**SUPPLEMENTAL MATERIAL**

Time to treatment failure following initiation of fingolimod versus teriflunomide for multiple sclerosis: A retrospective U.S. claims study

**Table S1. Codes used to identify MS treatments in medical and pharmacy claims**

|  |  |  |
| --- | --- | --- |
| **Treatment** | **GPI codes** | **HCPCS codes** |
| **Disease-modifying therapies** |  |  |
| Alemtuzumab | 62 40 50 10 00 xx xx | J0202, J9010, Q9979 |
| Daclizumab | 62 40 50 25 00 xx xx | J7513 |
| Dimethyl fumarate | 62 40 55 25 00 xx xx96 48 58 37 40 xx xx |   |
| Fingolimod | 62 40 70 25 10 xx xx |   |
| Glatiramer acetate | 62 40 00 30 10 xx xx | J1595 |
| Interferon beta-1a | 62 40 30 60 45 xx xx | J1825, J1826, Q3025, Q3026, Q3027, Q3028  |
| Interferon beta-1b | 62 40 30 60 50 xx xx | J1830  |
| Mitoxantrone | 21 20 00 55 00 xx xx | J9293 |
| Natalizumab | 62 40 50 50 00 xx xx | J2323, Q4079 |
| Peginterferon beta-1a | 62 40 30 75 30 xx xx |   |
| Rituximab | 21 35 30 60 00 xx xx | J9310 |
| Teriflunomide | 62 40 40 70 00 xx xx |   |
| **Acute treatments for MS** |  |  |
| Corticosteroids | 22 10 00 15 10 xx xx22 10 00 20 00 xx xx22 10 00 20 10 xx xx22 10 00 20 20 xx xx22 10 00 30 00 xx xx22 10 00 30 10 xx xx22 10 00 30 20 xx xx22 10 00 45 00 xx xx22 10 99 02 60 xx xx | J1020, J1030, J1040, J1094, J1100, J2920, J2930, J7506, J7509, J7512, J8540 |
| Corticotropin | 30 30 00 10 00 xx xx30 30 00 20 10 xx xx | J0800 |
| *GPI* Generic Product Identifier, *HCPCS* Healthcare Common Procedure Coding System, *MS* multiple sclerosis |

**Table S2. Codes used to identify MS symptoms in medical claims**

|  |  |
| --- | --- |
| **Condition** | **ICD-9-CM diagnosis codes** |
| Demyelinating disease of CNS, unspecified | 341.9x |
| Disorders of optic nerve and visual pathways | 377.xx |
| General symptoms: dizziness and giddiness | 780.4x |
| General symptoms: fatigue/malaise | 780.7x |
| Neurogenic bladder NOS | 596.54 |
| Other causes of myelitis | 323.82 |
| Other disorders of soft tissues: neuralgia, neuritis, and radiculitis, unspecified | 729.2x |
| *CNS* Central nervous system, *ICD-9-CM* International Classification of Diseases, 9th Revision, Clinical Modification*, MS* multiple sclerosis, *NOS* Not otherwise specified |

**Table S3. Kaplan-Meier analysis of time to treatment failure by age group**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Age group / cohort** | **N** | **Median(months)** | **IQR (months)** | **Proportion of patients with event (%)** | **Log-rankp-value** |
| **12-month** | **18-month** | **24-month** |
| **18 to <35 years** |  |  |  |  |  |  |  |  |
| Teriflunomide | 142 | 8.0 | (2.8, 16.3) | 63.7% | 77.0% | 84.8% | - |  |
| Fingolimod | 620 | 18.0 | (5.9, NR) | 38.7% | 50.3% | 56.5% | <0.001 | \* |
|  |  |  |  |  |  |  |  |  |
| **35 to <45 years** |  |  |  |  |  |  |  |  |
| Teriflunomide | 393 | 9.3 | (2.8, 28.8) | 54.5% | 65.0% | 70.7% | - |  |
| Fingolimod | 822 | 24.6 | (7.7, NR) | 34.3% | 43.6% | 49.4% | <0.001 | \* |
|  |  |  |  |  |  |  |  |  |
| **45 to <55 years** |  |  |  |  |  |  |  |  |
| Teriflunomide | 701 | 10.4 | (3.0, 35.5) | 53.7% | 62.0% | 69.5% | - |  |
| Fingolimod | 842 | 18.3 | (5.9, 40.5) | 40.9% | 49.3% | 59.0% | <0.001 | \* |
|  |  |  |  |  |  |  |  |  |
| **55 to <65 years** |  |  |  |  |  |  |  |  |
| Teriflunomide | 623 | 10.1 | (2.8, 34.1) | 54.5% | 63.4% | 69.6% | - |  |
| Fingolimod | 420 | 18.8 | (6.0, 41.3) | 39.9% | 49.4% | 55.8% | <0.001 | \* |

