**Supplementary materials**

Table A Adverse event costs

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse event** | **Annual probability** | **Cost (€)**1–3 | **Assumption** |
| **Alemtuzumab** | | | |
| Respiratory infection | 29.43%4 | 124.43 | Medical specialist visit |
| Herpes infection | 8.62%4 | 160.64 | GP visit, treatment with zinc sulfate cream, outpatient specialist visit and treatment with acyclovir5,6 |
| Urinary tract infection | 10.67%4 | 156.09 | GP visit, outpatient specialist visit, and treatment with trimethoprim7 |
| Autoimmune thyroid-related adverse events: |  |  |  |
| - Hypothyroidism | 1.69% - 5.35%8\* | 259.52 | Two specialist visits, blood test and treatment with levothyroxine9 |
| - Hyperthyroidism | 1.59% - 6.67%8\* | 645.16 | Five specialist visits, blood test and treatment with thiamazol9 |
| - Graves’ disease | 1.19% - 6.11%8\* | 645.16 | Five specialist visits, blood test and treatment with thiamazol9 |
| -Thyroidectomy | 3.21%8\*\* | 4570.0010 | Thyroidectomy including hospital stay |
| -Iodine ablation | 2.97%8\*\* | 1,515.0010 | Iodine ablation and max. 2 hospital days |
| Immune thrombocytopenia: | 0.4%4, of which: |  |  |
| - Observation only | 13.33%4 | 1,111.12 | Two hospital days11 |
| - Steroids only | 46.67%4 | 1,149.88 | Two days and treatment with IV methylprednisolone11 |
| - Steroids and immunoglobulin | 13.33%4 | 8,426.20 | Two hospital days and treatment with IV methylprednisolone and immunoglobulin11 |
| - Steroids and rituximab ±immunoglobulin | 20.00%4 | 10,055.11 | Two hospital days and treatment with IV methylprednisolone, treatment with immunoglobulin and rituximab11 |
| - Steroids and splenectomy | 6.67%4 | 2,672.76 | Treatment with IV methylprednisolone and operation of 1.5 hours, and 2 days of stay after laparoscopic splenectomy11 |
| - Good pasture’s syndrome | 0.0001%4 | 7,827.28 | Plasmapheresis, treatment with prednisone, methylprednisolone, combined with cyclophosphamide or azathioprine |
| **Fingolimod** |  |  |  |
| Macular oedema | 0.23%12 | 265.00 | Two ophthalmologist visits12 |
| Atrioventricular block, first degree | 0.12%12 | 1,199.10 | Two hospital days, 2 ECGs12 |
| Atrioventricular block, second degree | 0.12%12 | 1,199.10 | Two hospital days, 2 ECGs12 |
| Bronchitis | 4.08%13 | 126.09 | Specialist visit and course of amoxicillin14 |
| Back pain | 6.07%13 | 33.00 | GP visit |
| Diarrhea | 6.07%13 | 194.61 | Specialist visit and medication15 |
| **Natalizumab** |  |  |  |
|  |  |  |  |
| Urinary tract infection | 2.00%16 | 156.09 | GP visit, secondary outpatient visit, and treatment with trimethoprim7 |
| Progressive multifocal leukoencephalopathy | 1st year: 0.02%, year 2+: 0.16%17 | 6,599.21 | Hospitalization for two weeks, MRI, JC virus PCR and lumbar puncture16,18 |
| Headache | 21.30%19 | 124.43 | Specialist visit |
| Fatigue | 14.60%19 | 124.43 | Specialist visit |
| Arthralgia | 10.00%19 | 261.77 | GP visit, methylprednisolone injections and outpatient pain management appointment, including 3 outpatient visits. |
| Allergic reaction | 4.60%19 | 276.44 | One week course of treatment with methylprednisolone and cost of neurology visits in 25% of patients. |

\*See table B. \*\*5-year probability calculated from the proportion of patients that experienced thyroid AE times the proportions receiving thyroidectomy or iodine ablation. Costs were conservatively applied in the first year and thus not discounted.

