**Resolution**
**by the Federal Joint Committee**
**on an amendment to the Pharmaceutical Directive (AM-RL):**
**Appendix XII – Resolutions on the benefit assessment of pharmaceuticals with new active ingredients, in accordance with the German Social Code, Book Five (SGB V), section 35a**
**Abiraterone acetate**
**(new therapeutic indication)**

**from 4 July 2013**

In its session on 4 July 2013, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 4 July 2013 (Federal Gazette, AT 2 August 2013 B7), as follows:

I.

In Appendix XII, the following information shall be added to the details following number 4 on the benefit assessment of abiraterone acetate for the indication "in combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen" in accordance with the resolution of 29 March 2012:

Abiraterone acetate

New therapeutic indication from 18 December 2012:

Zytiga® is authorized in combination with prednisone or prednisolone:

– for the treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen-deprivation therapy in whom chemotherapy is not yet clinically indicated.

1. Additional benefit of the pharmaceutical over appropriate comparator

   Appropriate comparator:

   The appropriate comparator for abiraterone acetate for the treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen-deprivation therapy is a watchful waiting approach while continuing ongoing conventional androgen deprivation or, if applicable, the combined maximum androgen blocker with a non-steroid anti-androgen (flutamide, bicalutamide).

   Notes:

   For this indication, conventional androgen-deprivation therapy is understood as surgical castration or medicinal castration using LHRH analogues or GnRH antagonists, and "failure" as disease progression defined on the basis of surrogate parameters (e.g. PSA increase and radiographic progress or upgrading). After failure of conventional androgen-deprivation therapy, combined maximum androgen blocker with a non-steroid anti-androgen is a treatment option which must be carefully considered with the patient due to the expected stronger side effects as opposed to the slight extension of life. As therapy for metastatic castration resistant prostate cancer is palliative care, maintaining quality of life and controlling symptoms are of particular significance.

   Extent and probability of additional benefit over a watchful waiting approach while continuing ongoing conventional androgen deprivation:

   Indication of a considerable additional benefit.

Study results according to endpoints[1]:

| Abiraterone acetate/ predniso(lo)ne/ ADT | | Placebo/ predniso(lo)ne/ ADT | | Intervention vs. monitoring | |
|---|---|---|---|---|---|
| **Mortality** | | | | | |
| **Median survival** | | | | | |
| N | Months [95% CI] | N | Months [95% CI] | HR [95% CI], absolute difference | p-value |
| 546 | 35.3 [31.2; 35.3] | 542 | 30.1 [27.3; 34.1] | 0.79 [0.66; 0.96][2], 5.2 months | 0.015[2] |
| **Morbidity** | | | | | |
| **Time to start of opium therapy (severe pain) in months** | | | | | |
| N | Months [95% CI] | N | Months [95% CI] | HR [95% CI], absolute difference | p-value |
| 546 | Median incident time: n/a[3]<br>25% quantile[4]: 14.8 [13.0; 17.2] | 542 | Median incident time: 23.7 [20.4; 30.3]<br>25% quantile[4]: 12.0 [10.2; 13.0] | n/a<br>0.71 [0.59; 0.85][2], 2.8 months | n/a<br>< 0.001[2] |
| **Pain (BPI-SF)** | | | | | |
| N | Mean value (Standard error) | N | Mean value (standard error) | Difference of means (95% CI) | p-value |
| **Strongest pain in the last 24 hours (questions 3 of the BPI-SF: 0 to 10 points)** | | | | | |
| 511 | Mean value at start of study 1.11 (0.08)<br>Mean value over observation period: 1.31 (0.06) | 502 | Mean value at start of study 1.13 (0.08)<br>Mean value over observation period: 1.67 (0.06) | – 0.36<br>[– 0.53; – 0.19] | < 0.001 |
| **Impairment due to pain in the last 24 hours (question 9 A to G: 0 to 10 points)** | | | | | |
| 497 | Mean value at start of study 0.68 (0.06)<br>Mean value over observation period 0.96 (0.05) | 493 | Mean value at start of study 0.68 (0.06)<br>Mean value over observation period 1.13 (0.05) | – 0.17<br>[– 0.31; – 0.02] | 0.025 |
| **Health-related quality of life** | | | | | |
| **Quality of life (FACT-P version 4; 0 to 156 points)** | | | | | |
| N | Mean value (standard error) | N | Mean value (standard error) | Difference of means [95% CI] | p-value |
| 513 | Mean value at start of study 123.10 (0.63)<br>Mean value over observation period 123.64 (0.55) | 507 | Mean value at start of study 123.23 (0.63)<br>Mean value over observation period 120.83 (0.61) | 2.81 [1.19; 4.42] | 0.001 |
| **Adverse events[5]** | | | | | |
| N | n (%) | N | n (%) | RR [95% CI] | p-value |
| **Overall rate AE** | | | | | |
| 542 | 538 (99.3%) | 540 | 524 (97.0%) | 1.02 [1.01; 1.04] | 0.007 |
| **Overall rate SAE (without deaths)** | | | | | |
| 542 | 188 (34.7%) | 540 | 146 (27.0%) | 1.28 [1.07; 1.54] | 0.007 |