*IQR* interquartile range, *NR* not reached

**Table S4. Multivariable Cox proportional hazards model of time to first relapse**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **HR** | **95% CI** | **P-value** |
|  |  |  |  |  |
| **Estimated effect of fingolimod (vs. teriflunomide), unadjusted** | 0.772 | (0.694, 0.860) | <0.001 | \* |
| **Estimated effect of fingolimod (vs. teriflunomide), adjusted** | 0.757 | (0.674, 0.849) | <0.001 | \* |
| Age (years) | 0.997 | (0.992, 1.003) | 0.352 |  |
| Female | 1.111 | (0.972, 1.271) | 0.124 |  |
| US geographic region (vs. South) |  |  |  |  |
| Northeast | 1.023 | (0.882, 1.186) | 0.767 |  |
| North central | 1.137 | (0.991, 1.305) | 0.068 |  |
| Other (i.e., West or unknown) | 0.984 | (0.838, 1.155) | 0.843 |  |
| Insurance type (vs. preferred provider organization) |  |  |  |  |
| Health maintenance organization (HMO) | 1.145 | (0.971, 1.352) | 0.108 |  |
| Other | 1.022 | (0.900, 1.161) | 0.734 |  |
| Index year (vs. 2012) |  |  |  |  |
| 2013 | 0.972 | (0.805, 1.174) | 0.768 |  |
| 2014 | 0.990 | (0.811, 1.209) | 0.925 |  |
| 2015 | 1.066 | (0.861, 1.319) | 0.557 |  |
| Symptoms during the 1-year baseline period |  |  |  |  |
| Demyelinating disease of CNS, unspecified | 0.853 | (0.701, 1.039) | 0.114 |  |
| Disorders of optic nerve and visual pathways | 1.034 | (0.899, 1.188) | 0.640 |  |
| General symptoms: dizziness and giddiness | 1.057 | (0.886, 1.261) | 0.539 |  |
| General symptoms: fatigue/malaise | 1.318 | (1.174, 1.479) | <0.001 | \* |
| Neurogenic bladder NOS | 1.354 | (1.119, 1.639) | 0.002 | \* |
| Other causes of myelitis | 1.445 | (0.878, 2.379) | 0.147 |  |
| Other disorders of soft tissues: neuralgia, neuritis, and radiculitis, unspecified | 0.989 | (0.734, 1.333) | 0.944 |  |
| CCI1 during the 1-year baseline period | 1.079 | (1.029, 1.131) | 0.002 | \* |
| Number of relapses during the 1-year baseline period | 1.544 | (1.459, 1.633) | <0.001 | \* |
| Use of ≥1 DMT during the 1-year baseline period | 1.014 | (0.904, 1.137) | 0.817 |  |
|   |   |   |   |   |
|  |  |  |  |  |
| *\* p-value < 0.05; HR: Hazard ratio; CI: Confidence interval; US: United States; CNS: Central nervous system; NOS: Not otherwise specified; CCI: Charlson comorbidity index; DMT: Disease modifying therapy* |

