Cost-effectiveness Of Ofatumumab In Comparison With Other Disease Modifying Therapies And Best Supportive Care For The Treatment Of Relapsing-Remitting Multiple Sclerosis In Canada

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Poster number: 3753
Session name: P1 – Poster Session 1
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Poster Presentation at the American Academy of Neurology (AAN) 2022, April 2-7, 2021
Soukaïna Mouallif and François Blanchette are employees of Novartis Pharmaceutical Canada Inc.

Kim Thomas, Barkha P. Patel, and Daniel Grima are employees of CRG-EVERSANA Canada Inc. which received funding from Novartis Pharmaceutical Canada Inc. to conduct this analysis.

Nicholas Adlard is an employee of Novartis International AG.

Philip Cooney is an employee of Novartis Ireland Limited.

Virender Bhan has received compensation for activity with Biogen, BMS, Celgene, EMD Serono, Genzyme, Novartis, Roche, Sanofi and Teva.

Moogeh Baharnoori has received compensation for advisory board/consulting services to Alexion, Biogen, BMS, EMD Serono, Novartis, Pendopharm, Genzyme, Teva Neuroscience, Roche and Xfacto communications.

Fraser Clift has received compensation for activity with Biogen, BMS, Celgene, EMD Serono, Genzyme, Novartis, Roche, Sanofi and Teva.

Funding source: This study is supported by Novartis Pharmaceutical Canada Inc.
• Ofatumumab is the first fully human monoclonal anti-CD20 antibody approved in Canada for the initial treatment of relapsing-remitting multiple sclerosis (RRMS) with active disease

• A network meta-analysis (NMA) demonstrated that ofatumumab has similar effectiveness to other highly efficacious monoclonal antibody therapies with respect to reducing relapse rates and disability progression\(^1\)

• Ofatumumab has a favourable safety profile that is similar to the widely used first-line disease modifying therapy (DMT), teriflunomide\(^2\)

• It is important to assess the cost effectiveness of ofatumumab compared to currently available DMTs for RRMS

DMT: disease modifying therapy; NMA: network meta-analysis; RRMS: relapsing-remitting multiple sclerosis.
• To evaluate the cost effectiveness of ofatumumab against other DMTs and best supportive care for the treatment of adult patients with RRMS from a Canadian public healthcare system perspective

DMT: disease modifying therapy; RRMS: relapsing-remitting multiple sclerosis.
• **Model overview**

  o A Markov cohort model with 10 total health states representing disability status defined by the Expanded Disability Status Scale (EDSS) levels 0 to 9 and a single state for death (EDSS 10) was constructed
    - Run over 65-years using annual cycle lengths
    - Costs and effects discounted at 1.5% per annum
    - 100% treatment discontinuation imposed at 10 years
    - Analyses conducted probabilistically using an incremental analysis considering dominance
  
  o Baseline patient distribution was informed by a pooled analysis of the ASCLEPIOS trials

  o Each year, patients could transition between EDSS states, experience a relapse, discontinue therapy, or die (Figure 1; next slide)

EDSS: Expanded Disability Status Scale.
Methods

**Figure 1. Model Structure**

Time horizon = 65 years/cycle length = 1 year

Rounded squares: health states; rounded rectangles: events that patients could experience at any time. Patients who reached an EDSS score of $\geq 7$ while on treatment would discontinue and receive BSC.

BSC: best supportive care; EDSS: Expanded Disability Status Scale.
• **Natural history data**

  - Transition probabilities between EDSS states were informed by the British Columbia MS database\(^3\)
  
  - Annualized relapse rates (ARR) were EDSS-dependent\(^4\)-\(^6\)
  
  - Relapse severity was defined as mild (47%), moderate (35%) or severe (18%)\(^7\)
  
  - Mortality rates were adjusted for the MS population using an EDSS-dependent MS-specific hazard ratio\(^8\)

ARR: annualized relapse rates; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis.

Methods

- **Treatment-specific model inputs**
  - Treatment effects for each DMT were modelled using hazard ratios for 6-month confirmed disability progression and ARR from an NMA\(^1\).
  - Discontinuation rates for each DMT were calculated using the relative effect estimates from the NMA using ofatumumab as a reference arm\(^1\).
  - Discontinuation rates for first-line DMTs were constant for 9 years, followed by 100% discontinuation at 10 years based on clinician opinion; the discontinuation rate for cladribine was adjusted to 16% after 2 years\(^9\).
  - Adverse event probabilities were modelled as non-serious and serious, sourced from each of the treatments’ pivotal trials, or from a pivotal trial where the treatment was a comparator.