[1] Data from the COU-AA-302 on the third data cut-off on 22 May 2012 from the IQWiG benefit assessment of 11 April 2013 (A13-06), the addendum to the benefit assessment from 13 June 2013 (A13-22), and the dossier of the pharmaceutical company. Intention to treat (ITT) evaluation (except adverse events).

[2] Adjusted according to ECOG (Eastern Cooperative Oncology Group) performance status (0 or 1).

[3] The median time until the incident could not be estimated in the study arm due to the large proportion of censored data.

[4] The 25% quantile shows the time at which the probability of an event occurrence is 25%.

[5] Number of patients with at least one relevant adverse event Evaluation based on the safety population.

| Abiraterone acetate/ predniso(lo)ne/ ADT | | Placebo/ predniso(lo)ne/ ADT | | Intervention vs. monitoring | |
|---|---|---|---|---|---|
| Severe AE (CTCAE grade 3 and 4) | | | | | |
| 542 | 267 (49.3%) | 540 | 235 (43.5%) | 1.13 [0.995; 1.29] | 0.06 |
| AE leading to death | | | | | |
| 542 | 21 (3.9%) | 540 | 16 (3.0%) | 1.31 [0.69; 2.48] | 0.41 |
| Terminations of treatment due to AE | | | | | |
| 542 | 58 (10.7%) | 540 | 53 (9.8%) | 1.09 [0.77; 1.55] | 0.63 |

Abbreviations used: ADT = androgen deprivation therapy (conventional androgen deprivation); BPI-SF = brief pain inventory short form; CTCAE = common terminology criteria for adverse events; FACT = functional assessment of cancer therapy; FACT-P = – for patients with prostate cancer; HR = hazard ratio; n/a = not available; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with incident; N = number of patients evaluated; RR = relative risk; (S)AE = (serious) adverse events

2. Number of patients and criteria for defining patients eligible for treatment

   Target population: approx. 15,000 to 28,800 patients

3. Requirements for quality-assured administration

   The specifications outlined in the summary of product characteristics are to be followed. The European Medicines Agency (EMA), the European regulatory authority, provides the contents of the product information for Zytiga® (active ingredient: abiraterone acetate) at the following public link (last accessed: 29 Mai 2013):

   http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002321/WC500112858.pdf

   The EMA addresses mineralocorticoidal side effects (such as fluid retention/oedema, hypokalaemia, hypertension), hepatotoxicity, and cardiovascular side effects (such as arrhythmia, angina pectoris, heart failure) as adverse events of particular interest in its public assessment report – variation (EPAR).