**Table S5. Multivariable Cox proportional hazards model of time to treatment discontinuation**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **HR** | **95% CI** | **P-value** |
|  |  |  |  |  |
| **Estimated effect of fingolimod (vs. teriflunomide), unadjusted** | 0.568 | (0.515, 0.625) | <0.001 | \* |
| **Estimated effect of fingolimod (vs. teriflunomide), adjusted** | 0.550 | (0.495, 0.610) | <0.001 | \* |
| Age (years) | 0.994 | (0.989, 0.999) | 0.025 | \* |
| Female | 1.151 | (1.019, 1.300) | 0.023 | \* |
| US geographic region (vs. South) |  |  |  |  |
| Northeast | 1.053 | (0.922, 1.202) | 0.446 |  |
| North central | 1.034 | (0.910, 1.175) | 0.610 |  |
| Other (i.e., West or unknown) | 1.030 | (0.894, 1.186) | 0.687 |  |
| Insurance type (vs. preferred provider organization) |  |  |  |  |
| Health maintenance organization (HMO) | 1.070 | (0.916, 1.250) | 0.393 |  |
| Other | 1.137 | (1.016, 1.272) | 0.025 | \* |
| Index year (vs. 2012) |  |  |  |  |
| 2013 | 1.020 | (0.860, 1.211) | 0.820 |  |
| 2014 | 0.939 | (0.784, 1.125) | 0.493 |  |
| 2015 | 0.948 | (0.783, 1.148) | 0.585 |  |
| Symptoms during the 1-year baseline period |  |  |  |  |
| Demyelinating disease of CNS, unspecified | 0.839 | (0.699, 1.006) | 0.058 |  |
| Disorders of optic nerve and visual pathways | 1.004 | (0.882, 1.143) | 0.948 |  |
| General symptoms: dizziness and giddiness | 1.026 | (0.869, 1.212) | 0.762 |  |
| General symptoms: fatigue/malaise | 1.117 | (1.004, 1.244) | 0.043 | \* |
| Neurogenic bladder NOS | 1.258 | (1.047, 1.512) | 0.015 | \* |
| Other causes of myelitis | 1.029 | (0.636, 1.666) | 0.907 |  |
| Other disorders of soft tissues: neuralgia, neuritis, and radiculitis, unspecified | 0.833 | (0.616, 1.126) | 0.235 |  |
| CCI1 during the 1-year baseline period | 1.025 | (0.976, 1.077) | 0.320 |  |
| Number of relapses during the 1-year baseline period | 1.116 | (1.048, 1.188) | <0.001 | \* |
| Use of ≥1 DMT during the 1-year baseline period | 0.795 | (0.719, 0.880) | <0.001 | \* |
|  |  |  |  |  |
| *\* p-value < 0.05; HR: Hazard ratio; CI: Confidence interval; US: United States; CNS: Central nervous system; NOS: Not otherwise specified; CCI: Charlson comorbidity index; DMT: Disease modifying therapy* |

**Table S6. Univariate and multivariable negative binomial regressions of ARR**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **IRR** | **95% CI** | **P-value** |
|  |  |  |  |  |
| **Estimated effect of fingolimod (vs. teriflunomide) on ARR, unadjusted** | 0.77 | (0.67, 0.88) | <0.001 | \* |
| **Estimated effect of fingolimod (vs. teriflunomide) on ARR, adjusted** | 0.78 | (0.68, 0.89) | <0.001 | \* |
| Age (years) | 1.00 | (0.99, 1.01) | 0.705 |  |
| Female | 1.20 | (1.02, 1.42) | 0.026 | \* |
| Census region (vs. South) |  |  |  |  |
| Northeast | 1.04 | (0.87, 1.24) | 0.669 |  |
| North central | 1.17 | (1.00, 1.39) | 0.057 |  |
| Other (i.e., West or unknown) | 1.06 | (0.88, 1.28) | 0.547 |  |
| Insurance type (vs. preferred provider organization) |  |  |  |  |
| Health maintenance organization (HMO) | 1.19 | (0.98, 1.45) | 0.087 |  |
| Other | 0.94 | (0.81, 1.10) | 0.457 |  |
| Index year (vs. 2012) |  |  |  |  |
| 2013 | 0.97 | (0.76, 1.24) | 0.816 |  |
| 2014 | 0.94 | (0.74, 1.21) | 0.646 |  |
| 2015 | 1.12 | (0.87, 1.44) | 0.370 |  |
| Symptoms during 1-year baseline period |  |  |  |  |
| Demyelinating disease of CNS, unspecified | 0.87 | (0.69, 1.10) | 0.232 |  |
| Disorders of optic nerve and visual pathways | 1.00 | (0.85, 1.18) | 0.978 |  |
| General symptoms: dizziness and giddiness | 1.10 | (0.90, 1.35) | 0.359 |  |
| General symptoms: fatigue/malaise | 1.29 | (1.13, 1.48) | <0.001 | \* |
| Neurogenic bladder NOS | 1.41 | (1.13, 1.75) | 0.002 | \* |
| Other causes of myelitis | 1.45 | (0.81, 2.58) | 0.207 |  |
| Other disorders of soft tissues: neuralgia, neuritis, and radiculitis, unspecified | 1.19 | (0.85, 1.65) | 0.309 |  |
| CCI during 1-year baseline period | 1.12 | (1.06, 1.19) | <0.001 | \* |
| Number of relapses during 1-year baseline period | 1.66 | (1.55, 1.78) | <0.001 | \* |
| Use of ≥1 DMT during 1-year baseline period | 1.02 | (0.89, 1.17) | 0.739 |  |
|   |   |   |   |   |
|  |  |  |  |  |

