Triptans for the acute treatment of migraine: a drug class review

Final report and reimbursement option recommendations

April 2014
Ontario Drug Policy Research Network
The Ontario Drug Policy Research Network (ODPRN) is funded to conduct drug class reviews as part of an initiative to modernize the public drug formulary in Ontario. As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP), Ministry of Health and Long-Term Care to select key priority areas and topics for formulary modernization, then conducts independent drug class reviews. The results of each of these reviews are disseminated directly to the OPDP to facilitate informed decision making on public drug funding policies.

Conflict of Interest Statement
Muhammad Mamdani was a member of an advisory board for Hoffman La Roche, Pfizer, Novartis, GlaxoSmithKline and Eli Lilly Canada. Nav Persaud is an associate editor for the Canadian Medical Association Journal.

No other study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the Triptan Drug Class Review.

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**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AB</td>
<td>Alberta</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>BC</td>
<td>British Columbia</td>
</tr>
<tr>
<td>CED</td>
<td>Committee to Evaluate Drugs</td>
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<td>CDR</td>
<td>Common Drug Review</td>
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<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
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<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>EAP</td>
<td>Exceptional Access Program</td>
</tr>
<tr>
<td>FDA</td>
<td>Food Drug Administration</td>
</tr>
<tr>
<td>GB</td>
<td>General benefit</td>
</tr>
<tr>
<td>ICES</td>
<td>Institute for Clinical Evaluative Sciences</td>
</tr>
<tr>
<td>LU</td>
<td>Limited use</td>
</tr>
<tr>
<td>MB</td>
<td>Manitoba</td>
</tr>
<tr>
<td>MOHLTC</td>
<td>Ministry of Health and Long-term Care</td>
</tr>
<tr>
<td>NB</td>
<td>New Brunswick</td>
</tr>
<tr>
<td>NIHB</td>
<td>Non-insured Health Benefits</td>
</tr>
<tr>
<td>NL</td>
<td>Newfoundland</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>NS</td>
<td>Nova Scotia</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NT</td>
<td>Northwest Territories</td>
</tr>
<tr>
<td>NU</td>
<td>Nunavut</td>
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<tr>
<td>ODB</td>
<td>Ontario Drug Benefit</td>
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<td>ODPRN</td>
<td>Ontario Drug Policy Research Network</td>
</tr>
<tr>
<td>ODT</td>
<td>Oral disintegrating tablet</td>
</tr>
<tr>
<td>ON</td>
<td>Ontario</td>
</tr>
<tr>
<td>OPDP</td>
<td>Ontario Public Drug Programs</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-the-counter</td>
</tr>
<tr>
<td>PEI</td>
<td>Prince Edward Island</td>
</tr>
<tr>
<td>Q3</td>
<td>Third quarter</td>
</tr>
<tr>
<td>QC</td>
<td>Quebec</td>
</tr>
<tr>
<td>SD</td>
<td>Standard dose</td>
</tr>
<tr>
<td>SK</td>
<td>Saskatchewan</td>
</tr>
<tr>
<td>SMH</td>
<td>St. Michael’s Hospital</td>
</tr>
<tr>
<td>SNRI</td>
<td>Selective serotonin/norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>YK</td>
<td>Yukon Territories</td>
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Executive Summary

In Ontario, most triptans (i.e., almotriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan) are currently available through the publicly funded drug program via the Exceptional Access Program (EAP). As part of the formulary modernization review, an evaluation of triptans for the acute treatment of migraine in adults was undertaken to provide recommendations for funding changes of these drugs in Ontario, if appropriate. Potential issues identified during the review included medication overuse headache with frequent use of triptans, varying reimbursement policies among provinces and current EAP process viewed by some clinicians as being too restrictive.

Key Considerations for Reimbursement Options

Efficacy and Safety

Overall, triptans were found to be efficacious for the treatment of acute migraine. There was no high quality evidence of differences between the triptans in terms of efficacy, safety (e.g., cardiovascular events, risk of serotonin syndrome) and tolerability. However, a potential concern with frequent use of triptans (i.e., >9 days of use per month) is development of medication overuse headache. Quantity limits have been used to help decrease the risk of medication overuse headache as well as to curb the costs of triptans in public and private drug programs.

Accessibility

Ontario has among the lowest rates of publicly-funded triptan use in Canada. Despite the availability of triptans through EAP, some physicians perceived that accessing triptans through EAP was a particularly significant and cumbersome barrier. Proposed general benefit or limited use reimbursement options would potentially expand triptan use by 1900% (from 1218 patients to 24,000 patients). Actions to streamline the current EAP process (e.g., use of a standardized form) may increase the number of ODB-eligible patients receiving triptans, although the extent of this potential increase is unknown.

Pharmacoeconomics

Projected cost analyses based on various hypothetical reimbursement models were performed to determine the economic impact of various policy options. Proposed EAP strategies suggest a reduction in total triptan costs (approximately $1.1-1.4 million, or 69-84% reduction), while alternative general benefit/limited-use strategies suggest an increase in total costs (approximately $2.4-5.3 million, or 139% to 302% increase). Currently, generic interchangeability in not enforced through the EAP program, and as a result, Ontario has the highest quarterly costs per user when compared to other provinces.

Reimbursement Options

Three main reimbursement options for triptans currently available through EAP (i.e., almotriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan) are proposed.
Option 1: General benefit listing for triptans
- When generic products are available (i.e., for all listed oral triptans and injectable sumatriptan), a 25% generic pricing agreement would be in effect.

Option 2: Limited use listing for triptans with quantity limit of 12 doses/month
- Impose enforced quantity limit of 12 doses per month.
- When generic products are available, then 25% generic pricing agreement would be in effect.

Options 3a and 3b: Exceptional Access Program (EAP) for triptans
Option 3a:
- When generic products are available, then the 25% generic pricing agreement would be in effect.
Option 3b:
- When generic products are available, then the 25% generic pricing agreement would be in effect.
- Impose quantity limit of 12 doses per month

Recommendation
Triptans are an effective and safe treatment for the management of acute migraine. However, under the current Exceptional Access Program in Ontario, only a fraction of potentially eligible patients are receiving this medication. Based on the results of the review, input from stakeholders and feedback from the ODPRN Citizens’ Panel, two primary reimbursement options for triptans are recommended as funding alternatives for the Ontario Public Drug Program:
- Limited use with quantity limit of 12 per month
  OR
- Exceptional Access Program (EAP) with generic pricing, quantity limit of 12 per month, revised criteria and a streamlined application process
# Table of Contents

- Ontario Drug Policy Research Network ................................................................. 2
- Conflict of Interest Statement ............................................................................. 2
- Acknowledgments ................................................................................................. 2
- Study Team ........................................................................................................... 2
- List of Abbreviations ............................................................................................ 3
- Executive Summary .............................................................................................. 4
  - Key Considerations for Reimbursement Options ............................................. 4
  - Reimbursement Options ................................................................................... 4
  - Recommendation ............................................................................................... 5
- List of Exhibits ..................................................................................................... 8
- Introduction .......................................................................................................... 9
- Rationale for Review ........................................................................................... 9
- Objective .............................................................................................................. 9
- Methods ............................................................................................................... 9
- Overview ............................................................................................................. 10
  - Migraine prevalence ......................................................................................... 10
  - Treatment strategies ......................................................................................... 10
  - Public plan reimbursement of triptans in Canada .......................................... 11
- Perspectives of Patients and Healthcare Providers .............................................. 12
  - Patient impact ................................................................................................. 12
  - Challenges in appropriately treating acute migraines .................................... 13
  - Accessibility of triptans ................................................................................... 13
- Current Utilization in Canada ............................................................................. 13
- Efficacy ................................................................................................................. 15
  - Triptans vs. placebo ........................................................................................ 15
  - Functional Status .............................................................................................. 16
  - Triptans vs. triptans ........................................................................................ 17
  - Triptans vs. non-triptan treatments for migraines ............................................ 18
Safety and tolerability.................................................................................................................. 18
Commonly reported adverse events ......................................................................................... 18
Cardiovascular and cerebrovascular adverse events.............................................................. 18
Serotonin syndrome .................................................................................................................. 18
Use in the elderly ......................................................................................................................... 18
Medication overuse headache.................................................................................................... 19
Quantity Limits........................................................................................................................... 19
Advantages of quantity limits .................................................................................................... 19
Disadvantages of quantity limits............................................................................................... 19
Consideration for quantity limits for triptans.......................................................................... 20
Use of quantity limits in Canada .............................................................................................. 20
Potential triptan overuse in Canada .......................................................................................... 20
Pharmacoeconomics.................................................................................................................. 21
Cost-effectiveness literature review ......................................................................................... 21
Reimbursement-based economic assessment ............................................................................ 21
Health Equity Issues.................................................................................................................. 23
Accessibility of triptans .............................................................................................................. 23
Use in elderly ............................................................................................................................. 24
Use in women ............................................................................................................................ 24
Reimbursement Options for Consideration ............................................................................ 24
Key considerations .................................................................................................................... 24
Reimbursement options ............................................................................................................ 25
Other Issues for Consideration ................................................................................................ 29
Stakeholder Review .................................................................................................................. 30
Findings from the ODPRN Citizens’ Panel .............................................................................. 31
Final Policy Recommendations and Conclusion .................................................................... 31
Appendix A: Health Equity Considerations for Triptan Drug Class Review .......................... 35
Appendix B: Assessment of criteria for coverage (for both LU and EAP listing) ..................... 36
Appendix C: Suggested Limited Use and Exceptional Access Program criteria ..................... 39
List of Exhibits

