

## Appendix

### Early benefit assessment in Germany

In Germany, new legislation regulating the reimbursement of innovative medicines (new active substances or new chemical entities) within the statutory health insurance system (*Arzneimittelmarktneuordnungsgesetz, AMNOG*) was introduced on 1 January 2011.

According to this law, new products are subject to an early benefit assessment to determine whether there is sufficient evidence of added clinical benefits compared with appropriate therapeutic alternatives. For OMPs with an annual outpatient budget impact of no more than €50 million (for all indications combined), the additional benefit is assumed to be proven. In this case, the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG*) will be commissioned with a formal assessment of the annual treatment costs but not of additional benefits. The German Joint Federal Committee (*Gemeinsamer Bundesausschuss, G-BA*) appraises the additional benefit and classifies it in one of four categories: major added benefit („*erheblich*“), considerable added benefit („*beträchtlich*“), minor added benefit („*gering*“), and added benefit proven but not quantifiable („*nicht quantifizierbar*“). Manufacturers and representatives of the statutory health insurance are expected to agree on an appropriate reimbursement price within 6 months, starting from the completion of the benefit appraisal by the G-BA. If drug makers and health insurers cannot agree on the price, a final decision on the reimbursement price will be made by an arbitration body.

**Table A1. Studies on budget impact of (ultra-)orphan drugs in Europe.**

| Region                                 | Type of drugs                                   | Annual budget impact (€) | % pharmaceutical expenditure | Annual per-capita spending (€)* | Year | Type of study | Consideration of substitution effects | Consideration of uptake | Reference                  |
|--|---|--------------------------|------------------------------|---------------------------------|------|---------------|---------------------------------------|-------------------------|----------------------------|
| Belgium                                | Orphan drugs                                    | 66,200,000               | 5% (hospitals only)          | 5.79                            | 2008 | Empirical     | No                                    | NA                      | Denis et al. 2010 [35]     |
| Bulgaria                               | Orphan drugs                                    | 38,091,635               | 7.8%                         | 5.29                            | 2014 | Empirical     | No                                    | NA                      | Iskrov et al. 2015 [36]    |
| Europe                                 | Ultra-orphan drugs for non-oncological diseases | 1,113,137,781            | 0.7%                         | 1.50                            | 2012 | Modeling      | No                                    | Yes                     | Schlander et al. 2015 [33] |
| Eurozone countries plus United Kingdom | Orphan drugs                                    | 4,620,000,000            | 3.3%                         | 11.73                           | 2010 | Modeling      | No                                    | Yes                     | Schey et al. 2011 [34]     |

|             |              |               |      |       |      |           |    |    |                            |
|-------------|--------------|---------------|------|-------|------|-----------|----|----|----------------------------|
| France      | Orphan drugs | 460,700,000   | 1.7% | 7.20  | 2007 | Empirical | No | NA | Orofino et al. 2010 [37]   |
| France      | Orphan drugs | 1,054,000,000 | 3.1% | 16.05 | 2012 | Empirical | No | NA | Hutchings et al. 2014 [38] |
| Germany     | Orphan drugs | 525,000,000   | 2.1% | 6.38  | 2007 | Empirical | No | NA | Orofino et al. 2010 [37]   |
| Italy       | Orphan drugs | 235,500,000   | 1.5% | 4.03  | 2007 | Empirical | No | NA | Orofino et al. 2010 [37]   |
| Latvia      | Orphan drugs | 2,641,727     | 0.8% | 1.32  | 2014 | Empirical | No | NA | Logviss et al. 2016 [39]   |
| Netherlands | Orphan drugs | 260,400,000   | 4.2% | 15.55 | 2012 | Empirical | No | NA | Kanters et al. 2014 [40]   |
| Spain       | Orphan drugs | 256,000,000   | 2.0% | 5.66  | 2007 | Empirical | No | NA | Orofino et al. 2010 [37]   |

|                |              |             |      |       |      |           |    |    |                            |
|----------------|--------------|-------------|------|-------|------|-----------|----|----|----------------------------|
| Sweden         | Orphan drugs | 107,170,800 | 2.5% | 11.26 | 2012 | Empirical | No | NA | Hutchings et al. 2014 [38] |
| United Kingdom | Orphan drugs | 162,000,000 | 1.0% | 2.64  | 2007 | Empirical | No | NA | Orofino et al. 2010 [37]   |

\*Population size refers to the same year as budget impact.

NA = not applicable

**Table A2. Non-oncological orphan medicinal products included in the analysis**

|                       | Prevalence per 100 000 persons | Population with expected benefit in the German statutory health insurance system | Availability of alternative treatments (1 = yes, 0 = no) | Effect on mortality (1 = yes, 0 = no) | Annual treatment cost (€) | Extent/probability of benefit (1 = non-quantifiable, 0 = minor) |
|-----------------------|--------------------------------|--|--|---------------------------------------|---------------------------|---|
| Afamelanotide         | 0.92                           | 815  | 0  | 0                                     | 58,699                    | 1   |
| Albutrepenonacog alfa | 1.7                            | 881  | 1  | 0                                     | 364,264                   | 1   |
| Alipogene tiparvovec  | 0.2                            | 26   | 0  | 0                                     | 1,007,631                 | 1   |
| Asfotase alfa         | 0.21                           | 1000   | 0  | 1                                     | 1,647,627                 | 1   |
| Cholic acid           | 0.6                            | 18   | 0  | 1                                     | 155,203                   | 1   |
| Eftrenonacog alfa     | 1.7                            | 620  | 1  | 0                                     | 343,344                   | 1   |
| Eliglustat            | 0.3                            | 325  | 1  | 0                                     | 234,581                   | 1   |

|                 |      |      |   |   |         |   |
|-----------------|------|------|---|---|---------|---|
| Elosulfase alfa | 15   | 55   | 0 | 0 | 472,630 | 0 |
| Idebenone       | 4.3  | 2250 | 0 | 0 | 75,571  | 1 |
| Isavuconazole   | 0.6  | 1659 | 1 | 1 | 125,653 | 1 |
| Ivacaftor       | 7.4  | 210  | 1 | 0 | 224,857 | 0 |
| Macitentan      | 3.3  | 4215 | 1 | 1 | 32,047  | 0 |
| Migalastat      | 0.22 | 256  | 1 | 0 | 208,017 | 1 |

|                     |      |      |   |   |         |   |
|---------------------|------|------|---|---|---------|---|
| Nintedanib          | 30   | 7550 | 0 | 1 | 27,811  | 0 |
| Pasireotide         | 9.5  | 959  | 1 | 0 | 31,488  | 0 |
| Pirfenidone         | 11.5 | 7481 | 1 | 1 | 36,288  | 1 |
| Riociguat           | 20   | 3703 | 1 | 1 | 33,823  | 0 |
| Sebelipase alfa     | 2    | 433  | 0 | 1 | 445,583 | 1 |
| Tafamidis meglumine | 1    | 40   | 1 | 0 | 147,614 | 0 |
| Teduglutide         | 3.4  | 1750 | 0 | 0 | 264,890 | 0 |

