

Triptans for Migraine Therapy

Environmental Scan and Local/Historical Context

February 4, 2014

Executive Summary

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

There are seven triptans available in Canada: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan. Triptans are available as oral tablets, oral disintegrating tablets, injectable and nasal spray. Most oral triptans, with the exception of frovatriptan, are available as generic formulations. The cost of a single tablet of a brand-name triptan ranges from approximately \$13.75 - \$17.65. Wholesale generic prices range from 46-75% of brand name prices. The most common package size is 6 for the majority of oral dosage forms, 2 sprays for the nasal formulations and 2 syringes for the injectables.

Triptans are available as insured benefits through public drug programs in Canada; they are listed as general benefits (without restrictions) in 3 funding programs, general benefits (with quantity limits) in one, and restricted access in 8 funding programs, including Ontario where they are listed as part of the Exceptional Access Program (EAP).

The most common reimbursement strategy for triptans is the use of quantity limits. Quantity limits are used in many public drug programs in Canada (but not Ontario), by private and public payers in the United States and in the public healthcare system in Australia. Other reimbursement schemes that are employed include step therapy (e.g., use of other non-triptan medications prior to triptan use) and prophylactic migraine medication in patients who exceed the defined quantity limit.

Part B: Guidelines for the management of acute migraine

Five guidelines were reviewed: Canadian Headache Society Guideline (2013), American Academy of Neurology (2000), British Association for the Study of Headache Guidelines (2010), ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013), and NICE (2012). Four guidelines that reviewed the early vs. late treatment of migraines with triptans, state that patients should take triptans as early as possible during their migraine attacks. Guidelines are consistent in the definition of medication over-use headache associated with triptans, i.e., regular use of triptans (or combinations of triptans with opioids) on 10 days a month or more on a regular basis for greater than 3 months places the patient at risk for the development of medication over-use headache. Two guidelines state that prophylactic therapy should be considered for patients with greater than 3 moderate or severe headache days a month that fail to respond to symptomatic therapy.

Part C: Impact of different drug reimbursement schemes for triptans

Five studies have shown a reduction in triptan cost and total number of triptan prescriptions when quantity limits were imposed. Two of 3 studies have shown a decrease (11-26%) in overall medical costs (including triptan drug costs, prophylactic medications, other acute drug costs, office visits, emergency room visits) whereas one study showed a slight increase (2.7%) following quantity limit implementation. 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. Limited studies have shown that patients receiving drug prophylaxis had lower migraine-related costs, including triptan costs, than those using acute treatment alone.

Part D: Rapid Reviews of Selected Topics

The evidence for the diagnostic criteria for medication overuse headache (MOH) is based primarily on one observational study. Although the mean number of doses associated with the development of MOH with triptans was 18, it was as low as 10 single doses per month in some patients.

Patients may prefer certain dosage formulations of triptans based on associated migraine symptoms. For example, non-oral routes preferred for patients with migraines associated with severe nausea and/or vomiting.

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Acknowledgments

This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and Drug Innovation Fund. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

A special thank you to all of the provincial and territorial representatives in Canada from the respective Ministries of Health as well as the representative from the Non-Insured Health Benefits for First Nations and Inuit (NIHB) who participated in the telephone survey.

Introduction

Migraine headache is a common 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%.¹ In Canada, migraine prevalence rates have been estimated to be approximately 23-26% in women and 8-10% in men.²⁻⁴ In one population-based study, the estimated lifetime prevalence of migraine was 7.8% in males (95% CI, 6.4-9.2) and 24.9% in females (95% CI, 22.7-27.0) with an overall lifetime prevalence rate of 17%.³ These rates are slightly higher than reported in the United States, where migraine prevalence has ranged from 5.6- 8.6% in males and 17.1-17.5% in females.^{5;6}

Migraine most frequently begins at puberty, reaching a peak at age 35-45 years.¹ The age distribution of migraine prevalence is especially prevalent in females, with an increased rate at ages 35-54 years.³ 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. In a population-based survey, migraine prevalence in the elderly population (65 years and older) was found to be 1.9% in men (OR 0.17, 95 % CI 0.04-0.74) and 11.7% (OR 0.80, 95% CI 0.46-1.41) in women, with an overall prevalence rate of 7.8%. The overall lifetime prevalence rate for adults (18-64 years of age) was 18.3%.³ In a report from Statistics Canada based on the National Population Health Survey from 1998/99, the overall prevalence of migraine in was 8%; in those aged 70 and older, the rate was 3.4%.⁷ A more recent report from the 2012 CCHS provides age specific prevalence of migraine of 11.8% for those under 65 and 9.2% for those over 65.⁸ A US study suggests that triptans were used by 19.4% of migraineurs aged under 60 and 12.7% of those over 60.⁹ These figures would suggest uptake of 2.5% in those under 60 and 0.8% in those over 60. Based on these estimates, there would be approximately 24,000-40,000 Ontario Drug Benefit (ODB) eligible patients receiving triptans through ODB.