Exhibit 1: Public plan listings in Canada .............................................................. 12
Exhibit 2: Population-adjusted utilization of non-provincially funded triptans in Canada by province .... 14
Exhibit 3: Population-adjusted utilization of provincially-funded triptans in Canada, by province ......... 14
Exhibit 4: Percent of patients* and Number-Needed-to-Treat (NNT) for headache relief at 2 hours,
freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at
hours, and use of rescue medications* ................................................................. 16
Exhibit 5: Functional status-odds ratios of triptans compared to placebo ........................................ 17
Exhibit 6: Head-to-head comparisons of the triptans on the outcomes: headache relief at 2 hours,
freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at
hours, and use of rescue medications* .................................................................. 17
Exhibit 7: Potential Triptan Overuse, By Province in 2012 ......................................................... 21
Exhibit 8: Reimbursement strategies for triptans ........................................................................ 23
Exhibit 9: Assessment of Reimbursement Options ..................................................................... 27
Exhibit 10: Final Ranking of Policy Options ............................................................................. 31
Introduction
Migraine is a common and potentially disabling neurological condition affecting approximately 10-15% of Canadians (about 4 million people). The condition causes short and long-term disability, reduces quality of life, and often impacts work productivity, social relationships and family life. The acute management of migraines includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, ergots, opioids and triptans. Triptans (serotonin receptor agonists, 5-hydroxytryptamine agonists), regarded as specific anti-migraine treatment options, are generally considered to be effective, well tolerated and safe medications for the treatment of acute migraines. For many patients with moderate to severe migraine, triptans are considered first-line therapy.

This report outlines the key findings for each of the components of the review. More detailed information for each of the reviews can be found on the ODPRN website: www.odprn.ca

Rationale for Review
Triptans are available as insured benefits through public drug programs in all Canadian jurisdictions. However, the listing status (either as a general benefit or as a restricted benefit) and the use of monthly quantity limits differ between provinces. In Ontario, five triptans (i.e., almotriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan) are currently available through the publicly funded drug program via the Exceptional Access Program (EAP). Sumatriptan, the first triptan to be reviewed by the Ontario’s Committee to Evaluate Drugs (CED) in 1992, was made available through EAP (previously known as Section 8) due to lack of studies comparing this drug to standard therapy, cost, and potential for misuse for unapproved indications. Subsequent to that decision, other triptans reviewed by the CED were also placed on EAP. Eletriptan and frovatriptan are not funded in Ontario. Many of the triptans are now available generically, possibly making them more attractive from a cost-effectiveness standpoint, and more evidence is available regarding the comparative efficacy and safety of triptans relative to standard therapies.

As part of the formulary modernization review, an evaluation of triptans for the acute treatment of migraine in adults was undertaken to provide recommendations for funding changes of these drugs in Ontario, if appropriate.

Objective
The objective of the triptan drug class review is to provide evidence-informed recommendations for the funding of triptans through the publicly funded drug program in Ontario.

Methods
The comprehensive approach to triptans drug class review is comprised of:
- qualitative analyses of perspectives of patients, pharmacists and prescribers
  - one-on-one semi-structured telephone interviews regarding specific experiences and perceptions relevant to funding policies for triptans,
• environmental scans of:
  o national and international drug policies
  o considerations relating to health equity,
• analysis of real-world drug utilization using:
  o administrative claims data from Ontario and across Canada
  o summaries of relevant observational literature,
• systematic review of the literature,
• reimbursement-based economic analyses.

Results from all of the above components were reviewed and consolidated into a set of options for potential drug reimbursement models. Final recommendations were selected based on feedback from the ODPRN Citizen’s Panel as well as comments received from various stakeholders during the stakeholder review period.

Overview

Migraine prevalence
Migraine headache is a common neurological condition, affecting females more than males. The World Health Organization (WHO) estimates the worldwide prevalence of migraine to be approximately 10% and the lifetime prevalence to be 14%. In Canada, migraine prevalence rates have been estimated to be approximately 23-26% in women and 8-10% in men.

Migraine most frequently begins at puberty, reaching a peak at age 35-54 years. In this age group, the prevalence in females has been shown to be 33%, and in males 8%. Similar to those aged 65 years and younger, the prevalence of migraines in the elderly population has been found to be significantly higher in women than in men. Migraine prevalence in the elderly population (65 years and older) was found to be 1.9% in men and 11.7% in women, with an overall prevalence rate of 7.8%. Analysis of the 2012 Canadian Community Health Survey provides age specific prevalence of migraine of 11.8% for those under 65 and 9.2% for those over 65. A US study suggests that triptans were used by 19.4% of migraineurs aged under 60 and 12.7% of those over 60. These figures would suggest uptake of 2.5% in those under 60 and 0.8% in those over 60.

Treatment strategies
The management of episodic migraine is divided into acute and/or symptomatic strategies (to relieve headache attack) and preventive strategies (to reduce frequency, duration and intensity of attack). Pharmacological management of migraines is generally divided into two categories: non-specific treatments (e.g., acetaminophen, NSAIDs) and specific anti-migraine treatments (e.g., triptans and ergotamine). Nausea associated with migraine headache is often treated with anti-emetics and/or neuroleptic drugs. The Canadian Headache Society Guidelines for the use of acute drug therapy for migraine headaches recommends the use of triptans for migraine headaches that are likely to become moderate or severe.
There are currently seven triptans available in Canada: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan. Various dosage forms are available, including oral tablets, oral disintegrating tablets (ODT), injectable and nasal formulations. Factors to consider in terms of patient preference include use of non-oral routes for patients with migraines associated with severe nausea or vomiting. All oral dosage forms are available through generic manufacturers except for frovatriptan.

**Public plan reimbursement of triptans in Canada**

Triptans are available as insured benefits through all public drug programs in Canada, either as a general benefit or as a restricted benefit. The restricted benefit can be passive (e.g., adjudicated at the pharmacy level) or enforced (e.g., prescriber is required to provide information, often in writing, regarding justification for use of triptans). Triptans are listed as general benefits (without restrictions) in three publically-funded programs, general benefits (with quantity limits) in one, and restricted access in 8 publically-funded programs, including Ontario where they are listed as part of the Exceptional Access Program (EAP) (for details on coverage for publically-funded programs in Canada, see Exhibit 1). Frovatriptan is not covered under any publicly-administered drug plan in Canada because the manufacturer has never made a submission to the Common Drug Review (CDR). Eletriptan is only covered in Quebec. The decision to exclude eletriptan from most provincial formularies (including Ontario) is likely driven by the CDR review in 2005, which recommended not to list this product because: efficacy data showed that eletriptan is equivalent to or no better than other triptans; eletriptan is not more cost-effective than other triptans; and eletriptan has the potential for drug interactions.
Exhibit 1: Public plan listings in Canada

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name and/or generic</th>
<th>BC</th>
<th>AB</th>
<th>SK</th>
<th>MB</th>
<th>ON</th>
<th>QC</th>
<th>NB</th>
<th>NS</th>
<th>PEI</th>
<th>NL</th>
<th>YK</th>
<th>NIHB/NT/NU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eletriptan</td>
<td>Relpax, generic</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Ben</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Frova</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Maxalt, generic</td>
<td>Ben</td>
<td>Res#</td>
<td>Res*</td>
<td>Ben</td>
<td>Res</td>
<td>Res</td>
<td>No</td>
<td>Res</td>
<td>Ben</td>
<td>Ben</td>
<td>Ben***</td>
<td></td>
</tr>
</tbody>
</table>

Quantity Limits (monthly) None None 6 12 None None 6 6 6 6 None 12

No=not listed
Res=restricted listing (enforced); Pas=restricted listing (passive)
Ben=unrestricted listing
*EAP=Exceptional Access Program
**Special authority required for injectable sumatriptan
***General benefit with quantity limits imposed
#Restricted listing enforced for patients 65 years and older
##Restricted listing passive for patients aged 18-64

Perspectives of Patients and Healthcare Providers

Patient impact
Our qualitative analysis found that migraine sufferers may experience significant productivity losses and may become socially isolated during repeated migraine episodes. Migraineurs are consistently anxious that their next migraine will be experienced at an inopportune time (e.g., social event, work) and that they will have no access to medication when they experience a migraine. In addition, patients may experience persistent anxiety associated with migraine management, particularly those who have limits on drug coverage or those with no drug coverage at all.