\*p-value < 0.05; *ARR* Annualized relapse rate, *CCI* Charlson comorbidity index, *CI* Confidence interval, *CNS* Central nervous system, *DMT* Disease modifying therapy, *IRR* Incidence rate ratio, *NOS* Not otherwise specified

**Notes:** ARR was calculated as the number of relapses divided by total time at risk (in years). Time at risk started at the index date and ended at one year after the index date or end of eligibility, whichever occurred first. The multivariable analysis of ARR was conducted using a negative binomial regression model with number of relapses (numerator of ARR) as the dependent variable and the natural logarithm of years at risk (denominator of ARR) as the offset variable. Baseline characteristics were included as control variables.

**Table S7. Univariate and multivariable logistic regressions of adherence measured by MPR ≥80%**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Odds Ratio** | **95% CI** | **P-value** |
|  |  |  |  |  |
| **Estimated effect of fingolimod (vs. teriflunomide) on MPR ≥80%, unadjusted** | 1.75 | (1.45, 2.12) | <0.001 | \* |
| **Estimated effect of fingolimod (vs. teriflunomide) on MPR ≥80%, adjusted** | 1.94 | (1.58, 2.39) | <0.001 | \* |
| Age (years) | 1.02 | (1.01, 1.03) | <0.001 | \* |
| Female | 0.92 | (0.73, 1.17) | 0.506 |  |
| Census region (vs. South) |  |  |  |  |
| Northeast | 1.11 | (0.85, 1.44) | 0.456 |  |
| North central | 1.21 | (0.93, 1.57) | 0.156 |  |
| Other (i.e., West or unknown) | 1.12 | (0.85, 1.46) | 0.430 |  |
| Insurance type (vs. preferred provider organization) |  |  |  |  |
| Health maintenance organization (HMO) | 0.78 | (0.59, 1.04) | 0.087 |  |
| Other | 1.08 | (0.85, 1.37) | 0.539 |  |
| Index year (vs. 2012) |  |  |  |  |
| 2013 | 0.95 | (0.68, 1.33) | 0.787 |  |
| 2014 | 1.19 | (0.84, 1.69) | 0.317 |  |
| 2015 | 1.28 | (0.89, 1.84) | 0.188 |  |
| Symptoms during 1-year baseline period |  |  |  |  |
| Demyelinating disease of CNS, unspecified | 1.19 | (0.83, 1.70) | 0.334 |  |
| Disorders of optic nerve and visual pathways | 1.01 | (0.78, 1.31) | 0.928 |  |
| General symptoms: dizziness and giddiness | 0.94 | (0.68, 1.30) | 0.702 |  |
| General symptoms: fatigue/malaise | 0.92 | (0.74, 1.14) | 0.433 |  |
| Neurogenic bladder NOS | 1.40 | (0.91, 2.17) | 0.130 |  |
| Other causes of myelitis | 0.84 | (0.32, 2.17) | 0.716 |  |
| Other disorders of soft tissues: neuralgia, neuritis, and radiculitis, unspecified | 1.25 | (0.68, 2.29) | 0.480 |  |
| CCI during 1-year baseline period | 0.91 | (0.83, 1.00) | 0.044 | \* |
| Number of relapses during 1-year baseline period | 1.03 | (0.90, 1.17) | 0.693 |  |
| Use of ≥1 DMT during 1-year baseline period | 1.11 | (0.91, 1.36) | 0.322 |  |
|   |   |   |   |   |
|  |  |  |  |  |

\*p-value < 0.05; *CCI* Charlson comorbidity index, *CI* Confidence interval, *CNS* Central nervous system, *DMT* Disease modifying therapy, *MPR* Medication possession ratio, *NOS* Not otherwise specified

**Notes:** MPR was calculated as the fraction of days with an available index drug supply out of the total number of days during the measurement period (from index date until the earliest of index drug discontinuation date, end of continuous eligibility, or one year after the index date).