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 acute headaches is generally divided into two categories: non-specific treatments (e.g., acetaminophen, nonsteroidal anti-inflammatory agents) 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.¹⁰

There are currently seven triptans available in Canada: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan. Although triptans are effective in the treatment of acute migraine headaches, they have the potential to be overused or inappropriately used. For example, evidence suggests that overuse of triptans could lead to medication over-use headache (rebound or drug-induced headache).¹¹ Various public and private payers have adopted different reimbursement schemes for triptans in order to increase more appropriate utilization of these drugs. Different strategies have included implementation of quantity limits, use of prophylactic medications, use of a preferred triptan and multipronged disease management programs.

The objectives of this report are:

- **Part A:** To summarize coverage of triptans through public drug programs in Ontario and across Canada, as well as in select international jurisdictions
- **Part B:** To summarize the guidelines for management of acute treatment of migraines
- **Part C:** To review the evidence relating to the impact of different triptan drug reimbursement schemes (e.g. quantity limits, restricted access) on patient access and/or utilization and costs
- **Part D:** To provide summaries on selected topics, such as medication-overuse headaches (specifically related to triptans), and patient preferences and triptan formulations

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability and Costs of Triptans in Canada

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, injectable and nasal formulations. The oral dosage forms are available through generic manufacturers except for frovatriptan. Note that the patent expiry date for Frova is 2013-12-16.¹² Currently in Ontario, wholesale generic prices for oral dosage forms range from 46-75% of brand name prices.

Oral triptans are most commonly packaged in blister packs containing a small number of tablets. The most common package size is 6 for oral dosage forms, including brand name and generic products. Exceptions for oral dosage forms include: rizatriptan (Maxalt) packaged as 12 tablets; naratriptan (generic), packaged as 8 tablets; naratriptan (Amerge), packaged as 2 and 6 tablets; frovatriptan (Frova), packaged as 7 tablets. Sumatriptan injectable is packaged as 2 syringes. Sumatriptan nasal spray is packaged as 2 sprays. Zolmitriptan nasal spray is packaged as 2 sprays and as 3x2sprays (i.e., 6 sprays).

Exhibit 1 outlines the dosage forms, costs (based on wholesale costs) and date generic formulations became available for all triptans available in Canada. For further information see Appendix 1 for listing of all available triptans (generic and brand name), including drug identification number (DIN) and package sizes.

Exhibit 1: Triptans available in Canada

Drug Name	Generic available	Brand name/ generic	Dosage form	Cost of 6 doses (\$)*	Date generics available
Almotriptan	Yes	Axert	Oral tablet (6.25, 12.5mg)	82.57	8-Dec-03
		Generic	Oral (6.25, 12.5mg)	58.70	22-Jul-13

Eletriptan	Yes	Relpax	Oral tablet (20,40mg)	86.65	13-Oct-04
		Generic	Oral tablet (20,40mg)	60.51	11-Oct-12
Frovatriptan	No	Frova	Oral tablet (2.5mg)	87.19	16-Dec-13**
Naratriptan	Yes	Amerge	Oral tablet (1, 2.5mg)	89.70 94.55	5-May-98
		Generic	Oral tablet (1, 2.5 mg)	62.47 49.28	1-Dec-09
Rizatriptan	Yes	Maxalt	Oral tablet (5, 10mg),	98.66	31-Aug-99
		Maxalt RPD	wafers (5, 10mg)	98.66	
		Generic	Oral tablet (5, 10mg)	66.69	3-May-12
		Generic	Oral disintegrating tablet (5, 10mg)	66.69	30-Jan-12
Sumatriptan	Yes	Imitrex	Subcutaneous (12 mg/mL)	251.40	30-Aug-99
		Generic	Subcutaneous (12 mg/mL)	185.16	6-Jun-11
	Yes	Generic	Oral (25,50,100mg)	53.94	24-Aug-05
				54.39	
				59.92	
	Yes	Imitrex DF	Oral tablet (25,50,100mg)	95.95 105.69	11-Feb-97
		Generic DF	Oral (25,50,100mg)	53.94 54.39 59.92	30-Oct-06
	No	Imitrex	Transnasal (5 mg/dose, 20 mg/dose)	92.43 95.13	19-Feb-97
Zolmitriptan	Yes	Zomig	Oral tablet (2.5 mg)	88.69	5-Mar-01
		Generic	Oral tablet (2.5 mg)	41.15	7-Jun-11
	Yes	ZomigRapimelt	Rapid dissolving tablet (2.5mg)	88.69	5-Mar-11
		Generic	Rapid dissolving tablet (2.5 mg)	41.18	7-Jun-11
	No	Zomig	Transnasal (2.5 mg/spray, 5 mg/spray)	88.69	23-Dec-04
				88.71	

*Based on costs obtained from McKesson (December 6 2013); **Patent expiry date

Summary

1. Most oral triptan formulations are available through generic manufacturers.
2. Wholesale generic prices range from 46-75% of brand name prices.
3. The most common package size is 6 for oral dosage forms, including brand name and generic products.