Triptan users stated that this drug class helped to restore daily functionality and the ability to work. Studies in the literature have supported the concept that triptans reduce migraine-associated lost workplace productivity (both presenteeism and absenteeism), although these studies are industry-funded and there are concerns over the potential bias due to sponsorship.10-12
Challenges in appropriately treating acute migraines
Challenges were identified by the patients and prescribers in appropriately treating acute migraines. Use of over-the-counter analgesics is common but not ideal due to limited effectiveness, potential side effects, addictive properties of some of these drugs as well as their associated risk of medication overuse headache. Although triptans were described as the most effective drug class for the treatment of migraine, finding the most effective triptan for an individual patient can be difficult as some patients may need to try several triptans before one is identified as being effective. This is consistent with published guidelines on the treatment of acute migraines; in general, failure with one triptan does not necessarily predict failure for the entire drug class.\(^{13,14}\)

Accessibility of triptans
Our qualitative analysis found that accessing triptans was a challenge for many patients, especially in terms of affordability. Although most patients interviewed had access to private insurance plans, coverage limitations (e.g., quantity limits) can impact treatment adherence, as patients are anxious about exceeding monthly coverage limits and may use half the recommended dose or may delay the use of triptans until the pain is unbearable, thus leading to reduced efficacy as the best outcomes are achieved with early treatment. For patients with no third party drug coverage, out-of-pocket expenses can be prohibitively expensive due to the high cost of triptans. As well, accessing triptans through EAP for those eligible for Ontario Drug Benefit coverage was described as a particularly significant barrier as many physicians and patients are unaware of the EAP criteria or that triptans can be accessed through the EAP. In addition, the EAP application process to obtain triptans was perceived by physicians to be cumbersome. Patients who are unable to access triptans may have increased use of other healthcare resources. For example, clinical experts cite instances of patients without triptan access who visit the Emergency Room to receive treatment for their poorly managed migraine headaches.

Current Utilization in Canada
Triptan use in Canada has increased by 13% over the past 4 years. Over 3 million units were dispensed in Canada in the third quarter (Q3) of 2013. In Ontario, the overall rates of triptan use and costs were similar to other provinces (7,480 units and $86,133 per 100,000 population in Ontario compared to an average of 7,678 units and $86,588 per 100,000 population across Canada, Q3 2013) (Exhibit 2). However, the Ontario Public Drug Program only paid for 2.8% of all triptan prescriptions dispensed in Ontario, with the majority of triptans being paid for by private drug plans (77.4%) and cash (19.3%). As a result, Ontario has among the lowest rates of publically-funded triptan use in Canada (931 units per 100,000 eligible population in Q3 2013 compared to the national average of 5,358 units per 100,000 eligible Canadians; Exhibit 3), which is balanced by having among the highest rates of triptan use paid by other means (e.g. cash, private insurance; 7,271 units per 100,000 population in Ontario compared to a national average of 6,473 units per 100,000 population across Canada; Q3 2013).
Exhibit 2: Population-adjusted utilization of non-provincially funded triptans in Canada by province

Exhibit 3: Population-adjusted utilization of provincially-funded triptans in Canada, by province
Efficacy
Network meta-analyses were conducted for five efficacy outcomes, namely: headache relief at 2 hours (proportion of patients who felt that the drug had started working by 2 hours), freedom from pain at 2 hours (proportion of patients who felt their headache was completely gone at 2 hours), sustained freedom from pain at 24 hours, headache relief at 24 hours, and use of rescue medication. Functional status was also evaluated. The choice of these outcomes for network meta-analysis was based on their importance and the sufficiency of the data available to derive robust and consistent network models.

Triptans vs. placebo
The systematic review used data from a total of 133 unique randomized controlled trials to conduct network meta-analyses. Overall, triptans were found to be efficacious for the treatment of acute migraine relative to placebo (see Exhibit 4).

- Standard dose (SD) triptans relieved headaches within 2 hours in 43 to 76% of patients. The number of patients needed to treat (NNT) in order for one patient to experience 2 hour headache relief ranged from 3 to 7 patients. In particular, at standard dose, eletriptan tablet, rizatriptan tablet and ODT, sumatriptan subcutaneous injection, and zolmitriptan ODT had a substantive effect on 2 hour headache relief relative to placebo.
- Only 18 to 50% of patients had freedom from pain within 2 hours with SD triptans. The NNT in order for one patient to experience 2 hour freedom from pain ranged from 3 to 15 patients.
- SD triptans provided sustained headache relief at 24 hours in 29 to 50% of patients. Data on sustained headache relief at 24 hours was not available for frovatriptan. The NNT in order for one patient to experience 24 hour headache relief ranged from 4 to 9 patients. Except for low dose rizatriptan tablet, all triptans had a significant effect on sustained headache relief at 24 hours compared to placebo. In particular, SD eletriptan had a substantive effect.
- Only 18 to 33% of patients had sustained freedom from pain at 24 hours. The NNT in order for one patient to experience 24 hour freedom from pain ranged from 5 to 12 patients.
- All triptans SD had a significant effect on reducing use of rescue medications compared to placebo. The NNT for avoiding use of rescue medication ranged from 4-6 patients.
Exhibit 4: Percent of patients\(^+\) and Number-Needed-to-Treat (NNT) for headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications\(^*\)

<table>
<thead>
<tr>
<th></th>
<th>2h headache relief (%)</th>
<th>2h freedom from pain (%)</th>
<th>24h sustained headache relief (%)</th>
<th>24h sustained freedom from pain (%)</th>
<th>Use of rescue medications (%)</th>
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<tr>
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<td>NNT</td>
<td>NNT</td>
<td>NNT</td>
<td>NNT</td>
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<td>52</td>
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<tr>
<td>Tablet SD</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Almotriptan</td>
<td>49*</td>
<td>5</td>
<td>24*</td>
<td>8</td>
<td>36*</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>56*</td>
<td>4</td>
<td>39*</td>
<td>4</td>
<td>47*</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>43*</td>
<td>7</td>
<td>35*</td>
<td>5</td>
<td>--</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>44*</td>
<td>6</td>
<td>18*</td>
<td>15</td>
<td>39*</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>57*</td>
<td>4</td>
<td>37*</td>
<td>4</td>
<td>29*</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>50*</td>
<td>5</td>
<td>28*</td>
<td>6</td>
<td>33*</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>50*</td>
<td>5</td>
<td>27*</td>
<td>7</td>
<td>38*</td>
</tr>
<tr>
<td>ODT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>68*</td>
<td>3</td>
<td>50*</td>
<td>3</td>
<td>--</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>66*</td>
<td>3</td>
<td>37*</td>
<td>4</td>
<td>50*</td>
</tr>
<tr>
<td>Nasal Spray</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>53*</td>
<td>4</td>
<td>21</td>
<td>10</td>
<td>--</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>52*</td>
<td>5</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Subcutaneous Injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>76*</td>
<td>3</td>
<td>37*</td>
<td>10</td>
<td>--</td>
</tr>
</tbody>
</table>

NNT: Number needed to treat  
SD: standard dose  
ODT: oral disintegrating tablet  
+ Percent of patients with outcome based on the odds ratios from the network meta-analysis and mean proportion of patients who experience the outcome in the placebo group  
* p<0.05 indicating that the triptan is significantly better than placebo (comparing the odds ratio of the triptan vs. placebo)