Table B Annual probabilities of acquiring autoimmune thyroid-related adverse events by year from alemtuzumab initiation8

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Year 1 & 2 | Year 3 | Year 4 | Year 5 |
| Hypothyroidism | 2.18% | 5.35% | 2.76% | 1.69% |
| Hyperthyroidism | 1.59% | 6.67% | 3.73% | 2.96% |
| Graves’ disease | 1.19% | 6.11% | 2.57% | 1.69% |

Annual probabilities were derived from the reported incidence rates using *p=1-exp(-r/100)*, with *p* being the probability and *r* the rate in events per 100 patient-years. Events and time periods are not mutually exclusive, meaning that a single patient can be represented in multiple figures. To avoid double-counting of patients, and due to a lack of data on the duration of the thyroid-related adverse events, costs reported in table A are applied to the year of thyroid-related adverse event diagnosis.

**References**

1. Nederlandse Zorgautoriteit (NZa). DBC zorgproducten tariefapplicatie. http://dbc-zorgproducten-tarieven.nza.nl/nzaZpTarief/ZoekfunctieDot.aspx. Accessed October 13, 2015.

2. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. *Kostenhandleiding: Methodologie van Kostenonderzoek En Referentieprijzen Voor Economische Evaluaties in de Gezondheidszorg*.; 2015.

3. Organisation for Economic Co-operation and Development (OECD). Harmonized consumer price index. http://stats.oecd.org/. Accessed September 29, 2015.

4. European Medicines Agency (EMEA). *European Public Assessment Report Lemtrada (Alemtuzumab). EMA/563018/2013.*; 2013.

5. Nederlands Huisartsen Genootschap. *NHG-Standaard Herpes Labialis*.; 2007.

6. Nederlands Huisartsen Genootschap. *NHG-Standaard Herpes Zoster*.; 2003.

7. Van Pinxteren B, Knottnerus B, Geerlings S, et al. NHG-standaard Urineweginfecties. *Huisarts Wet*. 2013;56(6):270-280.

8. Senior PA, Arnold DL, Cohen JA, et al. Incidence and Timing of Thyroid Adverse Events in Patients With RRMS Treated With Alemtuzumab Through 5 Years of the CARE-MS Studies. *Present 68th Am Acad Neurol Annu Meet*. 2016;(P2.086).

9. Van Lieshout J, Felix-Schollaart B, Bolsius E, et al. NHG-standaard Schildklieraandoeningen. *Huisarts Wet*. 2013;56(7):320-330.

10. Nederlandse Zorgautoriteit (NZa). Open DIS Data. http://www.opendisdata.nl/zorgproduct/. Accessed March 15, 2016.

11. Nederlandse Vereniging voor Hematologie. Richtlijn ITP. *2013*.

12. Novartis Pharmaceutical UK Ltd. *Fingolimod for the Treatment of Relapsing-Remitting Multiple Sclerosis in Adults: NICE Single Technology Appraisal.*; 2011.

13. Kappos L, Radue E, O’Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387-401.

14. Verheij T, Hopstaken R, Prins J, et al. NHG-standaard acuut hoesten. *Huisarts Wet*. 2011;54(2):68-92.

15. Belo J, Bos M, Bruhl P, et al. NHG-standaard acute diarree. *Huisarts Wet*. 2014;57(9):462-471.

16. Biogen Idec. *Natalizumab (Tysabri) for the Treatment of Adults with Highly Active Relapsing Remitting Multiple Sclerosis: Single Technology Appraisal (STA) Submission to the National Institute for Health and Clinical Excellence*.; 2006.

17. Kappos L, Bates D, Edan G, Eraksoy M, Garcia-Merino A. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. *Lancet Neurol*. 2011;10(8):745-758.

18. Baldwin K, Hogg J. Progressive multifocal leukoencephalopathy in patients with multiple sclerosis. *Curr Opin Neurol*. 2013;26(3):318-323.

19. Polman C, O’Connor P, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):899-910.