Common Drug Review

The Common Drug Review (CDR) is a single process for reviewing new drugs and providing listing recommendations to participating publicly funded federal, provincial and territorial drug benefit plans in Canada; it was established in September 2003. Only two products have been reviewed by the Common Drug Review: almotriptan and eletriptan (Exhibit 2). Rizatriptan, sumatriptan, naratriptan and zolmitriptan were available prior to 2003 and thus were not reviewed by the CDR. No submission to the Common Drug Review was made by the manufacturer of frovatriptan.

Exhibit 2: Common Drug Review for Triptans

Generic name	Trade Name	Common Drug Review
Almotriptan	Axert	Listed similar to other triptans (2004) Reasons for recommendation: 1. In RCTs against placebo, almotriptan had a significant benefit in terms of migraine headache pain control in the first 24 hours of therapy. In a RCT vs. sumatriptan, almotriptan had no significant efficacy difference. 2. Almotriptan's adverse effect profile appears similar to other triptans, although it may be associated with fewer adverse effects including chest pain, than sumatriptan. 3. Almotriptan is similar in cost to zolmitriptan and rizatriptan.
Eletriptan	Relpax	Not listed (2005) Reasons for recommendation: 1. 11 RCTs of short duration compare eletriptan to either placebo or another triptan. Studies comparing eletriptan to placebo show that it is more effective in relieving migraine symptoms. Studies comparing eletriptan to other triptans show that it is either equivalent to or better than these triptans for some but not all migraine relief outcomes. The only meta-analysis that includes an unpublished randomized controlled trial found similar efficacy for eletriptan and sumatriptan. 2. Eletriptan, unlike other triptans, is primarily metabolized by cytochrome P-450 enzyme CYP3A4. Drugs that inhibit this enzyme raise plasma levels of eletriptan and may increase the risk of serious adverse events, including chest symptoms and coronary artery vasoconstriction. For this reason, Health Canada has limited the maximum daily dose to 40 mg. The use of eletriptan within 3 days of a potent CYP3A4 inhibitor is contraindicated. 3. Eletriptan has not been clearly shown to be more cost-effective than other triptans.

Summary

1. Most triptans were available prior to the inception date of the Common Drug Review process. As such, no review was conducted by CDR for naratriptan, rizatriptan, sumatriptan and zolmitriptan.
2. The manufacturer of frovatriptan (Frova), which was marketed in 2008, did not submit a request for CDR review.

Triptan listing in Ontario

The Exceptional Access Program:

Sumatriptan (oral, nasal, injectable), rizatriptan (oral), naratriptan (oral), almotriptan (oral) and zolmitriptan (oral) are available to eligible patients through the Exceptional Access Program. The Exceptional Access Program (EAP) facilitates patient access to drugs not funded on the Ontario Drug Benefit (ODB) Formulary, or where no listed alternative is available. In order to receive coverage, the patient must be eligible to receive benefits under the Ontario Drug Benefit (ODB) program.

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.

Overall, 63% of requests for triptans are approved. For first-step triptans (i.e., almotriptan, naratriptan, rizatriptan, sumatriptan) approval rates were between 67 and 70%. For zolmitriptan, a second-step triptan, approval rates were 5% of all submissions. A summary of triptan requests through EAP is summarized in Exhibit 3.

Committee to Evaluate Drugs:

The Committee to Evaluate Drugs (CED) is the Ministry of Health and Long-term care's independent expert advisory committee on drug-related issues. The CED reviewed and recommended listing for all triptans available through the EAP program.

Eletriptan is not available through the EAP program. This product was reviewed by the CED in April 2005. The CED noted that there was a lack of compelling evidence demonstrating that eletriptan is therapeutically superior to other triptans that are considered for reimbursement via the EAP mechanism (i.e., sumatriptan, almotriptan, naratriptan, and rizatriptan). The cost-effectiveness of eletriptan compared to the other triptans was also not clearly established. Additionally, the committee noted that eletriptan, unlike other drugs in this class, is primarily metabolized by the cytochrome P450 (CYP3A4) pathway, thus increasing its potential to cause drug interactions and adverse effects.

Frovatriptan is also not available through the EAP program. For drug products to be eligible for listing in the Formulary, a drug manufacturer must provide a complete submission. However, the manufacturer of frovatriptan did not submit a request for review to the Ontario Public Drug Programs (OPDP).

Zolmitriptan was added to the EAP listing in 2011. Currently, it is considered a step-two triptan i.e., patients must have failed an adequate trial or experienced intolerance to other covered triptans (i.e., sumatriptan, rizatriptan, almotriptan and naratriptan) prior to receiving coverage for zolmitriptan. It was noted that the commonly used dose for zolmitriptan is 5mg; however, only the 2.5mg strength is available on the Canadian market. Therefore, use of zolmitriptan 5mg would result in doubling of the cost.