**Functional Status**

Functional status was evaluated by considering the proportion of patients who experienced an improvement in functional disability (usually described as the effort required to perform usual activities and a return to normal function with the use of the study medication). The meta-analyses of functional status are summarized in Exhibit 5 for the standard dose triptans involving different routes of administration. Overall, based on 55 studies involving 11,266 patients on a triptan and 7283 on placebo, functional status is significantly better on triptans compared to placebo (OR 2.54; 95% CI 2.20, 2.92).
### Exhibit 5: Functional status-odds ratios of triptans compared to placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No of participants (studies)</th>
<th>Heterogeneity ($I^2$)</th>
<th>Odds ratio (OR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD Almotriptan Tablet</td>
<td>694 (2 studies)</td>
<td>0%</td>
<td>2.18 (1.60, 2.97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Rizatriptan Tablet</td>
<td>4177 (12 studies)</td>
<td>42%</td>
<td>2.84 (2.32, 3.46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Naratriptan Tablet</td>
<td>1430 (6 studies)</td>
<td>0%</td>
<td>1.84 (1.47, 2.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Sumatriptan Subcutaneous Injection</td>
<td>1178 (6 studies)</td>
<td>43%</td>
<td>5.07 (3.50, 7.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Sumatriptan Nasal Spray</td>
<td>923 (3 studies)</td>
<td>0%</td>
<td>1.73 (1.33, 2.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Eletriptan Tablet</td>
<td>4790 (10 studies)</td>
<td>92%</td>
<td>2.32 (1.43, 3.77)</td>
<td>0.0007</td>
</tr>
<tr>
<td>SD Sumatriptan Tablet</td>
<td>2400 (7 studies)</td>
<td>0%</td>
<td>2.77 (2.28, 3.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Frovatriptan Tablet</td>
<td>672 (2 studies)</td>
<td>72%</td>
<td>1.38 (0.62, 3.10)</td>
<td>0.43</td>
</tr>
<tr>
<td>SD Zolmitriptan Tablet</td>
<td>741 (6 studies)</td>
<td>75%</td>
<td>2.15 (1.40, 3.30)</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

### Triptans vs. triptans

In general, there were more favourable results observed for eletriptan and rizatriptan, compared to other triptans (see Exhibit 6) for efficacy outcomes. Results were less favorable for naratriptan and sumatriptan. Data for frovatriptan at 24 hours were not available, and the results for the 2 hour outcomes were not favourable compared to eletriptan and rizatriptan. In general, use of rescue medications was not significantly different between the triptans, although sumatriptan had a significantly favourable result compared to zolmitriptan.

### Exhibit 6: Head-to-head comparisons of the triptans on the outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications*

<table>
<thead>
<tr>
<th></th>
<th>Almotriptan</th>
<th>Eletriptan</th>
<th>Frovatriptan</th>
<th>Naratriptan</th>
<th>Rizatriptan</th>
<th>Sumatriptan</th>
<th>Zolmitriptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan</td>
<td></td>
<td>●●●●●</td>
<td>○○○○○</td>
<td>●●●○○</td>
<td>●●●○○○</td>
<td>●●●○○○○</td>
<td>○○○○○</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>●●●○○</td>
<td></td>
<td>○○○●●●</td>
<td>○○○○○</td>
<td>●●●○○○</td>
<td>●●●○○○○</td>
<td>○○○○○</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>○○○○○</td>
<td>●●●○○○○○</td>
<td></td>
<td>○○○○○</td>
<td>●●●○○○</td>
<td>●●●○○○○</td>
<td>○○○○○</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>○○○○○</td>
<td>●●●○○○○○</td>
<td>●○○○○</td>
<td></td>
<td>●●●○○○</td>
<td>●●●○○○○</td>
<td>○○○○○</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>○○○○○</td>
<td>●●●○○○○○</td>
<td>○○○○○</td>
<td>●○○○○</td>
<td></td>
<td>●●●○○○○</td>
<td>○○○○○</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>○○○○○</td>
<td>●●●○○○○○</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>●●●○○○</td>
<td></td>
<td>○○○○○</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>○○○○○</td>
<td>●●●○○○○○</td>
<td>○○○○○</td>
<td>●○○○○</td>
<td>●○○○○</td>
<td>●●●○○○</td>
<td></td>
</tr>
</tbody>
</table>

* The 5 contiguous circles correspond, respectively, to the five efficacy outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications.

- The green circle indicates that the ‘row’ triptan is significantly better than the ‘column’ triptan.
- The red circle indicates that the ‘row’ triptan is significantly worse than the ‘column’ triptan.
- The blank circle indicates that there is no significant difference between the ‘row’ and ‘column’ triptan.

A missing circle indicates that the outcome was not available for analysis.
**Triptans vs. non-triptan treatments for migraines**
When compared to active non-triptan treatments, SD triptan tablets (except for naratriptan and frovatriptan) were associated with equal or more favourable results relative to NSAIDs, acetylsalicylic acid (ASA) and acetaminophen with respect to 2-hour outcomes. As well, SD triptans were associated with more favorable results than ergots for 2 hour and 24 hour headache relief and freedom from pain outcomes.

**Safety and tolerability**

**Commonly reported adverse events**
Triptans are generally well tolerated medications; the most commonly reported adverse events include chest tightness and central nervous system symptoms such as dizziness, numbness, tingling and drowsiness. Zolmitriptan oral tablet and to a lesser extent rizatriptan oral tablet were associated with significantly more adverse events compared to placebo, whereas sumatriptan oral tablet was not significantly associated with adverse events.

**Cardiovascular and cerebrovascular adverse events**
The limited data available for serious adverse events (e.g., myocardial infarction, stroke, serious ventricular arrhythmia) makes interpretation difficult; however, based on studies where there were serious adverse events, there was no difference between the triptans and placebo.

Triptans are contraindicated in patients with cardiovascular or cerebrovascular disease. A consensus statement by the American Headache Society, based on review of the literature, indicates that rates of triptan-related cardiovascular events are low, and that triptans are likely safe among patients with no known cardiovascular risks.\(^{15}\)

**Serotonin syndrome**
There has also been concern about the development of serotonin syndrome, especially when triptans are used concomitantly with other drugs that enhance the serotonergic pathways. In 2006, the United States Food and Drug Administration (FDA) issued an alert regarding the potential for serotonin syndrome in patients taking triptans and selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) concomitantly.\(^{16}\) In 2010, the American Headache Society reviewed the literature and stated that the currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs, or the use of triptan monotherapy, due to the concerns for serotonin syndrome.\(^{17}\)

**Use in the elderly**
Recommendations for triptan use in the elderly has been hampered by lack of enrollment of patients over the age of 65 in clinical trials, product monographs cautioning or not recommending use of triptans in the elderly, and the scarcity of evidence relating to the cardiovascular safety of triptans in the elderly. However, despite the lack of information available regarding triptan use in the elderly, triptans are used by patients aged 65 and older. Our pharmacoepidemiologic analysis found that the rate of triptan use in
older public drug plan beneficiaries (aged 65 and older) has increased in all provinces since 2000 (range 11-222 per 100,000 beneficiaries). In addition, over 50% of older triptan users were also treated with an opioid during their course of therapy, and approximately 40% were also treated with NSAIDs. Although the indication for these therapies is unknown, a 50% prevalence of opioid use in this population is much higher than the average population rate, and therefore it is likely that much of this use is for treatment of migraines.

**Medication overuse headache**

A potential concern with frequent use of triptans (and other medications used in the treatment of acute migraine headaches) is development of medication overuse headache.\(^1\) To avoid medication overuse headache, the Canadian Headache Society suggests avoidance of use of triptans, ergots, opioids or combination analgesics on more than 9 days per month (i.e., maximum quantity of 18 tablets, assuming that the patient uses 2 triptan doses/migraine).\(^2\) In reality, it is often difficult to determine if medication overuse headache is a result of triptan utilization, another analgesic medication or a combination of a triptan and another drug.

In a prospective study of 96 patients with medication overuse headache after different acute headache drugs, triptan overuse in 38 patients (39%) led to medication overuse headache approximately 1.7 years after starting a triptan.\(^1\) The number of doses associated with the development of medication overuse headache in this study was 18 single doses per month for triptans although 10 single doses of triptans per month may place some patients at risk for the development of medication overuse headache.

**Quantity Limits**

**Advantages of quantity limits**

Quantity limits for triptans have been used in various jurisdictions, both public and private. The rationale for imposing quantity limits is multi-faceted, with purported clinical as well as economic benefits. From a clinical perspective, quantity limits have been implemented to prevent medication overuse headaches. As well, the use of quantity limits can result in cost-savings for the payer.\(^18\,\,20\)

**Disadvantages of quantity limits**

As described in the qualitative findings and in a broader review of the literature, a potential concern with imposition of severely restrictive quantity limits is that some patients with migraines may delay treatment until the pain is moderate or severe in order to conserve the limited number of tablets allotted per month.\(^21\,\,22\) This strategy is in contrast to that recommended by most guidelines, including the Canadian Headache Society Guideline; in general, it is recommended that patients treat migraine headaches as early as possible during their migraine attacks.\(^2\,\,23\,\,25\)
Consideration for quantity limits for triptans

- In order to avoid medication overuse headache, triptans should be used on no more than 9 days per month\(^2\) (i.e., maximum quantity of 18 tablets, assuming that the patient uses 2 triptan doses/migraine).
- More than 85% of migraine patients experience four or fewer headache occurrences per month (i.e., may require up to 8 tablets/month).\(^{26}\)
- Therefore, a quantity limit of 12 doses has been recommended by some clinicians in order to allow the patient flexibility to treat migraines early, provide cost savings and not to lead to medication overuse headache.\(^{21}\)
- Guidelines suggest that migraine prophylactic therapy should be considered in patients with three or more severe migraine attacks per month who fail to respond adequately to symptomatic therapy.\(^{27}\) Therefore, patients exceeding a quantity limit of 12 doses/month would be candidates for prophylactic therapy.
- Oral triptans are most commonly packaged in blister packs of 6 tablets. Common dispensing quantities include 6, 12 and 18 tablets.

