IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-01

Vandetanib (thyroid cancer) –

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 (Schilddrüsenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 1 June 2017). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Vandetanib (thyroid cancer) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
13 January 2017

Internal Commission No.:
A17-01

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:

- Matthias Breidert, Kösching Hospital, Kösching, 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[2]:

- Lisa Junge
- Catharina Brockhaus
- Thomas Kaiser
- Michaela Florina Kerekes
- Christopher Kunigkeit
- Regine Potthast
- Dorothea Sow
- Carolin Weigel

Keywords: vandetanib, thyroid neoplasms, child, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
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
RET	rearranged during transfection
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

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 13 January 2017.

Research question

The aim of the present report was to assess the added benefit of vandetanib compared with best supportive care (BSC) as appropriate comparator therapy (ACT) in adolescents and children aged 5 years and older with aggressive and symptomatic medullary thyroid carcinoma (MTC) with unresectable, locally advanced or metastatic disease.

Table 2 shows the therapeutic indication to be assessed and the ACT specified by the G-BA for it.

Table 2: Research question of the benefit assessment of vandetanib

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Adolescents and children aged 5 years and older with aggressive and symptomatic MTC with unresectable, locally advanced or metastatic disease	Best supportive care[b]

a: Presentation of the ACT specified by the G-BA.
b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer

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

Results

For the derivation of the added benefit, the company tried to extrapolate the results of the adult study 58 on the comparison of vandetanib (plus BSC) with the ACT BSC (plus placebo) to the target population of children and adolescents. Study 58 was already known from previous benefit assessments on vandetanib in adults. On the basis of study 58, the G-BA had derived a hint of a minor added benefit of vandetanib for adults, limiting this decision until 1 October 2020.

The company additionally used the results of the single-arm study 98 with vandetanib in children and adolescents for the extrapolation. This study included a total of 16 patients

between 9 and 17 years of age with hereditary MTC that was unresectable, recurrent or metastatic. The mean age at study inclusion was 14.2 years.

The company's approach to conduct an extrapolation of the study results for adults to children and adolescents is comprehensible due to the missing comparative data for children and adolescents. However, the concrete implementation of the extrapolation by the company was insufficient for various reasons. No added benefit of vandetanib in comparison with the ACT in children and adolescents could therefore be derived. The following aspects in particular were decisive for this:

- The company made statements on whether children and adolescents have a similar course of disease under vandetanib as adults, but did not address this issue for the comparator therapy at all. There was no search for corresponding studies or data; the question to what extent the prognosis differed between adults on the one hand and children and adolescents on the other was not addressed at all. There are justified doubts about a comparable prognosis between adults versus children and adolescents. These are due to the partly advanced age in the adult population, but also based on the data on overall survival and progression of the disease under vandetanib presented by the company and available from the earlier dossier assessment in adults. In addition, the origin of the disease differed between the populations (mainly sporadic in adults, only hereditary in the paediatric population). Even under the assumption that the course of disease under vandetanib is similar, a more detailed explanation is required to justify that the effects of vandetanib versus BSC in adults are comparable with the effects of vandetanib versus BSC in the paediatric patient population.
- The outcome "time to worsening of pain", which was decisive for the derivation of the added benefit of vandetanib in adults, was not recorded in the paediatric study 98. There was also no search on and investigation of the topic of pain progression or pain in children and adolescents and of their treatment, particularly in comparison with adults.
- The company presented the results of the paediatric study 98 and drew conclusions only for individual outcomes whether it considered the results under vandetanib to agree with the results from the adult study 58. Irrespective of this, the data presented by the company and available from the earlier dossier assessment on vandetanib only partly supported the postulate of a comparable course of disease under vandetanib in children and adolescents in comparison with adults. The results on overall survival, severe (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) adverse events (AEs) and serious adverse events (SAEs) as well as on QTc prolongation and diarrhoea notably differed between the vandetanib arms of the studies 58 and 98.