Exhibit 3: Summary of EAP Triptan Requests since 2010

Triptan	Number of EAP Requests	Number Approved N (%)
Almotriptan	282	198 (70.2%)
Naratriptan	116	79 (68.1%)
Rizatriptan	780	531 (68.1%)
Sumatriptan	875	591 (67.5%)
Zolmitriptan	186	9 (4.8%)
OVERALL	2239	1408 (62.9%)

Summary

1. Between 67% and 70% of EAP requests for almotriptan, naratriptan, rizatriptan and sumatriptan are approved.
2. Approval for zolmitriptan, which has more restrictive EAP criteria (patients must have failed or demonstrated intolerance to other triptans), is rare. This may reflect lack of awareness of these criteria among prescribers.
3. The majority of requests that were not approved had missing information or had no description of migraine headaches, use of preventative therapy or intolerance to oral triptan.

Public Plan Listings in Canada

Part 1: In order to determine the listing of triptans in each province, the relevant webpages of the provincial drug formularies were searched (See Appendix 2). All public drug programs provide coverage for triptans for eligible patients, either as a general benefit or as a restricted benefit. The restricted benefit is 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). A summary of the various listings is as follows:

- General benefits without restrictions: British Columbia, Yukon, Quebec
- General benefits with quantity limits: NIHB
- Restricted (passive): Manitoba, Alberta (Alberta Health Restricted Benefit)
- Restricted (enforced): Alberta (Alberta Health Special Authorization), Saskatchewan, Ontario, Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland

An overview of the listings is found in Exhibit 4.

Exhibit 4: Public plan listings in Canada

Drug (brand name and/or generic availability)	Dosage form	BC	AB	SK	MB	ON	QC	NB	NS	PEI	NL	YK	NIHB/NT/NU
Almotriptan (Axert, generic)	Tablet	Ben	Res# Pas##	Res	No	Res*	Ben	Res	Res	Res	Res	Ben	Ben**
Eletriptan (Relpax, Generic)	Tablet	No	No	No	No	No	Ben	No	No	No	No	No	No
Frovatriptan (Frova)	Tablet	No	No	No	No	No	No	No	No	No	No	No	No
Naratriptan (Amerge, generic)	Tablet	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	Res	Res	Ben	Ben**
Rizatriptan (Maxalt, generic)	Tablet	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	No	Res	Ben	Ben**
	ODT	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	No	Res	Ben	Ben**
Sumatriptan (Imitrex, generic)	Tablet	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	Res	Res	Ben	Ben**
	Nasal spray	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	Res	Res	Ben	Ben**
	Injectable	Res	Res# Pas##	Res	No	Res*	Ben	Res	Res	Res	Res	Ben	Ben**
Zolmitriptan (Zomig, generic)	Tablet	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	Res	Res	Ben	Ben**
	ODT	Ben	Res# Pas##	Res	Pas	Res*	Ben	Res	Res	No	Res	Ben	Ben**
	Nasal spray	Ben	Res# Pas##	Res	Pas	No	Ben	Res	Res	No	Res	No	No
Quantity Limits (monthly)		None	None	6	12	None	None	6	6	6	6	None	12

No=not listed; Res=restricted listing – enforced; Pas= restricting listing – passive; Ben=unrestricted listing
ODT=oral disintegrating tablet

*EAP=Exceptional Access Program;

**General benefit with quantity limits imposed

#Restricted listing enforced for patients 65 years and older

##Restricted listing passive for patients aged 18-64

Restriction Criteria

In order for patients to be eligible for publically funded triptan use, various funding programs use restriction criteria, including quantity limits, prior use of other acute treatments (e.g., acetaminophen and/or non-steroidal anti-inflammatory drugs) and/or concomitant use of prophylactic medications.

Although almotriptan is funded in the Atlantic Provinces, first-line triptans (i.e., rizatriptan, naratriptan, sumatriptan or zolmitriptan) must have been tried initially before approval is granted for almotriptan. This decision was mainly based on the availability of generic products for rizatriptan, naratriptan, sumatriptan and zolmitriptan, but not almotriptan at the time of the review by the Atlantic Common Drug Review committee. Note: as of July 2013, almotriptan is now available as a generic product.

Quantity limits for triptans are used by many of the funding programs. Seven of 12 funding programs (58%) have quantity limits that are applied to triptans, regardless of dosage forms (exception: British Columbia, Alberta, Ontario, Quebec, Yukon). Quantity limits of 6 dosages are used in Saskatchewan and the Atlantic provinces. Quantity limits of 12 dosages are used in Manitoba and the NIHB/NT/NU.

Summary of the restriction criteria is found in Exhibit 5. See Appendix 3 and 4 for detailed criteria for each public drug program with restricted listing status.