Because of the points above, potential quantity limits for triptans considered in this report were 6, 12 and 18 doses per month.

Use of quantity limits in Canada

Quantity limits for triptans are used by many of the jurisdictions in Canada (Exhibit 6). Seven of 12 jurisdictions (58%) have quantity limits that are applied to triptans, regardless of dosage forms (exception: British Columbia, Alberta, Ontario, Quebec, Yukon). Quantity limits of 6 doses are used in Saskatchewan and the four Atlantic provinces. Quantity limits of 12 doses are used in Manitoba and the NIHB/Nunavut/Northwest Territories.

Potential triptan overuse in Canada

Our pharmacoepidemiologic analysis found that the median number of triptan units dispensed per public drug plan beneficiary varied considerably between provinces, and aligned with differences in quantity limits (see Exhibit 7). In Ontario, where no quantity limits are in place, the median quantity dispensed per person annually (median 60 units) was the highest in Canada (range 18 to 36 units across other provinces studied). Furthermore, almost one in five publicly-funded triptan users in Ontario received more than 12 units per month, the highest quantity limit in place across the provinces. This surpassed utilization in all other provinces where data was available, including Alberta, which also does not have quantity limits in place.
### Exhibit 7: Potential Triptan Overuse, By Province in 2012

<table>
<thead>
<tr>
<th>Province</th>
<th>Quantity Limit Imposed by Province</th>
<th>Triptan Units Dispensed per Person Median</th>
<th>Overuse Definition*: 6 units/month</th>
<th>Overuse Definition*: 12 units/month</th>
<th>Overuse Definition*: 18 units/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontario</td>
<td>None</td>
<td>60</td>
<td>40-45%</td>
<td>15-20%</td>
<td>10-15%</td>
</tr>
<tr>
<td>Alberta</td>
<td>None</td>
<td>36</td>
<td>30-35%</td>
<td>10-15%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Manitoba</td>
<td>12 units/month</td>
<td>18</td>
<td>15-20%</td>
<td>0-5%</td>
<td>0-5%</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>6 units/month</td>
<td>NB: 30</td>
<td>15-20%</td>
<td>--†</td>
<td>--</td>
</tr>
<tr>
<td>&amp; PEI ‡</td>
<td></td>
<td>PEI: 36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>6 units/month</td>
<td>30</td>
<td>10-15%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>6 units/month</td>
<td>24</td>
<td>0-5%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Ranges reported represent the proportion of triptan users whose volume of use in 2012 would have exceeded one of 3 quantity limit scenarios being considered.
†Suppressed due to small cell sizes
‡Data for New Brunswick and PEI were merged for the quantity limit analysis due to small cell sizes.

Note: No data available for British Columbia, Quebec, Yukon, Newfoundland & Labrador, Nunavut, or the Northwest Territories

### Pharmacoeconomics

#### Cost-effectiveness literature review

A total of 21 published economic analyses of triptan use were identified, most of which were non-Canadian studies. Despite consistent concerns over the quality and relevance of the available studies, the weight of evidence suggests that triptans are more cost effective relative to other acute migraine treatments, including ergots and ASA in combination with an antiemetic. The studies found that for naïve patients, triptans were more cost effective relative to acetaminophen, ergots, and NSAIDs and that for experienced patients, the addition of NSAIDs or acetaminophen to triptans was dominated by triptans alone.²⁸

#### Reimbursement-based economic assessment

Alternative reimbursement strategies considered in the analysis varied according to the process of reimbursement: EAP and general benefit (GB) listing/limited use listing.

Two main options were considered under each reimbursement model: use of quantity limits (6, 12 or 18), and 25% generic pricing agreement in addition to the preferential use of generic drugs (when both generic and brand name drugs are available). For general benefit/limited use (GB/LU) listing, current prescribing data from Alberta and Manitoba were used and extrapolated to the Ontario population. A total of 20 different reimbursement strategies were assessed (see Exhibit 8).
Tripton funding under proposed EAP

- Tripton expenditures in Ontario under the EAP program are $1.7 million annually.
- Currently, 42.4% of prescriptions reimbursed under EAP are for brand name products. Using generic products when they are available in place of brand name products is not required under the EAP program.
- Applying the 25% generic pricing rule and requiring that generic products be used in place of brand names (when available), would result in a cost reduction of 69% (savings of $1.1 million).
- Imposing a 6 per month quantity limit in addition to the above would lead to a reduction in expenditure of 84% (savings of $1.4 million). Using a quantity limit of 12 doses per month would result in a 77% cost reduction (savings of $1.3 million).

Tripton funding under proposed GB/LU

- Expanding access through GB/LU, applying the 25% generic pricing rule, and requiring that generic products be used in place of brand names (when available) would result in a 302% increase in cost ($5.3 million).
- Imposing a 6 per month quantity limit in addition to the above would lead to an increase in cost of 139% ($2.4 million). Using a quantity limit of 12 doses per month would result in an increase in cost of 221% ($3.9 million).
### Exhibit 8: Reimbursement strategies for triptans

<table>
<thead>
<tr>
<th>Strategy Description</th>
<th>2014 Expected Cost (Budget impact: % change vs Status Quo)</th>
<th>2014 Expected Number of Triptan Users (Impact: % change vs Status Quo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status Quo</td>
<td>$1,752,377</td>
<td>1,218</td>
</tr>
<tr>
<td>EAP listing with strategies 1&amp;2</td>
<td>$550,268</td>
<td>1,218</td>
</tr>
<tr>
<td></td>
<td>($1,202,108 decrease: ↓69%)</td>
<td>(no change in # of users)</td>
</tr>
<tr>
<td>EAP listing with strategies 1&amp;2 and quantity limits 6/month</td>
<td>$277,003</td>
<td>1,218</td>
</tr>
<tr>
<td></td>
<td>($1,473,373 decrease: ↓84%)</td>
<td>(no change in # of users)</td>
</tr>
<tr>
<td>EAP listing with strategies 1&amp;2 and quantity limits 12/month</td>
<td>$398,617</td>
<td>1,218</td>
</tr>
<tr>
<td></td>
<td>($1,353,760 decrease: ↓77%)</td>
<td>(no change in # of users)</td>
</tr>
<tr>
<td>EAP listing with strategies 1&amp;2 and quantity limits 18/month</td>
<td>$490,977</td>
<td>1,218</td>
</tr>
<tr>
<td></td>
<td>($1,261,399 decrease: ↓72%)</td>
<td>(no change in # of users)</td>
</tr>
<tr>
<td>GB/LU listing with strategies 1&amp;2</td>
<td>$7,050,685*</td>
<td>24,344†</td>
</tr>
<tr>
<td></td>
<td>($5,298,309 increase: ↑302%)</td>
<td>(23,126 increase: ↑1900%)</td>
</tr>
<tr>
<td>GB/LU listing with strategies 1&amp;2 and quantity limits 6/month</td>
<td>$4,189,249*</td>
<td>24,344†</td>
</tr>
<tr>
<td></td>
<td>($2,436,872 increase: ↑139%)</td>
<td>(23,126 increase: ↑1900%)</td>
</tr>
<tr>
<td>GB/LU listing with strategies 1&amp;2 and quantity limits 12/month</td>
<td>$5,619,145*</td>
<td>24,344†</td>
</tr>
<tr>
<td></td>
<td>($3,866,768 increase: ↑221%)</td>
<td>(23,126 increase: ↑1900%)</td>
</tr>
<tr>
<td>GB/LU listing with strategies 1&amp;2 and quantity limits 18/month</td>
<td>$6,251,231*</td>
<td>24,344†</td>
</tr>
<tr>
<td></td>
<td>($4,498,855 increase: ↑257%)</td>
<td>(23,126 increase: ↑1900%)</td>
</tr>
</tbody>
</table>

*Based on data from Alberta
†Number of users in Ontario based on extrapolation from Alberta data

Strategy 1: 25% of average branded cost (generic pricing agreement); Strategy 2: use of generic products in place of brand names (when available)

### Health Equity Issues
Several health equity issues have been identified in this review including accessibility of triptans in Ontario, and consideration of differences in the use of triptans by age (e.g. the elderly) and gender in Ontario. See Appendix A for Health Equity Considerations.

