IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. A12-09

Vandetanib –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Vandetanib – Nutzenbewertung gemäß § 35a SGB V" (Version 1.9; Status: 13.06.2012). In the present extract, references to Sections 2.7 onwards relate to the full version of the assessment report (hereinafter called the "full dossier assessment"). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, she was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect her opinion.

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List of tables[3]

[3] Table numbers in this extract start with "2", as numbers follow the numbering in the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MTC	medullary thyroid carcinoma
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) 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 vandetanib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 15.03.2012.

Research question

The aim of this report is to assess the added benefit of vandetanib compared to best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with aggressive and symptomatic medullary thyroid carcinoma (MTC) with unresectable, locally advanced or metastatic disease.

The comparator therapy chosen by the company corresponded to the ACT previously specified by the G-BA.

In the current therapeutic situation, there is a need for all patients to be treated with BSC. Studies that compared vandetanib in combination with BSC with treatment consisting of BSC alone were therefore included in the benefit assessment. If available, studies in which vandetanib as monotherapy was compared with BSC could also be included. The assessment was carried out with respect to patient-relevant outcomes.

Results

One relevant study (D4200C00058, Study 58) was identified for the assessment. In this study, patients in the vandetanib treatment arm as well as those in the placebo treatment arm received a concomitant treatment rated as BSC. The study thus compared administration of vandetanib in combination with BSC with placebo in combination with BSC.

Study 58 was a multicentre, double-blind, randomized (placebo-)controlled trial (RCT). The benefit assessment found a serious deficiency in the company's dossier with regard to the group of patients included in the study: no data on the approval population of vandetanib were submitted, as is explained in more detail below:

According to the Summary of Product Characteristics (SPC), vandetanib is indicated for the treatment of **aggressive and symptomatic** MTC in patients with unresectable, locally advanced or metastatic disease [1]. In Study 58, patients were enrolled in whom the MTC was unresectable and in a locally advanced or metastatic stage, but the course of the disease did not necessarily have to be **aggressive and symptomatic**. Hence, the study population was wider than the group of patients specified in the approval (approval population). Comments of the European Medicines Agency (EMA) from the approval process prove that the approval

population is clearly definable and distinguishable within Study 58 (approximately half of the enrolled patients). In the Institute's view, the study submitted therefore included a relevant proportion of patients who cannot be allocated to the approval population. This opinion deviates substantially from that of the company, which described the study population as almost identical to the approval population, although in its decision to approve the drug, the EMA resorted to subgroup data of the study for the approval population. This was the company's justification in its dossier (Modules 1–4) for not submitting any separate data on the approval population and for using the entire study population for its assessment. In the Institute's view, a separate analysis of the approval population within the study would have been appropriate and also easy to undertake.

In summary, the contents of the company's dossier are incomplete. This is largely because no data on patient-relevant outcomes within the approval population are presented that would have enabled an assessment of the added benefit of vandetanib. The Institute considers that the data presented by the company do not adequately represent the relevant population and do not allow any valid conclusions to be drawn on the added benefit of vandetanib in the treatment of aggressive and symptomatic MTC.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Due to the incompleteness of the dossier contents, there is no proof of an added benefit of vandetanib compared to the ACT. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

According to the SPC, vandetanib is approved for the following therapeutic indication [1]:

- Treatment of aggressive and symptomatic MTC in patients with unresectable, locally advanced or metastatic disease

The company designated BSC as the ACT and thereby followed the specification of the G-BA, which named BSC as ACT. BSC is defined as a treatment that ensures the best possible supportive therapy, optimized for the individual patient, for the alleviation of symptoms and improvement in the quality of life (e.g. bisphosphonates for painful bone metastases, external radiotherapy).

[4]On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit of an intervention. 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 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 data not interpretable), see [2]. The extent of added benefit is graded into 6 categories: (1) major, (2) considerable, (3) minor, (4) non-quantifiable, (5) no added benefit, or (6) less benefit, see [3].

The aim of this report is thus to assess the added benefit of vandetanib compared to BSC in patients with aggressive and symptomatic MTC with unresectable, locally advanced or metastatic disease.

In the current therapeutic situation, there is a need for all patients to be treated with BSC. Studies were therefore included in the benefit assessment that compared vandetanib in combination with BSC with treatment consisting of BSC alone. If available, studies in which vandetanib as monotherapy was compared with BSC could also be included. One RCT with a placebo control (Study 58) could be included in the assessment. In this study, patients in the vandetanib treatment arm as well as those in the placebo treatment arm received concomitant treatment rated as BSC. The study thus compared administration of vandetanib in combination with BSC with placebo in combination with BSC.

The assessment was carried out with respect to patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

- Studies on vandetanib completed by the company up to 05.01.2012 (study list of the company).
- Results of a search for studies on vandetanib in trial registries (last search 05.01.2012, searches by the company).
- The Institute's own searches for studies on vandetanib in trial registries to check the search results of the company up to 29.03.2012. The check produced no deviations from the study pool presented in the company's dossier.

The resulting study pool corresponded to that used by the company.

Further information about the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.2 of the full dossier assessment.