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

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

Table 3: Vandetanib – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Adolescents and children aged 5 years and older with aggressive and symptomatic MTC with unresectable, locally advanced or metastatic disease	Best supportive care[b]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of vandetanib compared with BSC as ACT in adolescents and children aged 5 years and older with aggressive and symptomatic MTC with unresectable, locally advanced or metastatic disease.

Table 4 shows the therapeutic indication to be assessed and the ACT specified by the G-BA for it.

Table 4: Research question of the benefit assessment of vandetanib

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Adolescents and children aged 5 years and older with aggressive and symptomatic MTC with unresectable, locally advanced or metastatic disease	Best supportive care[b]

a: Presentation of the ACT specified by the G-BA.
b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer

[4] 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, no added benefit, or less benefit). For further details see [1,2].

The company followed the G-BA's specification of the ACT.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on vandetanib (status: 18 November 2016)
- bibliographical literature search on vandetanib (last search on 18 November 2016)
- search in trial registries for studies on vandetanib (last search on 1 December 2016)

To check the completeness of the study pool:

- search in trial registries for studies on vandetanib (last search on 25 January 2017)

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trials (RCTs) with the paediatric target population (adolescents and children aged 5 years and older) on the direct comparison of vandetanib versus the ACT or on a corresponding indirect comparison based on RCTs.

For the derivation of an added benefit, the company tried to extrapolate the results of a vandetanib study in adults (study 58) to the target population of children and adolescents. Study 58 was already known from previous benefit assessments on vandetanib in adults [3-7]. For the extrapolation, the company additionally used the results of a single-arm study on vandetanib, which was conducted in children and adolescents (study IRUSZACT0098 [8-10], hereinafter referred to as "study 98").

The company's approach to conduct an extrapolation of study results for adults to children and adolescents is comprehensible due to the missing comparative data for children and adolescents. However, the concrete implementation of the extrapolation by the company was insufficient for various reasons. No added benefit of vandetanib in comparison with the ACT in children and adolescents could be derived from it. This is justified below.

Single-arm vandetanib study (study 98)

Study 98 was a single-arm open-label study with vandetanib in adolescents and children with hereditary MTC that was unresectable, recurrent or metastatic. Patients additionally had to have documented mutation in the rearranged during transfection (RET) protooncogene. The study included a total of 16 patients between 9 and 17 years of age; the mean age at study inclusion was 14.2 years. Vandetanib was administered continuously, once daily, orally, in 28-day cycles using a dosing nomogram. The vandetanib treatment approximately concurred

with the specifications of the Summary of Product Characteristics [11]. The treatment phase ended with disease progression, occurrence of unacceptable toxicity, premature discontinuation of treatment for other reasons, or initiation of treatment with specific QTc-prolonging drugs. The median treatment duration was 107 weeks.

Further information on the study can be found in Section 2.7.2.3.2 and Appendix A to Appendix D of the full dossier assessment.

Approach of the company to extrapolate the study results of adult patients to the paediatric patient population

Besides the single-arm study 98, the company used study 58, which was conducted in adults, for the extrapolation of the results of adult patients to the paediatric target population.

Study 58 was an RCT already presented by the company for the benefit assessments A12-09 [5] and A13-09 [3] (and the corresponding addendum A13-26 [4]). On the basis of study 58, the G-BA had derived a hint of a minor added benefit of vandetanib for adults [12,13], limiting this decision until 1 October 2020 [6,7].

In study 58, vandetanib (plus BSC) was compared with the ACT BSC (plus placebo). The study was conducted in adult patients with the hereditary or sporadic form of unresectable, locally advanced or metastatic MTC.

According to the approval of vandetanib [11], only the data for patients with aggressive and symptomatic MTC from study 58 were relevant both for adults and for children and adolescents. Correspondingly, the company considered the subpopulation of patients with progressive and symptomatic disease from study 58 because this subpopulation can be considered to be an adequate approximation to the approval population (see dossier assessment A12-09 [5]). A detailed description of the study design and of the study results for the subpopulation can be found in dossier assessment A13-09 [3].