**Table S8. Multivariable logistic regression of adherence measured by PDC ≥80%**

|  |  |  |  |
| --- | --- | --- | --- |
|   | **Odds Ratio** | **95% CI** | **P-value** |
|  |  |  |  |  |
| **Estimated effect of fingolimod (vs. teriflunomide) on PDC ≥80%, unadjusted** | 2.25 | (1.93, 2.61) | <0.001 | \* |
| **Estimated effect of fingolimod (vs. teriflunomide) on PDC ≥80%, adjusted** | 2.33 | (1.98, 2.74) | <0.001 | \* |
| Age (years) | 1.01 | (1.00, 1.02) | 0.005 | \* |
| Female | 0.82 | (0.68, 0.98) | 0.032 | \* |
| Census region (vs. South) |  |  |  |  |
| Northeast | 0.90 | (0.73, 1.11) | 0.347 |  |
| North central | 0.97 | (0.80, 1.18) | 0.777 |  |
| Other (i.e., West or unknown) | 0.86 | (0.68, 1.08) | 0.187 |  |
| Insurance type (vs. preferred provider organization) |  |  |  |  |
| Health maintenance organization (HMO) | 0.90 | (0.71, 1.15) | 0.417 |  |
| Other | 0.94 | (0.78, 1.12) | 0.471 |  |
| Index year (vs. 2012) |  |  |  |  |
| 2013 | 0.87 | (0.66, 1.14) | 0.301 |  |
| 2014 | 0.99 | (0.75, 1.31) | 0.934 |  |
| 2015 | 0.91 | (0.67, 1.23) | 0.532 |  |
| Symptoms during 1-year baseline period |  |  |  |  |
| Demyelinating disease of CNS, unspecified | 1.14 | (0.87, 1.50) | 0.353 |  |
| Disorders of optic nerve and visual pathways | 1.13 | (0.92, 1.39) | 0.244 |  |
| General symptoms: dizziness and giddiness | 0.94 | (0.73, 1.23) | 0.669 |  |
| General symptoms: fatigue/malaise | 0.89 | (0.75, 1.06) | 0.196 |  |
| Neurogenic bladder NOS | 0.90 | (0.66, 1.22) | 0.494 |  |
| Other causes of myelitis | 1.99 | (0.77, 5.10) | 0.153 |  |
| Other disorders of soft tissues: neuralgia, neuritis, and radiculitis, unspecified | 0.94 | (0.60, 1.46) | 0.773 |  |
| CCI during 1-year baseline period | 0.97 | (0.90, 1.05) | 0.455 |  |
| Number of relapses during 1-year baseline period | 0.84 | (0.76, 0.93) | 0.001 | \* |
| Use of ≥1 DMT during 1-year baseline period | 1.31 | (1.11, 1.53) | 0.001 | \* |
|   |   |   |   |   |

\*p-value < 0.05; *CCI* Charlson comorbidity index, *CI* Confidence interval, *CNS* Central nervous system, *DMT* Disease modifying therapy, *NOS* Not otherwise specified, *PDC* Proportion of days covered

**Notes:** Patients were included in the estimation of PDC only if they had one year of continuous health plan enrollment following the index date. PDC was calculated as the fraction of days with an available index drug supply out of a fixed interval of 365 days.

**Figure S1. Time to first relapse**



\*p-value < 0.05; *IQR* Interquartile range*; NR* Not reached

†Median time to first relapse was not reached in the fingolimod cohort, as the cumulative proportion of patients experiencing relapse was below 50% at the end of the available post-index follow-up.

**Figure S2. Time to treatment discontinuation**



\*p-value < 0.05; *IQR* Interquartile range*; NR* Not reached