Exhibit 5: Summary of Provincial Criteria (for restricted listing)

Drug	Dosage form	Criteria for approval		
		Other acute treatment tried	Intolerance to or failed other triptan (or oral formulation)	Use of prophylactic treatment
Almotriptan	Tablet	AB, NB, NS, PEI, NL, ON, MB	NB, NS, PEI, NL	ON
Naratriptan	Tablet	AB, NB, NS, PEI, NL, ON, MB	PEI	ON
Rizatriptan	Tablet	AB, NB, NS, NL, ON, MB		ON
Sumatriptan	Tablet	AB, NB, NS, PEI, NL, ON, MB		ON
	Injection, nasal	AB, NB, NS, PEI, NL, ON, MB	NB, NS, NL, ON, PEI, BC	ON
Zolmitriptan	Tablet	AB, NB, NS, PEI, NL, ON, MB	PEI, ON	ON
	Nasal spray	AB, SK, NB, NS, PEI, NL, ON, MB	NB, NS, NL, ON, PEI	ON

NOTE: eletriptan and frovatriptan are not covered by most funding programs (exception: eletriptan is covered in Quebec)

Summary

1. Seven of 12 public drug programs in Canada (58%) have quantity limits that are applied to triptans, regardless of dosage forms (exception: British Columbia, Alberta, Ontario, Quebec, Yukon). A quantity limit of 6 is used in the Atlantic provinces and Saskatchewan and a quantity limit of 12 is used by Manitoba and NIHB/NT/NU.
2. Most public drug programs in Canada (9 of 12) have restriction criteria for use of triptans (such as quantity limits, use of other acute treatment prior to using triptans). Exceptions include: British Columbia (except for sumatriptan injection), Yukon Territories and Quebec where triptans are available as a general benefit for eligible patients.

Part 2: A representative from each public drug program (except Quebec) was contacted to participate in a 30 minute telephone interview to gather further information about formulary listing of triptans (see Appendix 5 for interview questions). Exhibit 6 summarizes the information obtained in the interviews.

Age limitations: Although some provinces had in the past restricted the use of triptans to patients younger than 65 years of age, no funding program in Canada currently restricts triptan use in patients over the age of 65 years. However, in Alberta, approval for triptans in patients over the age of 64 requires a written request by the prescriber (enforced restriction), whereas no written request by the prescriber is needed for patients between the ages of 18 and 64. Triptans are restricted for patients over the age of 18 in Alberta and Saskatchewan.

Review of criteria: Many of the funding programs have recently reviewed approval criteria for triptans. Internal review of triptan listing has occurred in the Atlantic provinces (2012) as well as NIHB (2012).

Exhibit 6: Summary of interviews with representative from public drug program

Province	Listing	Was there ever a change in listing?	What was the basis for listing/change in listing?	Any feedback from patients and/or healthcare professionals to public drug program regarding listing of triptans
British Columbia	General benefit (except for sumatriptan injectable)	No	NA	None
Alberta	Restricted (enforced for patients >64 years) Restricted (passive for 18-64 years)	Criteria reviewed in 2009. Previously 18-64 years only. Now covered for >18 years.	Triptans reviewed in 2009 as part of comprehensive review of SA criteria. Changes based on # significant advances in migraine treatment, significant cost (and cost differential between generics/brand)	None
Saskatchewan	Restricted (enforced)	Criteria reviewed in 2008 Q2 Previously 18-65 years only. Now covered for >18 years. Criteria reviewed in 2002Q1 Previously must have failed an analgesic/ergotamine. Now no requirement.	Internal review	1. some requests for cluster headache 2. complaints regarding the use of quantity limits 3. do not want to try/consider prophylactic therapy
Manitoba	Restricted (passive)	No	Expert Committee initially reviewed in triptans in 2002 and recommended quantity limit 12/month	None
Ontario	Restricted (enforced)	No	Not applicable	lack of availability of all triptans (including those not covered by EAP)
New Brunswick Nova Scotia Newfoundland	Restricted (enforced)	2009 Q2: preferentially list oral sumatriptan; quantity limits introduced 2013 Q2: list oral sumatriptan, zolmitriptan, rizatriptan and naratriptan (i.e., products that are available as generics)	Atlantic Common Drug Review recommendations	None

PEI	Restricted (enforced)	2009 Q2: preferentially list oral sumatriptan; eligibility no longer restricted to patients 18-65 years; quantity limits introduced	Atlantic Common Drug Review recommendations	None
NIHB	General benefit with quantity limit	2012 Q4: limit of 12/month	Internal review	Some patients initially complained when quantity limits first introduced
Yukon	General benefit	None	NA	None

NA: not applicable

Summary

1. Most provinces have restricted (enforced) criteria, requiring special authorization for triptans.
2. Internal review of triptan listing has occurred recently in the Atlantic provinces (2012) as well as NIHB (2012).
3. Age restrictions: Triptans are restricted to patients over the age of 18 in Alberta and Saskatchewan.