4. Costs of treatment

   Duration of treatment:

| Description of therapy | Mode of treatment | Number of treatments per patient per year | Duration per treatment (days) | Number of treatment days per patient per year |
|---|---|---|---|---|
| Pharmaceutical evaluated | | | | |
| Abiraterone | 1 x 1,000mg daily | ongoing | 365 | 365 |
| Prednisolone | 10 mg daily | ongoing | 365 | 365 |
| Therapy with LHRH analogue | once monthly to once annually subcutaneous deposit | ongoing | 30.4 to 365 | 365 |
| Appropriate comparator | | | | |
| Conventional androgen deprivation | | | | |
| Therapy with LHRH analogue | once monthly to once annually subcutaneous deposit | ongoing | 30.4 to 365 | 365 |
| Maximum androgen blockade | | | | |
| Bicalutamide<br>Flutamide | 1 x 50 mg daily<br>3 x 250 mg daily | ongoing | 365 | 365 |

   Consumption:

| Description of therapy | Strength | Number/amount per pack | Average annual consumption |
|---|---|---|---|
| Pharmaceutical evaluated | | | |
| Abiraterone acetate | 250 mg | 120 | 1,460 tablets |
| Prednisolone | 10 mg | 100 tablets[6] | 365 tablets |
| LHRH analogue | 3.6 to 41 mg | 1 to 3 administrations[6] | 1 to 12 administrations |
| Appropriate comparator | | | |
| Conventional androgen deprivation | | | |
| LHRH analogue | 3.6 to 41 mg | 1 to 3 administrations[6] | 1 to 12 administrations |
| Maximum androgen blockade | | | |
| Bicalutamide<br>Flutamide | 50 mg<br>250 mg | 90 tablets[6]<br>84 tablets[6] | 365 tablets<br>1,095 tablets |

[6] Largest pack.

Costs:

Cost of pharmaceutical:

| Description of therapy | Costs[7, 8, 11] | Cost after legally mandated rebates |
|---|---|---|
| Pharmaceutical evaluated | | |
| Abiraterone acetate | €5,450.21[7]; €4,911.44[8] | €4,275.92<br>[€1.85[9]; €633.67[10]] |
| Prednisolone | €17.29[11] | €14.93<br>[€1.85[9]; €0.51[10]] |
| LHRH analogue | €390.05 – €1,557.23 | €370.20 – €1,359.56<br>[€1.85[9]; €18.00 – €195.82[10]] |
| Appropriate comparator | | |
| Conventional androgen deprivation | | |
| LHRH analogue | €390.05 – €1,557.23 | €370.20 – €1,359.56<br>[€1.85[9]; €18.00 – €195.82[10]] |
| Maximum androgen blockade | | |
| Bicalutamide<br>Flutamide | €174.89[11]<br>€37.14[11] | €160.06 [€1.85[9]; €12.98[10]]<br>€33.21 [€1.85[9]; €2.08[10]] |

"Lauer-Taxe", effective 1 July 2013

Costs for additional, necessary statutory health insurance (SHI) benefits:

Not applicable.

Annual treatment costs:

| Description of therapy | Annual treatment costs per patient |
|---|---|
| Pharmaceutical evaluated | |
| Abiraterone acetate | €52,023.69 |
| Prednisolone | €54.49 |
| LHRH analogue | €1,359.56 – €1,480.80 |
| Appropriate comparator | |
| Conventional androgen deprivation | |
| LHRH analogue | €1,359.56 – €1,480.80 |
| Maximum androgen blockade | |
| Bicalutamide<br>Flutamide | €649.13<br>€432.92 |

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 4 July 2013.

The justification for this resolution will be published on the website of the Federal Joint Committee at www.g-ba.de.

Berlin, 4 July 2013

The Federal Joint Committee in
accordance with SGB V, section 91

The Chair
Hecken

[7] The pharmacy retail price shown in the Lauer-Taxe based on manufacturer's information.

[8] Pharmacy retail price based on reimbursable price.

[9] Rebate in accordance with SGB V, section 130.

[10] Rebate in accordance with SGB V, section 130a.

[11] Reference price.