### Accessibility of triptans
Lack of accessibility to triptans, especially in terms of affordability, was a key finding that was highlighted by patients interviewed by our Qualitative Research Team. As well, accessing triptans through the Exceptional Access Program (EAP) for those eligible for the Ontario Drug Benefit was described as a significant barrier as many physicians and patients are unaware of the EAP criteria or that triptans can be accessed through the EAP, demonstrating a gap in knowledge on how to access triptans.
In addition, the EAP application process itself was described to be particularly challenging and time-consuming and may possibly deter physicians from attempting to access triptans for their patients. In Ontario, approximately 65% of requests for triptans through the Exceptional Access Program are approved; the approval rate may increase if improvements were made to coverage criteria or the application process.

The pharmacoepidemiologic analysis suggests that highly restricted public drug coverage in Ontario has led to poorer access to these medications through public drug plans compared to most other provinces (Ontario has among the lowest rates of provincially-funded triptan use in Canada). Indeed, near the end of 2013, more than 75% of triptan prescriptions in Ontario were paid for by private drug plans, 20% were paid for out of pocket and less than 5% were paid for by ODB. Although many of these individuals may not be eligible for public drug coverage, migraine prevalence estimates suggest that there are likely a substantial number of Ontarians who are eligible for coverage, but do not have access triptans through ODB. If these individuals do not have private drug insurance or cannot afford out of pocket purchases, this may be indicative of a significant access issue.

**Use in elderly**
A rising prevalence of use of triptans among older (aged 65+) adults was observed in all provinces studied; however, use in the elderly in Ontario was the lowest of all provinces (11 per 100,000 in Ontario, compared to a range of 65 to 222 per 100,000 eligible population in all other provinces studied; 2012 data). This suggests that there may be an increasing demand of these drugs among older adults that is not being met in Ontario. Of note is that rates of triptan overuse appear to be higher among older adults treated with this class of drugs. This discrepancy between younger and older triptan users highlights an important safety issue that should be considered.

**Use in women**
In Canada, migraine prevalence rates have been estimated to be approximately 23-26% in women and 8-10% in men. This higher prevalence in women is reflected in the patterns of use of triptans. Overall, triptans funded through public drug plans were more widely used by women (approximately 80% across Canada). No accessibility issues specific to women were identified.

**Reimbursement Options for Consideration**

**Key considerations**

**Efficacy**
- Overall, triptans were found to be efficacious for the treatment of acute migraine and more effective than placebo.
- When triptans were compared to each other (for standard dose oral formulations), in general there were more favourable results observed for studied outcomes for eletriptan and rizatriptan.
Safety and tolerability

- There is no high quality evidence of differences between the triptans in terms of safety (e.g., cardiovascular events, risk of serotonin syndrome) and tolerability.
- Use of triptans for more than 9 days/month (18 doses/month) may result in medication-overuse headache.

Accessibility

- Cost of triptans was noted as a factor leading to accessibility issues. As well, physicians perceived that accessing triptans through the Exceptional Access Program (EAP) for those eligible for the Ontario Drug Benefit was a particularly significant barrier, notwithstanding the availability of EAP criteria on the MOHLTC website. Ontario has among the lowest rates of publicly-funded triptan use in Canada.
- In Ontario, it is estimated that there are approximately 24,000-40,000 migraneurs eligible for OPDP coverage, who would be appropriate candidates for triptan use. However, currently only 1200 patients (approximately 5% of potentially eligible patients) are receiving triptans under the existing EAP program. It was noted that improvements to the current EAP process (e.g., use of a standardized form) would be beneficial, and may increase the number of ODB-eligible patients receiving triptans. However, the number of patients who potentially would receive triptans through a streamlined EAP process is unknown.
- Proposed GB/LU reimbursement options would expand triptan use by approximately 1900%.

Quantity Limits

- Quantity limits have been used to help decrease the risk of medication overuse headaches as well as curbing the costs of triptans in public and private drug programs.

Pharmacoeconomics

- Proposed EAP strategies suggest a reduction in total triptan costs (approximately 69-84% reduction), while alternative GB/LU-based strategies suggest an increase in total costs (139-302% increase).

Reimbursement options

Three main reimbursement options for the triptans generated from the findings of our drug class review are outlined below (see Exhibit 9). All triptans currently available through EAP (i.e., almotriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan) will be considered for coverage in each of the scenarios below. Note that in Ontario, eletriptan and frovatriptan are neither available on the Ontario Drug Benefit (ODB) formulary nor through the Exceptional Access Program and therefore are not included in the recommendations below.
Option 1: General benefit listing for triptans

- Triptans listed as a general benefit in the ODB formulary.
- Includes all formulations: oral products, nasal sprays and injectable sumatriptan.
- Generic costs equivalent to 25% of average branded cost, and requiring replacement of brand name agents with their generic formulation, when available, would be in effect.

Option 2: Limited use listing for triptans with quantity limit of 12 doses/month

- Triptans listed as Limited Use on the ODB formulary
- Restrict to use in patients with migraine (see Appendix and C for criteria for restriction of triptans)
- Impose enforced quantity limit of 12 doses per month.
  - Patients requiring more than 12 doses per month would need to submit an EAP request.
- Generic costs equivalent to 25% of average branded cost, and requiring replacement of brand name agents with their generic formulation, when available, would be in effect.

Options 3a and 3b: Exceptional Access Program (EAP) for triptans

Option 3a:

- Triptans covered under the ODB’s EAP program (see Appendix and C for criteria for restriction of triptans)
  b. Generic costs equivalent to 25% of average branded cost, and requiring replacement of brand name agents with their generic formulation, when available, would be in effect.

Option 3b:

- Triptans covered under the ODB’s EAP program (see Appendix and C for criteria for restriction of triptans)
  b. Generic costs equivalent to 25% of average branded cost, and requiring replacement of brand name agents with their generic formulation, when available, would be in effect.
  c. Impose quantity limit of 12 doses per month.
  d. Patients requiring more than 12 doses per month would need to meet additional criteria, including a requirement for concomitant prophylaxis (preventive therapy) for migraines.
### Exhibit 9: Assessment of Reimbursement Options

<table>
<thead>
<tr>
<th></th>
<th>Option 1: General Benefit with no quantity limits</th>
<th>Option 2: Limited Use with quantity limit of 12/month</th>
<th>Option 3a: EAP with generic pricing agreement</th>
<th>Option 3b: EAP with generic pricing agreement and quantity limit of 12/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accessibility</td>
<td>Allow for greatest accessibility to all ODB eligible patients (approximately 24,000-40,000 patients with migraine and eligible for coverage)</td>
<td>No increase in number of patients currently receiving triptans through EAP anticipated(approximately 1200)†</td>
<td>Risk of development of medication overuse headache is reduced with the implementation of quantity limits</td>
<td>Risk of development of medication overuse headache is reduced with the implementation of quantity limits</td>
</tr>
<tr>
<td>Budget Impact (current annual expenditures approximately $1.7 million)</td>
<td>302% increase over current funding, with budget impact of $5.3 million</td>
<td>221% increase over current funding, with budget impact of $3.9 million</td>
<td>Cost savings of 69% (savings of $1.2 million)</td>
<td>Cost savings of 77% (savings of $1.4 million)</td>
</tr>
<tr>
<td>Safety concerns</td>
<td>No quantity limit may result in some patients using excessive amounts of triptans which could lead to development of medication overuse headache</td>
<td>Risk of development of medication overuse headache is reduced with the implementation of quantity limits</td>
<td>No quantity limit may result in some patients using excessive amounts of triptans which could lead to development of medication overuse headache</td>
<td>Risk of development of medication overuse headache is reduced with the implementation of quantity limits</td>
</tr>
<tr>
<td>Alignment with other jurisdictions</td>
<td>BC, Yukon, Quebec</td>
<td>MB, AB*, NIHB/NT/NU</td>
<td>AB**, SK, NS, NB, PEI, NF</td>
<td>SK, NS, NB, PEI, NF</td>
</tr>
<tr>
<td>Prescribing Criteria</td>
<td>No prescribing criteria used with general benefits</td>
<td>Unenforced prescribing criteria used</td>
<td>Enforced criteria used</td>
<td>Enforced criteria used</td>
</tr>
<tr>
<td>Implementation of generic pricing agreement</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes†</td>
<td>Yes‡</td>
</tr>
</tbody>
</table>
| Indication creep | Unrestricted access may result in use of triptans for cluster or tension-headache. However, impact expected to be low for the following reasons:  
1. The prevalence of cluster headache is ~0.1%.  
2. Only 40% of patients with migraine and tension-type headache are diagnosed by a physician or other professional.  
3. Triptans do not have a clinically significant effect in patients with tension-type headache.  
Potential misuse of LU criteria (e.g. for cluster or tension-type headache) possible. However, impact expected to be low for the following reasons:  
1. The prevalence of cluster headache is ~0.1%.  
2. Only 40% of patients with migraine and tension-type headache are diagnosed by a physician or other professional.  
3. Triptans do not have a clinically significant effect in patients with tension-type headache.  
Indication creep unlikely due to individual clinical review | Indication creep unlikely due to individual clinical review |

*For patients aged 18-64  
**For patients 65 years and older  
†The number of users may increase if an EAP reform were initiated; however, the costs reported here are based on existing levels of EAP use.  
‡Currently there is no generic pricing agreement in effect for drugs listed on the Exceptional Access Program.
Other Issues for Consideration

Eletriptan, frovatriptan and zolmitriptan listing on the ODB formulary

Currently, neither eletriptan nor frovatriptan are funded by ODB. Zolmitriptan is funded through EAP but as step-therapy (i.e., another funded triptan must have been tried unsuccessfully in order to receive funding for zolmitriptan). Any cost estimates for proposed EAP and GB/LU listing may change if eletriptan and/or frovatriptan are added to the ODB formulary or accessible via EAP, or if zolmitriptan is no longer considered a second-step triptan.