Selected International Jurisdictions

United States

In the United States, various payers have introduced quantity limits and/or step therapy as part of the reimbursement strategies for triptans. Quantity limits vary across the plans, and usually based on number of doses.

For example, Blue Cross/Blue Shield Illinois uses quantity limits that are designed to accommodate two times the median frequency of migraine attacks (three headaches) and two times the median of attack duration (2 days). Therefore, the limit is set at six days of headache per month. The quantity limits range from 12 doses (for almotriptan) to 24 doses (for rizatriptan). As well, this plan uses prior authorization for patients requesting quantities in excess of the specified quantity limit. In addition, step therapy criteria for the triptan agents is used to accommodate for use of brand triptans when the more cost-effective generic sumatriptan cannot be used due to allergy, intolerance, contraindication, or treatment failure or the brand agent is a recommended first-choice agent for the diagnosis.¹³ Note that this recommendation is from 2009; other triptans are now available as generic products in the United States.

Criteria for prior authorization once quantity limits have been exceeded include:¹⁴

- Diagnosis of migraine or cluster headache AND
- Greater than six moderate or severe headache days a month AND
- Tried and failed nonsteroidal anti-inflammatory (NSAIDS) within the last year or currently using NSAIDS, unless contraindicated AND
- Currently be using migraine preventative medication(s) (i.e. Beta-Blockers, Tricyclic Antidepressants, Anticonvulsants) unless contraindicated, adverse effects occurred, or no clinical benefit occurred after at least a 90 day trial at maximum tolerated dose AND
- No history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes; cardiovascular diseases; any type of angina pectoris, myocardial infarction(MI), or strokes; silent myocardial ischemia; transient ischemic attacks; ischemic bowel disease; uncontrolled hypertension; concurrent MAO inhibitor therapy (or within 2 weeks of discontinuing MAO inhibitor therapy); concurrent use of (or use within 24 hours of) ergotamine-containing or ergot-type medication; or hemiplegic or basilar migraine AND
- Prescribing clinician has reviewed recommendations based on evidence based studies

Quantity limits that have been imposed by other plans: 18 oral or nasal dosage forms of all triptan brands per calendar month (e.g., Minnesota Department of Human Services)¹⁵, and 8 tablets/month (United Healthcare Oxford)¹⁶.

Other Countries

In Australia, the Pharmaceutical Benefits Scheme restricts triptans to those patients with migraines who have failed to respond to analgesics (depending on the triptan, either as an active restricted listing requiring prior approval, or passive restricted listing using a pre-approved code, similar to an LU listing in

Ontario) . Sumatriptan, eletriptan and rizatriptan are listed with a pre-approved code whereas naratriptan and zolmitriptan require prior approval before dispensing. Quantities are also limited to four triptan oral dosage forms in a 20-day period. For sumatriptan nasal spray, the number of sprays per 20-day period is two.¹⁷No applications for increased quantities are permitted for the triptans.

In the UK, sumatriptan 50mg tablets (Imigran Recovery) has been available over-the-counter since 2006. In Germany, almotriptan 12.5mg tablet (Dolortriptan) and naratriptan 2.5mg tablet (Formigran) are available over-the-counter.^{18;19}

Summary

3. Managed care organizations in the United States use quantity limits for triptans. If the patient requires quantities in excess of the prespecified limits, then prior authorization utilizing specific criteria is required.
4. The Pharmaceutical Benefits Scheme in Australia sets a limit of 4 oral dosage forms in a 20-day period (i.e., 6 oral dosage forms in 30 days). Prior approval is required for naratriptan and zolmitriptan, whereas a pre-approved code (similar to LU codes) is used for sumatriptan, eletriptan and rizatriptan.
5. In the UK and Germany, several oral triptans are available as over-the-counter medication.

Part B: Guidelines for the management of acute migraine

Various guidelines have been published for the management of migraine. Some of these guidelines have focused on the management of acute and chronic migraine headache^{20;21}, management of acute migraine headache only¹⁰, or management of all types of headaches^{22;23}. A summary of these guidelines, specifically related to the use of triptan in the acute management of migraine, is below:

Canadian Guidelines:

Canadian Headache Society Guideline (2013):¹⁰

- Twelve medications received a strong recommendation for use in acute migraine therapy (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, ASA, ibuprofen, naproxen sodium, diclofenac potassium and acetaminophen).
- For patients with mild to moderate attacks, acetaminophen or NSAIDs can be tried. Triptans are recommended for moderate-severe attacks, or in patients who are considered NSAID failures.
- “Stratified” care is recommended (i.e., first acute medication recommended is tailored to the patient’s attack severity or degree of disability). This is in contrast to the “step care within attacks” approach, in which the patient takes an NSAID or acetaminophen early in an attack, and moves up to a triptan several hours later if the first medication is ineffective.
 - Limit use of triptans, ergotamine, opioids and combination analgesics to a maximum of 9 days a month.
- For menstrual migraine management:
 - In most patients, acute treatment is similar to acute treatment occurring at other times during the menstrual cycle.
 - For patients with refractory menstrual migraine, prophylactic therapy may be an option
 - For selected patients with refractory menstrual migraine with predictable timing of menstrual cycles, short-term monthly prophylaxis with triptans can be considered (e.g., frovatriptan 2.5mg twice daily starting two days before menstruation onset and continuing for 6 days).
 - For selected patients, hormonal manipulation (e.g., continuous use of combination oral contraceptives) can be considered.