The company justified the extrapolation of results of the adult patient population to the paediatric population with sufficient comparability of the disease, an identical mechanism of action and comparable efficacy of vandetanib regarding selected outcomes (objective response rate, progression-free survival, change in tumour biomarkers, safety profile) between children and adolescents versus adults. Irrespective of the question whether this postulate by the company is supported by data, the company's approach was insufficient for extrapolation. The following aspects in particular were decisive for this:

- The company made statements on whether children and adolescents have a similar course of disease under vandetanib as adults, but did not address this issue for the comparator therapy at all. There was no search for corresponding studies or data; the question to what extent the prognosis differed between adults on the one hand and children and adolescents on the other was not addressed at all. There are justified doubts about a comparable

prognosis between adults versus children and adolescents. These are due to the partly advanced age in the adult population, but also based on the data [3,4] on overall survival and progression of the disease under vandetanib presented by the company and available from the earlier dossier assessment in adults. In addition, the origin of the disease differed between the populations (mainly sporadic in adults, only hereditary in the paediatric population) (see tables in Appendix B to Appendix D of the full dossier assessment). Even under the assumption that the course of disease under vandetanib is similar, a more detailed explanation is required to justify that the effects of vandetanib versus BSC in adults are comparable with the effects of vandetanib versus BSC in the paediatric patient population.

- The outcome "time to worsening of pain", which was decisive for the derivation of the added benefit of vandetanib in adults [3,4,12,13], was not recorded in the paediatric study 98. There was also no search on and investigation of the topic of pain progression or pain in children and adolescents and of their treatment, particularly in comparison with adults.
- The company presented the results of the paediatric study 98 and drew conclusions only for individual outcomes whether it considered the results to agree with the results from the adult study 58. For example, results for adult patients for the outcome "overall survival" were not presented at all in Module 4 A of the present dossier; for AEs, the company limited its presentation to determining a qualitative comparability of the side effect profile in children and adolescents versus adults. Irrespective of this, the data [3,4] presented by the company and available from the earlier dossier assessment on vandetanib only partly supported the postulate of a comparable course of disease under vandetanib in children and adolescents in comparison with adults (see tables in Appendix C and Appendix D of the full dossier assessment). As mentioned above, the results on overall survival and on AEs (SAEs, severe AEs [CTCAE grade ≥ 3], QTc prolongation, diarrhoea) differed notably between the vandetanib arms in the studies 58 and 98. In the adult study 58, 21 of 126 patients (16.7%) died, whereas in the paediatric study 98, 1 of 16 patients (6.3%) died. AEs under vandetanib were partly more common in adults (SAEs), partly in children and adolescents (severe AEs, QTc prolongation, diarrhoea).

Besides these decisive points it was unclear whether the company had presented all available data on vandetanib in adults: It did not check whether new studies with adult patients in the corresponding therapeutic indication had become available since the searches conducted for the preparation of the dossier of the year 2013. The last search for studies with adults was therefore from 11 January 2013. Since the data presented by the company were unsuitable for the derivation of an added benefit versus the ACT, this potential incompleteness of the dossier with regard to content had no consequences for the present benefit assessment.

2.4 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of vandetanib versus the ACT. This resulted in no hint of an added benefit of vandetanib in comparison with the ACT; an added benefit is therefore not proven.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of vandetanib in comparison with the ACT is summarized in Table 5.

Table 5: Vandetanib – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adolescents and children aged 5 years and older with aggressive and symptomatic MTC with unresectable, locally advanced or metastatic disease	Best supportive care[b]	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MTC: medullary thyroid cancer		

An added benefit of vandetanib is not proven because the company presented no suitable data.