ARR: annualized relapse rates; DMT: disease modifying therapy; NMA: network meta-analysis.
Methods

**Cost inputs**

- Direct medical costs for EDSS 1 to 6 were sourced from Grima et al.\(^{10}\), while EDSS 7 to 9 costs were extrapolated based on Patwardhan et al.\(^{11}\)

- Professional care costs were added to the total health state costs\(^{12}\)

- Mild/moderate relapse costs ($7,275) were informed by Karampampa et al.\(^{12}\)

- Severe relapse costs ($17,459) were extrapolated based on Patwardhan et al.\(^{11}\)

EDSS: Expanded Disability Status Scale.

• **Cost inputs - continued**

  - Drug acquisition costs (**Table 1; next slide**) were sourced from Ontario formularies\textsuperscript{13,14} and manufacturer anticipated list price for ofatumumab

  - Administration and monitoring costs (**Table 1; next slide**) were sourced from the Ontario Schedule of Benefits\textsuperscript{15,16}, Ontario Case Costing Initiative\textsuperscript{17}, formularies\textsuperscript{13,14}, published literature\textsuperscript{18}, and clinician opinion

  - Costs for a physician visit and an MS Day Case admission were assumed for non-serious adverse events ($84)\textsuperscript{16} and serious adverse events ($363)\textsuperscript{17}, respectively

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MS: multiple sclerosis.

### Methods

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug cost (Year 1)</th>
<th>Drug cost (Year 2)</th>
<th>A&amp;M cost (Year 1)</th>
<th>A&amp;M cost (Year 2+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case analysis (first-line therapies)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab(^a)</td>
<td>$30,917</td>
<td>$26,500</td>
<td>$1,136</td>
<td>$38</td>
</tr>
<tr>
<td>Ocrelizumab(^1^4)</td>
<td>$32,600</td>
<td>$32,600</td>
<td>$3,374</td>
<td>$1,581</td>
</tr>
<tr>
<td>Teriflunomide(^1^4)</td>
<td>$22,005</td>
<td>$22,005</td>
<td>$1,196</td>
<td>$38</td>
</tr>
<tr>
<td>Dimethyl fumarate(^1^4)</td>
<td>$26,606</td>
<td>$26,863</td>
<td>$1,141</td>
<td>$74</td>
</tr>
<tr>
<td>Glatiramer acetate(^1^3)</td>
<td>$11,834</td>
<td>$11,834</td>
<td>$1,125</td>
<td>$38</td>
</tr>
<tr>
<td>Avonex(^1^4)</td>
<td>$24,886</td>
<td>$24,886</td>
<td>$1,261</td>
<td>$84</td>
</tr>
<tr>
<td>Rebif 22(^1^4)</td>
<td>$23,610</td>
<td>$23,610</td>
<td>$1,261</td>
<td>$84</td>
</tr>
<tr>
<td>Rebif 44(^1^4)</td>
<td>$28,743</td>
<td>$28,743</td>
<td>$1,261</td>
<td>$84</td>
</tr>
<tr>
<td>Betaseron(^1^4)</td>
<td>$20,089</td>
<td>$20,089</td>
<td>$1,631</td>
<td>$70</td>
</tr>
<tr>
<td>Extavia(^1^4)</td>
<td>$19,119</td>
<td>$19,119</td>
<td>$1,631</td>
<td>$70</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td><strong>Scenario analysis (second-line therapies)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cladribine(^b,^1^4)</td>
<td>$44,968</td>
<td>$44,968</td>
<td>$1,158</td>
<td>$82</td>
</tr>
<tr>
<td>Natalizumab(^1^4)</td>
<td>$46,911</td>
<td>$46,911</td>
<td>$6,397</td>
<td>$3,681</td>
</tr>
<tr>
<td>Fingolimod(^1^3)</td>
<td>$26,996</td>
<td>$26,996</td>
<td>$1,682</td>
<td>$84</td>
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</tbody>
</table>

*Canadian dollars. \(^a\)Manufacturer’s submitted price; \(^b\)Cost for cladribine was only applied in Year 2 unless a patient was treated with a third dose, in which case the cost would also be applied to Year 3; Year 2+: year 2 and beyond. A&M = administration and monitoring.