Eletriptan:
- **Currently eletriptan is NOT funded through the EAP program.** This decision was based on lack of compelling evidence at the time demonstrating that eletriptan is therapeutically superior to other triptans. As well, it was noted that eletriptan, unlike other triptans, has a potential to interact with drugs metabolized by the cytochrome P450 (CYP3A4) pathway.
- **Efficacy:** Based on the network meta-analyses conducted, eletriptan may be superior to other triptans for many of the efficacy outcomes reviewed.
- **Safety:** Eletriptan has a similar safety and tolerability profile to other triptans. However, eletriptan is unique in that eletriptan may result in drug interactions with drugs metabolized by the cytochrome P450 pathway (e.g., ketoconazole). Specifically, eletriptan is contraindicated within 72 hours of treatment with potent CYP3A4 inhibitors (ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir). Note: there are no published case reports in the literature describing an adverse effect as a result of a potential interaction between eletriptan and CYP3A4 inhibitors.
- **Cost:** Generic forms of eletriptan are available; price is comparable to other oral triptan products.

**Summary:** Eletriptan may be more effective than other triptans and it is similarly priced. There is a potential for drug interactions with CYP3A4 inhibitors; however, the clinical significance of this drug interaction is unknown.

Frovatriptan:
- **Efficacy:** Results from the network meta-analyses for the 2-hour outcomes showed that frovatriptan was not as effective compared to eletriptan and rizatriptan. Data for frovatriptan at 24 hours were not available.
- Frovatriptan 2.5 mg twice a day starting two days before menstruation and continuing for six days has the strongest evidence for efficacy for short-term monthly prophylaxis for refractory menstrual migraine. Note that only the use of triptans for acute treatment of migraine (not short-term prophylaxis) was reviewed for this Drug Class Review.
- **Safety:** CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin) can increase half-life of frovatriptan. However, other triptans also can result in clinically significant drug interactions with other
substances (e.g., eletriptan and CYP450 interactions)\textsuperscript{31}.

- **Cost:** There is currently no generic form of frovatriptan available on the Canadian market. Therefore, the cost of frovatriptan is substantially greater than generic oral triptans commercially available.

**Summary:** Since frovatriptan was not shown to be as effective as other triptans and as there are no generic formulations available, no change in funding status for frovatriptan is suggested.

**Zolmitriptan:**
- Currently, zolmitriptan is funded as a step-two triptan i.e., patients must have failed an adequate trial or experienced intolerance to other covered triptans prior to receiving coverage for zolmitriptan. At the time of the decision, it was noted that the commonly used dose of zolmitriptan is 5mg; however only the 2.5mg strength is available on the Canadian market.
  - An informal survey conducted for this review of 6 neurologists suggests that 2.5mg is considered standard dose for 4 (67\%) and 2 neurologists use 5mg (33\%) as standard dose.
- **Efficacy:** Overall, based on the results of the network meta-analysis, zolmitriptan is at least as efficacious as other triptans (with the exception of eletriptan).
- **Safety:** Zolmitriptan has a similar safety and tolerability profile to other triptans.
- **Cost:** Generic forms of zolmitriptan oral tablet are available; price of the 2.5mg tablet is comparable to other triptans. Use of a quantity limit of 12 doses of zolmitriptan 2.5mg orally/month would result in a similar cost to other triptans.

**Summary:** Based on the results of this review, zolmitriptan (all dosage forms) should be considered for funding as this drug is similar to other triptans. A quantity limit of 12 doses of zolmitriptan 2.5mg oral/month is suggested.

**Discontinuation of Oral Ergot Products**
- Cafergot, containing caffeine 100mg and ergotamine tartrate 1mg, has been discontinued worldwide by Novartis (as of December 2013).
- Cafergot was previously listed as a general benefit in the ODB formulary.
- Users of Cafergot (approximately 800 in Q4 2012) will potentially need to use other acute migraine medications, such as triptans.

**Stakeholder Review**
Findings from the stakeholder review contributed to selection of final policy recommendations, and include feedback solicited from an open call for review, comments received during a workshop for stakeholders, as well as results from the ODPRN Citizen’s Panel.
Findings from the ODPRN Citizens’ Panel

Citizens’ Panel (CP) members rated each of the policy options on factors related to acceptability, accessibility and affordability, and ranked options from most to least preferable from a societal viewpoint. Through one teleconference meeting and two rounds of an online survey, CP members voiced the following perceptions:

- GB and LU options were considered the most accessible and the ones most likely to enable health equity
- EAP options were the most highly rated when considering the cost to the system, while the GB and LU options were highly rated when considering the cost to the patient
- The LU with quantity limits and EAP with quantity limits options were highly rated in terms of the safety to the patient.
- Overall, the LU option was considered the most acceptable option

CP members felt that placing quantity limits on triptans was an important consideration to ensure proper use and safety; in fact, safety outweighed accessibility for several participants. Many members felt that the GB option was too liberal, did not consider physician accountability for limiting triptans dosage, and was too high a cost to the system. The LU + quantity limits option was the most positively perceived option, with the EAP + quantity limits + generics option considered a good alternative if improvements to the EAP process can be made (e.g. standardized forms) (see Exhibit 10). Overall, CP members ranked the LU + quantity limits option as the most preferable policy option (70%, n = 7 of 10 responses ranked as first option), followed by EAP + generics + quantity limits in second place (45%, n = 5 of 11 responses ranked as second), EAP + generics option in third place (64%, n = 7 of 11 responses ranked as third), and GB in fourth place (67%, n= 6 of 9 responses ranked as fourth).

Exhibit 10: Final Ranking of Policy Options

<table>
<thead>
<tr>
<th>Policy Option</th>
<th>Final Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited Use + quantity limits</td>
<td>1</td>
</tr>
<tr>
<td>EAP + generic pricing rule + quantity limits</td>
<td>2</td>
</tr>
<tr>
<td>EAP + generic pricing rule</td>
<td>3</td>
</tr>
<tr>
<td>General Benefit</td>
<td>4</td>
</tr>
</tbody>
</table>

Final Policy Recommendations and Conclusion

Triptans are an effective and safe treatment for the management of acute migraine. However, under the current Exceptional Access Program in Ontario, only a fraction of potentially eligible patients are receiving this medication. Based on the results of the review, including the results from the Citizen’s Panel, two reimbursement options for triptans are favoured as funding alternatives for the Ontario Public Drug Program:

- Limited use with quantity limit of 12 per month
  OR
- Exceptional Access Program (EAP) with generic pricing, quantity limit of 12 per month, revised criteria and a streamlined application process
References


(13) Viana M, Genazzani A, Terrazzino S, et al. Triptan nonresponders: do they exist and who are
they? *Cephalgia* 2013; 33:891-896.


(18) Culley EJ, Wanovich RT. Medical and pharmacy cost and utilization outcomes of a quantity limit on the 5-HT1 agonists (triptans) by a managed care organization. *J Manag Care Pharm* 2001; 7:468-75.