International Guidelines:

American Academy of Neurology (2000):²⁰

Migraine Headache

- Use migraine-specific agents (triptans, dihydroergotamine) in patients with moderate or severe migraine or whose mild-to-moderate headaches respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or combinations such as aspirin plus acetaminophen plus caffeine.
- Select a nonoral route of administration for patients with migraine associated with severe nausea or vomiting.

Episodic Migraine Prevention (specifically menstrually associated migraine: MAM)(2012):²⁴

- Level A (established as effective and should be offered for migraine prevention)
 - Frovatriptan for short-term MAM prevention
- Level B (probably effective and should be considered for migraine prevention)
 - Naratriptan, zolmitriptan for short-term MAM prevention

British Association for the Study of Headache Guidelines (2010):²⁵

- Use of “stepped management” approach (failure on three occasions should be the criterion for progressing from each step to the next):
 - Step 1: OTC analgesic +/- antiemetic (e.g., ASA, ibuprofen)
 - Step 2: rectal analgesic +/- antiemetic (e.g., diclofenac suppositories +/- domperidone suppositories)
 - Step 3: specific anti-migraine drugs (e.g., triptan)
 - Triptans should be taken at the start of the headache phase.
 - Step 4: Combination of sumatriptan 50mg and naproxen 500mg (other combinations include steps one + three, followed by steps two + three).

ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013):²²

- Mild treatment: Clinicians may manage mild migraines with over-the-counter medications. Clinicians may use triptans for mild migraine pain levels.
- Moderate treatment: Consider use of DHE, ergotamine tartrate, lidocaine nasal, Midrin, NSAIDs or triptans.

NICE (2012):²³

Migraine with or without aura: acute treatment

- Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For young people aged 12–17 years consider a nasal triptan in preference to an oral triptan. [1.3.10]
- For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:
 - offer a non-oral preparation of metoclopramide, or prochlorperazine and
 - consider adding a non-oral NSAID or triptan if these have not been tried. [1.3.15]
- For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, aspirin (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events.
- When prescribing a triptan, start with the one that has the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans.

- Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting.
- Do not offer ergots or opioids for the acute treatment of migraine.

Early vs. late treatment of migraines

Four of the five guidelines that addressed this question recommended that patients treat migraine headaches as early as possible during their migraine attacks.^{10;20;22;25} (see Exhibit 7) Many studies concluded that early intervention with triptans when pain is mild results in higher pain-free and sustained pain-free rates.¹⁰ The Canadian Headache Society Guideline states that the benefits of early treatment must be balanced against the risk of medication overuse in patients with frequent migraine attacks.¹⁰

Exhibit 7: Early vs. late treatment of migraines

Guideline	Recommendation
American Academy of Neurology (2000): ²⁰	Treat attacks rapidly and consistently without recurrence. Failure to use an effective treatment promptly may increase pain, disability and the impact of the headache.
British Association for the Study of Headache Guidelines (2010): ²⁵	Triptans should be taken at the start of the headache phase. There is increasing evidence of greater efficacy when taken whilst pain is still mild, but triptans appear to be ineffective if administered during aura.
ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013): ²²	Studies on the treatment of migraine headache at the mild level show that triptans are more effective in abolishing pain at this stage than if the headache is more severe. Early treatment of migraines with effective medications improves a variety of outcomes including duration, severity and associated disability.
Canadian Headache Society Guideline (2013): ¹⁰	Patients with migraine attacks that are usually moderate or severe in intensity should be advised to take triptans early during their migraine attacks while pain is mild (caution the patient regarding medication overuse headache).
NICE (2012): ²³	Not addressed in review.

Prevention of medication overuse headache

Guidelines indicate that medication overuse headache can occur with acute treatment strategies, including the use of triptan (Exhibit 8). Four of the five guidelines indicate that taking triptans on 10 or more days per month may be associated with the development of medication-overuse headache.^{10;22;23;25} For further discussion on medication overuse headache, see Medication Overuse Headache.

Exhibit 8: Prevention of medication over-use headache

Guideline	Recommendation
American Academy of Neurology (2000): ²⁰	Many experts limit acute therapy to two headache days per week on a regular basis. Patients with medication overuse should use preventive therapy.

