Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V – Vandetanib

of 5 September 2013

At its session on 5 September 2013, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on 15 August 2013 (Federal Gazette, BAnz AT 26 September 2013 B2), as follows:

I. In Annex XII, the inforamtion concerning the active ingredient vandetanib are summarised as follows:

Vandetanib

Resolution of: 5 September 2013

Entry into force on: 5 September 2013

Federal Gazette, BAnz. [ ] No. [..] ; dd mm yyyy, p.[..]

Approved therapeutic indication:

Caprelsa® is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

For patients in whom *Rearranged during Transfection* (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Appropriate comparator therapy:

The appropriate comparator therapy for vandetanib for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease is best supportive care.

Best supportive care is defined as the therapy that ensures the best possible, patient-individual optimised, supportive treatment to alleviate symptoms and improve quality of life (e.g. bisphosphonates for painful bone metastases, external radiotherapy).

Extent and probability of the additional benefit compared with best supportive care(BSC):

Hint for a minor additional benefit

Study results according to endpoints[1]:

Vandetanib + BSC		Placebo + BSC		Intervention vs control	
Mortality					
Overall survival[2]					
N	Median survival time [95% CI] (months)	N	Median survival time [95% CI] (months)	HR [95% CI]	p value
126	no data available	60	no data available	1.06 [0.50; 2.23]	0.879
Morbidity					
Time to worsening of pain (TWP)					

Vandetanib + BSC		Placebo + BSC		Intervention vs control	
N	Median time to pain progression [95% CI] (months)	N	Median time to pain progression [95% CI] (months)	HR [95% CI]	p value
126	11.07 [no data available]	60	3.42 [no data available]	0.62 [0.39; 0.99]	0.045
Progression-free survival (PFS)[3]					
N	Number of patients with progression (%)	Median PFS (months)	N	Number of patients with progression (%)	Median PFS (months)	HR [95% CI]	p value
126	46 (36.5)	28	60	35 (58.3)	16	0.47 [0.29; 0.77]	0.002
Health-related quality of life					
Quality of life (FACT-G)					
No usable data are available in the dossier of the pharmaceutical company.					
Side effects[4]					
Time-adjusted evaluations[5]					
N	Median time to event	N	Median time to event	HR [95% CI]	p value
Total rate of AE[6]					
126	no data available	59	no data available	no data available	no data available
SAE					
126	no data available	59	no data available	1.40 [0.74; 2.63]	no data available
Severe AE (CTCAE grade ≥ 3)					
126	no data available	59	no data available	2.27 [1.47; 3.52]	no data available
Therapy discontinuations because of AE					
126	no data available	59	no data available	2.75 [0.88; 8.60]	no data available
Frequent AE or AE of special interest					
Skin rash					
126	no data available	59	no data available	4.33 [3.04; 6.18]	no data available
QTc prolongation (all severities)[7]					
126	no data available	59	no data available	3.33 [1.30; 8.53]	no data available

Vandetanib + BSC		Placebo + BSC		Intervention vs control	
Incidence Density Ratio (IDR)[5]					
Diarrhoea (SAE)[8]					
N	Patients with event n (n/1000 patient years)	N	Patients with event n (n/1000 patient years)	IDR [95% CI]	p value
126	3 (16.6)	59	0 (0)	2.26 [0.12; 43.80]	0.589
QTc prolongation (CTCAE grade ≥ 3)					
N	Patients with event n (n/1000 patient years)	N	Patients with event n (n/1000 patient years)	IDR [95% CI]	p value
126	10 (55.2)	59	0 (0)	6.79 [0.40; 115.83]	0.186
Non-time-adjusted evaluations[3] (RR estimated using naïve proportions)					
N	Number of patients with event (%)	N	Number of patients with event (%)	RR [95% CI]	p value
Total rate of AE					
126	126 (100)	59	56 (94.9)	1.05 [0.99; 1.12]	no data available
SAE					
126	40 (31.7)	59	10 (16.9)	1.87 [1.01; 3.48]	no data available
Severe AE (CTCAE grade ≥ 3)					
126	77 (61.1)	59	14 (23.7)	no data available	no data available
Therapy discontinuations because of AE					
126	15 (11.9)	59	1 (1.7)	7.02 [0.95; 51.93]	no data available
Frequent AE or AE of special interest					
Skin rash					
126	62 (49.2)	59	8 (13.6)	no data available	no data available
Diarrhoea					
126	66 (52.4)	59	13 (22.0)	no data available	no data available
QTc prolongation (all severities)					
126	20 (15.9)	59	1 (1.7)	no data available	no data available

Vandetanib + BSC		Placebo + BSC		Intervention vs control	
QTc prolongation (CTCAE grade ≥ 3)					
126	10 (7.9)	59	0 (0)	no data available	no data available

Abbreviations used: BSC = best supportive care, CTCAE = Common Terminology Criteria for Adverse Events, FACT-G = Functional Assessment of Cancer Therapy-General, HR = Hazard Ratio, IDR = Incidence Density Ratio, CI = Confidence interval, n = number of patients with event, N = number of patients evaluated, RR = relatives risk, QTc = time interval between the start of the Q-wave and the end of the T-wave (corrected against the heart rate), SD = standard deviation, (S)AE = (serious) adverse events, TWP = Time to Worsening of Pain