(25) British Association for the Study of Headache. Diagnosis and management of headache, 3rd


# Appendix A: Health Equity Considerations for Triptan Drug Class Review

<table>
<thead>
<tr>
<th>Populations: Identify which populations may experience significant unintended health impacts (positive or negative) as a result of the planned policy, program or initiative.</th>
<th>Comments: Proposed Triptan Coverage under EAP/LU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aboriginal peoples</strong> (e.g., First Nations, Inuit, Métis, etc.)</td>
<td>No accessibility issues identified. Coverage of medications, including triptans, for aboriginal peoples is available through Ontario Ministry of Health and Long-term Care.</td>
</tr>
<tr>
<td><strong>Age-related groups</strong> (e.g., children, youth, seniors, etc.)</td>
<td>Children/youth: Triptan drug class review was restricted to adults 18 years and older. No recommendations for listing made for children and adolescents in the review. Elderly: No restrictions for triptan use in the elderly were identified in the review.</td>
</tr>
<tr>
<td><strong>Disability</strong> (e.g., physical, D/deaf, deafened or hard of hearing, visual, intellectual/developmental, learning, mental illness, addictions/substance use, etc.)</td>
<td>No accessibility issues identified. Patients with disability and receiving Ontario Disability Support Program Income Support, receive prescription drug coverage (including triptans) through ODB.</td>
</tr>
<tr>
<td><strong>Ethno-racial communities</strong> (e.g., racial/racialized or cultural minorities, immigrants and refugees, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td><strong>Francophone</strong> (including new immigrant francophones, deaf communities using LSQ/LSF, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td><strong>Homeless</strong> (including marginally or under-housed, etc.)</td>
<td>Not eligible for ODB coverage.</td>
</tr>
<tr>
<td><strong>Linguistic communities</strong> (e.g., uncomfortable using English or French, literacy affects communication, etc.).</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td><strong>Low income</strong> (e.g., unemployed, underemployed, etc.)</td>
<td>No accessibility issues identified; low income individuals who receive public drug coverage will have access to triptans through ODB.</td>
</tr>
<tr>
<td><strong>Religious/fairth communities</strong></td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td><strong>Rural/remote or inner-urban populations</strong> (e.g., geographic or social isolation, under-serviced areas, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td><strong>Sex/gender</strong> (e.g., male, female, women, men, trans, transsexual, transgendered, two-spirited, etc.)</td>
<td>Although migraine is approximately 3 times more prevalent in women than men, no accessibility issues identified for sex/gender in the review.</td>
</tr>
<tr>
<td><strong>Sexual orientation</strong>, (e.g., lesbian, gay, bisexual, etc.)</td>
<td>No accessibility issues identified.</td>
</tr>
<tr>
<td><strong>Other</strong>: please describe the population here.</td>
<td>None identified.</td>
</tr>
</tbody>
</table>

## Appendix B: Assessment of criteria for coverage (for both LU and EAP listing)

<table>
<thead>
<tr>
<th>Criteria (for triptans)</th>
<th>Rationale</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Use in patients with migraines                | This review only considered the use of triptans for management of migraine. In Canada, all triptans are only indicated for migraine.                                                                 | Triptans limited to patients with migraines (may prevent indication creep to cluster headache; however, this is not considered significant as prevalence of cluster headache is about 0.1%).  

29                                                                                               | May restrict access to those patients who may benefit from use of triptans for treatment of cluster headache                                                                                     |
| Use in patients over the age of 18 years       | This review only considered use of triptans in adult patients with migraines.                                                                                                                                | Triptans limited to patients over the age of 18 years (may prevent age creep to younger age group, where prevalence of migraine is about 5%).  

32                                                                                               | Almotriptan has an approved indication in adolescents  

Other triptans may also be beneficial for adolescents with migraines                                                                                         |
| Quantity limits 6 per month (NOTE: most oral triptans are packaged in packages of 6)            | Guidelines suggest that prophylaxis should be considered in patients with 3 moderate or severe headaches/month (assuming use of 2 triptans per migraine = 6/month)                                                                 | Would prevent medication overuse headache  

Economic benefit by limiting quantities                                                                                                                        | May be too restrictive; some patients may delay the use of triptans until the pain is unbearable or use half the recommended dosage  

Prophylaxis may not be appropriate for all patients                                                                                                           |
| Quantity limits 12 per month (NOTE: most oral triptans are packaged in packages of 6)          | Use of 12 tablets or less/month would prevent medication overuse headache but allow patient flexibility to treat migraine early                                                                        | Would prevent medication overuse headache  

Economic benefit by limiting quantities  

Allow patient flexibility to treat migraine early                                                                                                               | Some patients (e.g., women with menstrual-induced migraine) may require more than 12 doses/month                                                                                                     |
<table>
<thead>
<tr>
<th><strong>Quantity limits 18 per month (NOTE: most oral triptans are packaged in packages of 6)</strong></th>
<th>Patients should avoid use of triptans, ergots, opioids or combination analgesics on more than 9 days a month (allowing for use of 2 triptans per migraine = 18/month).</th>
<th>Allows greatest flexibility for patients to treat migraine early</th>
<th>Cost savings not as great as with smaller quantity limits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of other acute therapies prior to triptans (e.g., NSAIDs, acetaminophen)</strong></td>
<td>For treatment of mild to moderate migraine, acetaminophen or NSAIDs can be used. Triptans are used in patients with moderate to severe migraines, or in those patients who do not respond to NSAIDs.</td>
<td>Would limit triptans to patients with moderate to severe migraines</td>
<td>Most patients would have tried either acetaminophen or NSAIDs (which are available over-the-counter (OTC)) prior to triptan use. Would not be able to check records to see if patients have used another acute treatment as these are available OTC.</td>
</tr>
<tr>
<td><strong>Use oral triptans first, before approval for injectable or nasal products</strong></td>
<td>Oral triptans are used in most patients with migraines.</td>
<td>Oral products are less expensive than injectable or nasal products. Some patients on injectable/nasal products may be suitable candidates for oral products.</td>
<td>Patients with nausea/vomiting associated with migraine would require injectable/nasal product (oral product not appropriate). Injectable sumatriptan is the most effective triptan.</td>
</tr>
<tr>
<td><strong>Limit triptan to patients with moderate or severe migraine</strong></td>
<td>Guidelines recommend use of triptans in patients with moderate to severe migraines, or in those patients who do not respond to NSAIDs.</td>
<td>Would restrict triptans to patients with moderate/severe migraine; patients with mild migraine can be treated with simple analgesics (e.g., acetaminophen, NSAIDs).</td>
<td>Definition of moderate and severe is subjective, and not well established.</td>
</tr>
<tr>
<td><strong>Use zolmitriptan as a second-line agent after other oral agents have been tried</strong></td>
<td></td>
<td></td>
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<tr>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan (oral) only available a 2.5 mg tablet; for patients using 5mg/dose, the cost would be double that of other oral triptans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan 2.5mg is as effective as other standard dose triptans, except for eletriptan (which is more effective)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant difference for efficacy outcomes between zolmitriptan 5mg tablet and zolmitriptan 2.5mg tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionable whether zolmitriptan 5mg is used by most physicians; could impose quantity limits for zolmitriptan 2.5mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix C: Suggested Limited Use and Exceptional Access Program criteria

1. Limited Use Option with quantity limits of 12 doses/month
   a. Limited Use Criteria (for all funded triptans and dosage forms)
      • For the treatment of acute migraines with or without aura in patients who have failed adequate trials of other acute therapies for migraines (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen)
      • A quantity limit of 12 doses per month (regardless of dosage form) will be funded. Reimbursement will be available for a maximum quantity of 12 triptan doses per 30 days regardless of the agent(s) or dosage form used within the 30-day period. For patients who require more than 12 doses/month, a request through EAP is required.
   b. EAP criteria for patients who exceed 12 doses/month (maximum 18 doses/month)
      • For the treatment of patients with migraines with or without aura
      • Details of migraine prophylactic regimens (e.g., amitriptyline, beta-blockers) tried or rationale why they are inappropriate must be provided. Reimbursement will be available for a maximum quantity of 18 triptan doses per 30 days regardless of the agent(s) or dosage form used within the 30-day period.
   c. Therapeutic notes
      • Triptans are not indicated for use in children and adolescents (<18 years of age). The exception is almotriptan tablets which are indicated in adolescents 12-17 years of age.
      • Medication overuse headaches are frequent or daily chronic headaches that are caused by the frequent use of triptans and other medications used in the treatment of acute migraine headaches. To avoid medication overuse headache, The Canadian Headache Society suggests avoidance of use of triptans, ergots, opioids or combination analgesics on more than 9 days per month.

2. Exceptional Access Program (EAP) Option with quantity limits of 12 doses/month
   a. EAP Criteria (for all funded triptans and dosage forms)
      • For the treatment of patients with acute migraines with or without aura
      • A quantity limit of 12 doses per month (regardless of dosage form) will be funded. Reimbursement will be available for a maximum quantity of 12 triptan doses per 30 days
regardless of the agent(s) or dosage form used within the 30-day period.

- For patients who require more than 12 doses/month (up to a maximum of 18 doses/month)
  - Details of migraine prophylactic regimens (e.g., amitriptyline, beta-blockers) tried or rationale why they are inappropriate must be provided. Reimbursement will be available for a maximum quantity of 18 triptan doses per 30 days regardless of the agent(s) or dosage form used within the 30-day period.

NOTE: Only one EAP request is required for all triptan approvals.