.2 Data source requirement

- Preferable use of registries or with lower priority, if use of registries is not feasible, a data platform to be set up specifically for the present routine practice data collection as a data source, which meet the requirements of routine practice data collection and fulfil at least the following quality criteria[1]:
  - Detailed registry description or description of the data platform (protocol)
  - Exact definition or operationalisation of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints and confounders

[1] IQWiG Rapid Report A21-142: Concept for routine practice data collection – fedratinib.

- Use of standard classifications and terminologies
- Use of validated standard data collection tools (questionnaires, scales, tests)
- Training courses on data collection and recording
- Implementation of a consensus disease-specific core data set
- Use of exact dates for the patient, the disease, important examinations and treatments/ interventions
- Clearly defined inclusion and exclusion criteria for patients
- Strategies to avoid selection bias in patient inclusion to achieve representativeness
- Specifications to ensure completeness of data per data collection time point and completeness of data collection time points
- Source data verification for 100% of patients per data collection site for the primary endpoint and for at least 10% of randomly selected patients per data collection site for all other endpoints over the period since the start of data collection
- When using a registry: Ensuring scientific independence and transparency

- Preferably use of registries or, if the use of registries is not feasible, a data platform to be set up specifically for the present routine practice data collection as a data source, in which treatment of myelofibrosis is carried out in accordance with German daily care or is sufficiently similar to care in Germany.

1.2.3 Primary data source and integration of further data sources

For the study design in the form of a comparator registry study, the following specifications must be taken into account:

- Use of the GSG-MPN registry as primary registry, provided that the quality criteria mentioned in section 1.2.2 are fulfilled

An integration of further data sources (especially registries) is also possible, taking into account all the data source requirements mentioned in section 1.2.2.

1.3 Duration and scope of data collection

Taking into account initial indications that suggest that a relevant percentage of patients on ruxolitinib experience a loss of efficacy after approximately 3 years, the following duration of observation should be implemented during routine practice data collection:

- 24 months from end of recruitment

As an approximation of the appropriate sample size for routine practice data collection, two possible scenarios are assumed as a result of an orienting sample size estimate based on the

endpoints of severe AEs with CTCAE grade ≥ 3 in the system organ class (SOC) of infections and infestations and serious AEs in the SOC of infections and infestations:

- Endpoint of "serious AEs in the SOC of infections and infestations"; assumption of equal distribution between intervention and comparator group and an effect magnitude of RR = 0.29:
  - 2,400 patients
- Endpoint "severe AEs with CTCAE grade ≥ 3 in the SOC of infections and infestations"; assumption of a distribution of 4:1 between intervention and comparator group and an effect magnitude of RR= 0.12:
  - 1,200 patients

On the basis of this orienting sample size estimate on the basis of estimated or theoretically established effect assumptions, exemplary case numbers result in an order of magnitude at which it can be assumed that routine practice data collection for the present research question is feasible in principle. The final sample size planning is part of the study documents to be prepared (statistical analysis plan, study protocol; see section 1.5).

1.4 Evaluations of the data for the purpose of the benefit assessment

The pharmaceutical company shall submit the following evaluations to the G-BA:

- Interim analyses

  Evaluations of 3 interim analyses shall be presented. The relevant times for the performance of the interim analyses shall be the times specified in section 2.3.

  The interim analyses shall be performed according to the specifications in the study protocol and statistical analysis plan. In the process, a check for discontinuation due to futility must also be carried out for each interim analysis.

  On the 1st interim analysis:

  Based on this interim analysis, a final sample size estimate will be made using the more precise effect assumptions rendered possible. If necessary, this can also be carried out at this time on the basis of benefit endpoints other than those mentioned in the present resolution and taking into account a shifted hypothesis boundary in accordance with the procedure in IQWiG's concept[1].

The interim analyses shall be prepared on the basis of module 4 of the dossier template, providing the full texts and study documents.