2.3.1 Included studies

The study included in the benefit assessment is listed in the following table.

Table 2: Study pool – RCT on the drug to be assessed, direct comparison vandetanib versus BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
D4200C00058	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved.			

One RCT (Study 58) on the drug to be assessed was submitted for the assessment of vandetanib.

In this placebo-controlled study, patients in both treatment arms received concomitant treatment rated as BSC. The study compared administration of vandetanib in addition to BSC with placebo in addition to BSC. The study was therefore considered, in principle, as relevant for the present research question.

However, in the specific comparison with the requirements of the G-BA concerning the ACT, the restricted possibility of the use of radiotherapy in the study should be highlighted. In the Institute's view, although this restriction does not raise doubts about the basic suitability of the study, it should nonetheless be considered as a possible limitation when interpreting the results. However, in view of the demonstrated incompleteness of the dossier contents (explained in Section 2.3.2 below and in the Comment in Section 2.7.2.3 of the full dossier assessment), this is ultimately of no further consequence.

Section 2.6 contains a list of data sources cited by the company for the study included by the Institute.

Further information about the result of information retrieval and the resulting study pool can be found in Module 4, Section 4.3.1.1 of the dossier and in Section 2.7.2.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 describes the study used for the benefit assessment.

Table 3: Characteristics of the included study – vandetanib versus BSC

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study
D4200C00058	RCT, double-blind, placebo-controlled	Adult patients with measurable, unresectable, locally advanced or metastatic medullary thyroid carcinoma	Vandetanib (N = 231) Placebo (N = 100)	Treatment was given until objective progression of the disease, then option for open-label treatment with vandetanib (cross-over), subsequent follow-up for overall survival Analysis cut-off: 7/2009	Worldwide in 24 countries (Australia, South America, USA, Canada, Europe, Asia) in 63 study centres, 11/2006 – ongoing, probably up to 12/2016
N: number of patients, RCT: randomized controlled trial					

Study 58 was a multicentre, double-blind RCT with a placebo control.

Patients diagnosed with an unresectable and locally advanced or metastatic stage of hereditary or sporadic form of MTC were enrolled. The study population was wider than the patient population for which approval was declared. Since the entire study with this group of patients was included in the benefit assessment, the company's dossier had a serious deficiency: no data were submitted on the approval population of vandetanib, as is explained in more detail below:

According to the SPC, vandetanib is indicated for the treatment of **aggressive and symptomatic** MTC in patients with unresectable, locally advanced or metastatic disease [1]. The company submitted data from Study 58 to derive the added benefit of vandetanib. In this study, patients as described above were enrolled in whom the MTC was unresectable and in a locally advanced or metastatic stage, but the course of the disease did not necessarily have to be **aggressive and symptomatic**. Hence, the entire study population was wider than the group of patients specified in the approval (approval population). Comments of the EMA from the approval process prove that the approval population is clearly definable and distinguishable within the study (approximately half of the enrolled patients). In the Institute's view, the study submitted therefore includes a relevant proportion of patients who cannot be allocated to the approval population. This opinion deviates substantially from that of the company, which described the study population as almost identical to the approval population, although in its decision to approve the drug, the EMA resorted to subgroup data of the study for the approval population. This was the company's justification in its dossier (Modules 1–4) for not submitting any separate data on the approval population and for using the entire study population for its assessment. In the Institute's view, a separate analysis of the approval population within the study would have been appropriate and also easy to undertake.

In summary, the contents of the company's dossier are incomplete. This is largely because no data on patient-relevant outcomes within the approval population are presented that would have enabled an assessment of the added benefit of vandetanib. The Institute considers that the data presented by the company do not adequately represent the relevant population and do not allow any valid conclusions to be drawn on the added benefit of vandetanib in the treatment of aggressive and symptomatic MTC (for detailed reasoning see Section 2.7.2.3 of the full dossier assessment).

Further information about study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2 as well as in Appendix 4-G of the dossier and in Sections 2.7.2.3 and 2.7.2.4 of the full dossier assessment.

2.4 Results concerning added benefit

The result of the assessment by the Institute deviates from that of the company, which derived an added benefit for vandetanib.

Further information about the choice of outcome and risk of bias at outcome level and about the outcome results can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

Due to the incompleteness of the dossier contents, there is no proof of an added benefit of vandetanib compared to the ACT. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's assessment, which derived an overall major added benefit.

The decision regarding added benefit is made by the G-BA.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.4 of the full dossier assessment.

2.6 List of included studies

Study 58

AstraZeneca. An international, phase III, randomized, double-blinded, placebo-controlled, multi-center study to assess the efficacy of ZD6474 versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer: study D4200C00058; clinical study report [unpublished]. 2010.

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References for English extract

Please see full dossier assessment for full reference list.

1. European Medicines Agency. Caprelsa: European public assessment report; product information [online]. 17.02.2012 [accessed: 10.09.2012]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002315/WC500123555.pdf.

2. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23.09.2011 [accessed 05.05.2012]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

3. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to § 35a Social Code Book V; extract; commission no. A11-02 [online]. 29.09.2011 [accessed 05.05.2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

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