[1] Data of study D4200C00058 from the benefit assessment of the IQWiG (A13-09), the Addendum to the benefit assessment (A13-26), and the dossier of the pharmaceutical company.
[2] In both treatment groups, 21 (16.7%) (vandetanib + BSC) and 10 (16.7%) (placebo + BSC) patients died in the relevant sub-population. A representation of the median survival time or the 25% quantile of the time to death is therefore not possible.
[3] Data from the dossier of the pharmaceutical company.
[4] Evaluations based on the safety population.
[5] Survival time analysis with specification of the HR; if the HR is not specified, the IDR is displayed (treatment time in vandetanib arm: 181.0 years; comparator arm: 58.5 years).
[6] Total rate of AE could not be interpreted; therefore no indication of HR.
[7] In the statement of the pharmaceutical company only results for HR of QTc prolongations of all severity levels are available.
[8] SAE in the preferred term (PT) diarrhoea. According to the pharmaceutical company, the HR is not calculable.

2. Number of patients or demarcation of patient groups eligible for treatment

Target population: approx. 60 to 1,500 patients

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 Caprelsa® (active ingredient: vandetanib) at the following publicly accessible link (last access: 1 August 2013):

http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002315/WC500123555.pdf

This medicinal product was approved by the EMA under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated, particularly with regard to a benefit of Caprelsa® in patients without *Rearranged during Transfection* (RET) mutation. A study will be conducted in order to investigate this. The EMA will evaluate new information on this medicinal product at least once per year and, if necessary, the summary of product characteristics will be updated.

Treatment with Caprelsa® should be initiated and monitored only by specialists who are experienced in the treatment of patients with this disease. These are: specialists in internal medicine, haematology, and oncology, specialists in internal medicine and endocrinology, and specialists participating in the Oncology Agreement. Or the prescription is made on the recommendation of an interdisciplinary tumour conference. The aforementioned doctors must meet the conditions of the EPAR requirements regarding training material and equipment.

The training material provided by the marketing authorisation holder shall include the following:

- Summary of product characteristics (product information) and package leaflet
- Training material for doctors
- Patient passport (wording as agreed with the CHMP)

The training material for doctors should contain the following key messages:

- Vandetanib extends the QTc interval and can trigger torsade de pointes and sudden cardiac death
- Vandetanib should not be used in patients:
    - whose QTc interval in the ECG is greater than 480 ms
    - who have a congenital long QTc syndrome
    - who had torsade de pointes in the past unless all risk factors that contributed to the torsade de pointes were corrected
- The need for ECG and measurements of potassium, calcium, magnesium, and thyroid-stimulating hormone (TSH) levels as well as the frequency and occasions on which they should be taken.
- Patients whose corrected QTc interval in the ECG increases once to at least 500 ms should discontinue vandetanib. Administration can be resumed at reduced dosage after the QTc interval in the ECG has demonstrably returned to the same status as before treatment and the electrolytes are balanced.
- If the QTc interval increases significantly but remains below 500 ms, a cardiologist should be consulted.
- Information on medications for which concomitant administration of vandetanib is contraindicated or not recommended.
- That vandetanib may cause posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS)
- PRES should be considered in patients who experience seizures, headaches, visual disturbances, confusion, or a change in mental function. An MRI of the brain should be performed on any patient with seizures, confusion or altered mental function.
- The need to advise patients on the risks of QTc interval prolongation and PRES as well as the symptoms and signs to be considered and the appropriate measures to take
- The meaning and use of the patient passport

4. Treatment costs

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration/treatment (days)	Treatment days per patient per year
Medicinal product to be assessed				
Vandetanib	1 × 300 mg daily	continuously	365	365
Best supportive care (BSC)	Continuously, different for each individual patient	continuously	365	365
Appropriate comparator therapy				
Best supportive care (BSC)	Continuously, different for each individual patient	continuously	365	365

Usage and consumption:

Designation of the therapy	Potency (mg)[9]	Quantity per package (tablets)	Average annual consumption (tablets)
Medicinal product to be assessed			
Vandetanib	300	30	365
BSC	different for each individual patient		
Appropriate comparator therapy			
BSC	different for each individual patient		

[9] The potency of 300 mg is considered according to the recommended dose (300 mg once daily).

Costs:

Costs of the medicinal product:

Designation of the therapy	Costs (pharmacy sales price)[10]	Costs after deduction of statutory rebates
Medicinal product to be assessed		

Vandetanib	€ 6,185.82	€ 5,383.97 [€ 1.85[11]; € 800.00[12]]
BSC	different for each individual patient	
Appropriate comparator therapy		
BSC	different for each individual patient	

[10] The potency of 300 mg is considered according to the recommended dose (300 mg once daily).
[11] Rebate according to Section 130 SGB V.
[12] Rebate according to Section 130a SGB V.
Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2013

Costs for additionally required SHI services:
not applicable

Annual treatment costs:

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Vandetanib	€ 65,504.97
BSC	different for each individual patient
Appropriate comparator therapy	
BSC	different for each individual patient

II. Entry into force

1. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 5 September 2013.

2. The period of validity of the resolution is limited to 5 September 2016.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 5 September 2013

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Hecken