- Final evaluations for the purpose of the renewed benefit assessment

  The final evaluations shall be carried out according to the specifications in the study protocol and statistical analysis plan. For the transmission of the final evaluations to the G-BA, the time specified in section 3 applies.

The final evaluations shall be prepared in a dossier in accordance with the provisions of Section 9 paragraphs 1 to 7 of the Rules of Procedure of the G-BA.

1.5 Requirements for the preparation of the study protocol and statistical analysis plan

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out routine practice data collection and evaluations. In this context, they shall in particular provide the following information in advance with regard to the evaluation of the data:

- Information on the statistical methods and models used, as well as naming the procedures and the criteria used in model selection and adaptation
- Information on the expected scope and reasons for missing data, as well as measures to avoid missing data and evaluation strategies on the scope with missing data
- Information on dealing with implausible data and outliers
- Information on planned sensitivity analyses
- Information on the identification, as well as the adequate, pre-specified adjustment for confounders
- Information on the investigation of potential effect modifiers
- Information on interim analyses taking into account the requirements under section 1.4 and the specifications under section 2.3
- Information on discontinuation criteria due to futility

2. Specifications for reviewing whether the pharmaceutical company has fulfilled its obligation to carry out routine practice data collection and evaluations

2.1 Submission of a study protocol as well as the statistical analysis plan for coordination with the G-BA

The final drafts for a study protocol and for a statistical analysis plan prepared by the pharmaceutical company are to be submitted to the G-BA for approval by 3 April 2023 at the latest.

The G-BA, with the involvement of IQWiG, carries out a review of the study protocol and the statistical analysis plan and usually communicates the result to the pharmaceutical company in writing within 12 weeks.

Before submitting the requested documents to the G-BA, the pharmaceutical company has the option to request a consultation with the G-BA according to Section 35a, paragraph 7 SGB V in conjunction with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). The subject of such consultation is, in particular, the drafts for a study protocol as well as for a statistical analysis plan. In order to enable the pharmaceutical company to

adequately consider the aspects addressed in the consultation when preparing the study protocol and statistical analysis plan, the request for consultation must be submitted to the G-BA by 1 December 2022 at the latest.

If the G-BA determines during the first submission of the study protocol and statistical analysis plan that the requirements of routine practice data collection and evaluations are insufficiently implemented, the pharmaceutical company is given the opportunity to revise the study documents once. The G-BA shall adopt a declaratory resolution in this regard in the procedure for routine practice data collection and evaluations, which shall set out the necessary need for adaptation of the study documents. The deadline for submission of the revised statistical analysis plan and study protocol is 4 weeks, unless otherwise specified in the declaratory resolution.

The G-BA may come to the conclusion that the routine practice data collection can be carried out on the basis of the submitted study protocol and statistical analysis plan under the condition that further adaptations to the study documents deemed mandatory for the implementation of the requirements from this resolution must be made. In this case, the final versions of the statistical analysis plan and the study protocol are to be submitted to the G-BA for review as a rule 4 weeks after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution.

2.2 Submission of information on the course of data collection (in particular information on the status of recruitment)

6 months, 18 months, 36 months and 54 months after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution, the pharmaceutical company shall provide the G-BA in particular with the information on

- the number and the respective medicinal treatment of the patients included so far,
- patient-related observation periods, and
- any deviations regarding the expected number of recruits

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2.3 Submission of interim analyses

At the following time points after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution, interim analyses shall be carried out and corresponding evaluations shall be submitted to the G-BA, taking into account the requirements specified in section 1.4:

- 18 months after the start of routine practice data collection
- 36 months after the start of routine practice data collection

- 54 months after the start of routine practice data collection

3. Deadline for the submission of evaluations of the data collected as part of the routine practice data collection

For the performance of a new benefit assessment, the evaluations of data collected as part of the routine practice data collection must be submitted by 5 October 2028 at the latest.

The submission of these evaluations must be made in the form of a dossier in accordance with the provisions of Chapter 5, Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA, taking into account the requirements of this resolution in accordance with Chapter 5, Section 58 of the Rules of Procedure of the G-BA.