This deviates from the approach of the company, which, based on the extrapolation of results for adult patients to the paediatric target population in the present therapeutic indication, derived considerable added benefit of vandetanib without stating the probability of the added benefit.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no suitable data for the benefit assessment.

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 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.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

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vandetanib: Erneute Nutzenbewertung gemäß § 35a Absatz 5b SGB V; Dossierbewertung; Auftrag A13-09 [online]. 13.06.2013 [Accessed: 21.06.2013]. (IQWiG-Berichte; Volume 169). URL: https://www.iqwig.de/download/A13-09_Vandetanib_Erneute-Nutzenbewertung-35a-SGB-V.pdf.

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Addendum zum Auftrag A13-09 (Vandetanib [erneute Bewertung gemäß § 35a Absatz 5b SGB V]): Auftrag A13-26 [online]. 07.08.2013 [Accessed: 06.09.2013]. (IQWiG-Berichte; Volume 184). URL: https://www.iqwig.de/download/A13-26_Addendum-zum-Auftrag-A13-09_Vandetanib.pdf.

5. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vandetanib: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A12-09 [online]. 13.06.2012 [Accessed: 11.03.2013]. (IQWiG-Berichte; Volume 134). URL: https://www.iqwig.de/download/A12-09_Vandetanib_Nutzenbewertung_35a_SGB_V.pdf.

6. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über einen Antrag auf Verlängerung der Befristung der Geltungsdauer eines Beschlusses über die Nutzenbewertung nach § 35a SGB V: Vandetanib [online]. 04.08.2016 [Accessed: 29.03.2017]. URL: https://www.g-ba.de/downloads/40-268-3922/2016-08-04_AM-RL-XII_Vandetanib-Fristverlaengerung_TrG.pdf.

7. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über einen Antrag auf Verlängerung der Befristung der Geltungsdauer eines Beschlusses über die Nutzenbewertung nach § 35a SGB V: Vandetanib [online]. 04.08.2016 [Accessed: 29.03.2017]. URL: https://www.g-ba.de/downloads/39-261-2673/2016-08-04_AM-RL-XII_Vandetanib-Fristverlaengerung_BAnz.pdf.

8. Fox E, Widemann BC, Chuk MK, Marcus L, Aikin A, Whitcomb PO et al. Vandetanib in children and adolescents with multiple endocrine neoplasia type 2B associated medullary thyroid carcinoma. Clin Cancer Res 2013; 19(15): 4239-4248.

9. AstraZeneca. Phase I/II trial of vandetanib (ZD6474, ZACTIMA) in children and adolescents with hereditary medullary thyroid carcinoma: study IRUSZACT0098; clinical study report [unpublished]. 2013.

10. National Cancer Institute. Vandetanib to treat children and adolescents with medullary thyroid cancer: full text view [online]. In: ClinicalTrials.gov. 24.01.2017 [Accessed: 09.02.2017]. URL: https://clinicaltrials.gov/show/NCT00514046.

11. Sanofi Genzyme. Caprelsa 100 mg Filmtabletten, Caprelsa 300 mg Filmtabletten: Fachinformation [online]. 12.2016 [Accessed: 15.02.2017]. URL: http://fachinfo.de/.

12. Gemeinsamer Bundesausschuss. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V); Vandetanib [online]. 05.09.2013 [Accessed: 02.03.2017]. URL: https://www.g-ba.de/downloads/39-261-1807/2013-09-05_AM-RL-XII_Vandetanib_BAnz.pdf.

13. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL); Anlage XII: Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Vandetanib [online]. 05.09.2013 [Accessed: 02.03.2017]. URL: https://www.g-ba.de/downloads/40-268-2480/2013-09-05_AM-RL-XII_Vandetanib_TrG.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-01-vandetanib-medullary-thyroid-carcinoma-in-children-and-adolescents-from-the-age-of-5-benefit-assessment-according-to-35a-social-code-book-v.7784.html.