IQWiG Reports – Commission No. A18-33

Bosutinib (chronic myeloid leukaemia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of the executive summary of the dossier assessment *Bosutinib (chronische myeloische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 August 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Bosutinib (chronic myeloid leukaemia) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

18 May 2018

Internal Commission No.:

A18-33

Address of publisher:

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Richard F. Schlenk, NCT Trial Center, National Center for Tumor Diseases, Heidelberg, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment:

- Helmut Hörn
- Christiane Balg
- Anne Catharina Brockhaus
- Gertrud Egger
- Simone Johner
- Marco Knelangen
- Christopher Kunigkeit
- Beate Wieseler

Keywords: bosutinib, leukaemia – myelogenous – chronic – BCR-ABL positive, benefit assessment, NCT02130557

Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug bosutinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 18 May 2018.

Research question

The aim of this report is to assess the added benefit of bosutinib in comparison with imatinib, nilotinib or dasatinib as the appropriate comparator therapy (ACT) in adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in the chronic phase.

Table 2 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2[2]: Research question of the benefit assessment of bosutinib

Research question	Indication	ACT[a]
1	Treatment of adults with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in the chronic phase (CP)	**Imatinib** or nilotinib or dasatinib

a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**.
ACT: appropriate comparator therapy; CP: chronic phase; G-BA: Federal Joint Committee; Ph+ CML: Philadelphia chromosome-positive chronic myeloid leukaemia

The company followed the G-BA's specification and selected imatinib from the presented options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool and study characteristics

The BFORE study was included in the benefit assessment. The BFORE study is an open-label, randomized controlled trial (RCT) comparing bosutinib versus imatinib in adults with newly diagnosed chronic myeloid leukaemia (CNL) in the chronic phase.

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

The study randomized 536 patients (268 in each treatment arm). Of those patients, 487 (246 in the bosutinib arm and 241 in the imatinib arm) exhibited a mutation of the Philadelphia chromosome. These patients represent the relevant subpopulation for this benefit assessment.

In both study arms, the treatment administered was in accordance with approval. Treatment was to be discontinued in case of treatment failure, unacceptable toxicity, revocation of the declaration of consent or upon the investigator's discretion. The primary outcome of the BFORE study was major molecular response (MMR) at month 12. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life and adverse events (AEs).

Risk of bias

For the BFORE study, the risk of bias on the study level was rated as low. On the outcome level, the risk of bias was rated as low for overall survival and as high for the remaining outcomes.

Results

Mortality

For the outcome overall survival, no statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

Morbidity – transition to blast crisis

For the outcome transition to blast crisis, no relevant data were available. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

Morbidity – EQ-5Q VAS health state

For the outcome EQ-5D VAS health state, no statistically significant difference between treatment arms was found on the basis of the mean value difference. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

Health-related quality of life – Functional Assessment of Cancer Therapy – Leukaemia (FACT-Leu)

For the outcome health-related quality of life as measured by FACT-Leu, mean value comparisons of the FACT-Leu total score showed no statistically significant difference between treatment arms. This does not result in a hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

Adverse events – SAEs

For the outcome SAEs, no statistically significant difference between treatment arms was found. Consequently, there is no hint of greater or lesser harm of bosutinib in comparison with imatinib; greater or lesser harm is therefore not proven.

Adverse events – severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥ 3)

For the outcome severe AEs (CTCAE Grade ≥ 3), a statistically significant difference to the disadvantage of bosutinib in comparison with imatinib was found. For this outcome, there was also an effect modification for the attribute age. For both patients < 65 years of age and those ≥ 65 years of age, a statistically significant difference to the disadvantage of bosutinib was found. This results in a hint of greater harm of bosutinib in comparison with imatinib for both age groups, with the extent differing between them.

Adverse events – discontinuation due to AE

For the outcome discontinuation due to AE, a statistically significant difference to the disadvantage of bosutinib in comparison with imatinib was found. However, the extent of this effect on this non-serious/non-severe outcome is at most marginal. Consequently, there is no hint of greater or lesser harm of bosutinib in comparison with imatinib.

Adverse events – specific AEs: Gastrointestinal disorders, diarrhoea (CTCAE Grade ≥ 3), liver impairment (CTCAE Grade ≥ 3), elevated lipase (CTCAE Grade ≥ 3), skin rash, thrombocytopenia (CTCAE Grade ≥ 3), heart disease (CTCAE Grade ≥ 3)

For each of the outcomes gastrointestinal disorders, diarrhoea (CTCAE Grade ≥ 3), liver impairment (CTCAE Grade ≥ 3), elevated lipase (CTCAE Grade ≥ 3), skin rash (CTCAE Grade ≥ 3), thrombocytopenia (CTCAE Grade ≥ 3) and heart disease (CTCAE Grade ≥ 3), a statistically significant difference to the disadvantage of bosutinib in comparison with imatinib was found. This results in a hint of greater harm of bosutinib in comparison with imatinib in each case.

Adverse events – specific AEs: Oedema, musculoskeletal and connective tissue disorders

For the outcome oedema and the outcome musculoskeletal and connective tissue disorders, a statistically significant difference to the disadvantage of bosutinib in comparison with imatinib was found. This results in a hint of lesser harm of bosutinib in comparison with imatinib in each case.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug bosutinib compared with the ACT is assessed as follows:

Overall, the comparison of bosutinib with imatinib showed positive and negative effects exclusively for the outcome category adverse events. Concerning severe/serious adverse events, bosutinib in comparison with imatinib is exclusively associated with greater harm, whose extent is in some cases major. Concerning non-serious/non-severe adverse events, both lesser harm and greater harm were found in the analysis of 2 different specific AEs.

In summary, for patients with newly diagnosed Ph^+ CML in the chronic phase, there is a hint of lesser benefit of bosutinib in comparison with imatinib.

Table 3 presents a summary of the probability and extent of the added benefit of bosutinib.

Table 3: Bosutinib – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of adults with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia (Ph^+ CML) in the chronic phase (CP)	**Imatinib** or nilotinib or dasatinib	Hint of lesser benefit[b]
a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in **bold**. b: Only patients with an ECOG-PS of 0 or 1 were included in the study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2. ACT: appropriate comparator therapy; CP: chronic phase; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; Ph+ CML: Philadelphia chromosome-positive chronic myeloid leukaemia		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 04 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-33-bosutinib-chronic-myeloid-leukaemia-benefit-assessment-according-to-35a-social-code-book-v.9777.html.