• Utilities and Disutilities

  o Mean utility values were derived from normative utility data for the Canadian population (EDSS 0)\(^{19}\) and a Canadian study of MS patients (EDSS 1 to 9)\(^{20}\)

  o Relapse disutilities distinguished between mild or moderate and severe relapses and have been used in previous economic models\(^{21-23}\)

  o Disutilities for adverse events were based on assumptions and aligned with previous MS economic models\(^{4}\)

EDSS: Expanded Disability Status Scale; MS: multiple sclerosis.

• Considering DMTs with a first-line indication in pair-wise analyses, ofatumumab was dominant (more efficacy, lower costs) vs. teriflunomide, interferons, dimethyl fumarate, and ocrelizumab

• Ofatumumab resulted in incremental cost-effectiveness ratios (ICERs) of $24,177 CAD per quality-adjusted life-year (QALY) gained vs. glatiramer acetate and $28,034 vs. best supportive care (Table 2; next slide)

• Considering dominance in an incremental analysis resulted in only ofatumumab and best supportive care on the efficiency frontier; ofatumumab had an ICER of $28,034 vs. best supportive care

• At a willingness to pay threshold of $50,000/QALY gained, ofatumumab had the highest probability of being cost effective at 63.3%

• Scenario analysis results against DMTs with a second-line indication are presented in Table 2 (next slide); at a willingness to pay threshold of $50,000/QALY gained, ofatumumab had the highest probability of being cost effective at 40.9%

DMT: disease modifying therapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.
### Results

**Table 2. Results of the base case and scenario probabilistic analyses (pair-wise comparisons)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total cost (CAD)</th>
<th>QALY</th>
<th>Incremental cost (CAD)</th>
<th>Incremental QALY</th>
<th>ICER ($ per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case analysis (first-line therapies)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>$743,015</td>
<td>9.261</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>$784,832</td>
<td>9.131</td>
<td>-$41,817</td>
<td>0.130</td>
<td>Dominant†</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>$761,998</td>
<td>7.933</td>
<td>-$18,983</td>
<td>1.328</td>
<td>Dominant†</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>$771,029</td>
<td>8.327</td>
<td>-$28,014</td>
<td>0.934</td>
<td>Dominant†</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>$713,474</td>
<td>8.039</td>
<td>-$29,541</td>
<td>1.222</td>
<td>$24,177</td>
</tr>
<tr>
<td>Avonex</td>
<td>$770,188</td>
<td>8.102</td>
<td>-$27,173</td>
<td>1.159</td>
<td>Dominant†</td>
</tr>
<tr>
<td>Rebif 22</td>
<td>$756,048</td>
<td>8.072</td>
<td>-$13,033</td>
<td>1.189</td>
<td>Dominant†</td>
</tr>
<tr>
<td>Rebif 44</td>
<td>$781,810</td>
<td>7.978</td>
<td>-$38,795</td>
<td>1.283</td>
<td>Dominant†</td>
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<tr>
<td>Betaseron</td>
<td>$759,927</td>
<td>8.025</td>
<td>-$16,911</td>
<td>1.236</td>
<td>Dominant†</td>
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<tr>
<td>Extavia</td>
<td>$755,037</td>
<td>8.021</td>
<td>-$12,022</td>
<td>1.240</td>
<td>Dominant†</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>$689,506</td>
<td>7.352</td>
<td>$53,509</td>
<td>1.909</td>
<td>$28,034</td>
</tr>
<tr>
<td><strong>Scenario analysis (second-line therapies)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cladribine</td>
<td>$715,734</td>
<td>8.725</td>
<td>$27,282</td>
<td>0.536</td>
<td>$50,899</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>$869,833</td>
<td>9.123</td>
<td>-$126,818</td>
<td>0.138</td>
<td>Dominant†</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>$772,790</td>
<td>8.410</td>
<td>-$29,775</td>
<td>0.851</td>
<td>Dominant†</td>
</tr>
</tbody>
</table>

*Canadian dollars.†Ofatumumab dominant vs. comparator; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.*
Conclusions

- Ofatumumab is cost effective against all comparators and dominant compared to all currently approved and reimbursed DMTs with a first-line indication, except glatiramer acetate, from a Canadian public healthcare system perspective.

- Cost savings associated with ofatumumab suggest greater disease management, reflected by increased QALYs gained, at a lower cost.

- Ofatumumab’s cost effectiveness, alongside its high-efficacy and favourable safety profile, demonstrate its value as an early treatment option in RRMS.

References