British Association for the Study of Headache Guidelines (2010): ²⁵	Use of triptans on 10 or more days a month is inappropriate for migraine and is associated with a clear risk of medication-overuse headache. Use of either triptans or analgesics on two or more days every week calls for close enquiry into how it is used, and review of the diagnosis.
ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013): ²²	Definition: headache greater than or equal to 15 days/month Regular overuse of ergotamine, triptans, opioids or combinations on greater than or equal to 10 days/month on a regular basis for greater than 3 months.
Canadian Headache Society Guideline (2013): ¹⁰	Patients should avoid use of triptans, ergots, opioids or combination analgesics on more than 9 days a month.
NICE (2012): ²³	Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more: triptans, opioids, ergots or combination analgesics on 10 days per month or more.

The use of prophylactic medications: when to start

For patients with frequent migraine attacks who are at risk of developing medication overuse headache, the use of prophylactic medications as well as behavioural approaches to migraine management should be considered.¹⁰(See Exhibit 9) The Canadian Headache Society Guideline and the ICS Migraine Guidelines suggest that prophylactic therapy should be considered in patients with three or more severe migraine attacks per month that fail to respond adequately to symptomatic therapy.^{10;22}The use of prophylactic medication may be an important consideration in development of criteria for special authorization for triptan therapy.

Exhibit 9: The use prophylactic medications: when to start

Guideline	Recommendation
American Academy of Neurology (2000): ²⁰	Consider preventive treatment for those patients who migraine has a substantial impact on their lives and have not responded to acute care, or where the frequency of migraine attacks is such that the reliance on acute care medications would increase the potential for drug-induced (rebound) headache.
British Association for the Study of Headache Guidelines (2010): ²⁵	Prophylaxis is used to reduce the number of attacks in circumstances when acute therapy, used appropriately, gives inadequate symptom control. The judge of this is usually the patient.
ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013): ²²	Criteria: three or more severe migraine attacks per month that fail to respond adequately to symptomatic therapy OR less frequent but protracted attacks that impair the patient's quality of life OR patient is interested in prophylactic treatment.
Canadian Headache Society Guideline (2013): ^{10;26}	Migraine prophylaxis should be considered for patients with greater than 3 moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than 8 headache days a month even when acute medications are optimally effective because of the risk of medication overuse headache.
NICE (2012): ²³	Not assessed in review.

Menstrual Migraine Management

Patients with menstrual-related migraine have migraine without aura attacks that occur during the time period starting two days before menstruation onset to three days after onset in at least two out of three menstrual cycles and additionally at other times of the cycle.²⁷ Various management strategies have been evaluated including daily prophylactic medication, hormonal manipulation (e.g., continuous use of combined oral contraceptives) and short-term monthly prophylaxis (e.g., naproxen, percutaneous estrogen and triptans).¹⁰ A summary of recommendations for the use of short-term monthly prophylaxis with triptans is provided in Exhibit 10.

Exhibit 10: Use of Triptans as Short-term Prophylaxis for Management of Patients with Menstrually-related Migraine

Guideline	Recommendation
American Academy of Neurology (2000): ²⁰	Not assessed in review.
British Association for the Study of Headache Guidelines (2010): ²⁵	Acute treatment of menstrual attacks of migraine is the same as for non-menstrual attacks but, because the former may have longer duration, it may be necessary to repeat treatment over several consecutive days. Provided that this does not lead to treatment on 10 or more days a month with codeine-containing analgesics, ergot or triptans, there is no concern regarding medication overuse.
ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013): ²²	NSAIDs should be considered approaches of first choice in the prophylactic treatment of migraine associated with menses. Many providers consider triptans to be equally effective, but there are no comparative studies. There are good placebo studies supporting the use of triptans (sumatriptan, naratriptan, frovatriptan and zolmitriptan) for cyclic prophylaxis.
Canadian Headache Society Guideline (2013): ¹⁰	For selected patients with refractory menstrual migraine with predictable timing of menstrual cycles, short-term monthly prophylaxis can be considered. Among the available options (frovatriptan, zolmitriptan, naratriptan, and naproxen), frovatriptan 2.5 mg twice a day starting two days before menstruation and continuing for six days has the strongest evidence for efficacy.
NICE (2012): ²³	For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan (2.5 mg twice daily) or zolmitriptan (2.5 mg two or three times daily) on the days migraine is expected.

Switching triptans due to non-responsiveness

In general, failure with one triptan does not necessarily predict failure for the entire drug class.^{28;29} (see Exhibit 11) Approximately 30% of patients fail to respond to a particular triptan; non-responsiveness can be the result of low and inconsistent absorption, use of medication at wrong time (e.g., too late in the attack), too small a dose or individual biological variability.^{25;30}

A review of five clinical studies suggests that there is evidence that switching from a triptan that is ineffective to a second triptan can result in a beneficial response.²⁸ It should be noted that there are criticisms of the study design used (e.g., open label vs. placebo-controlled). As well, only two studies prospectively reassessed the response to the first drug, whereas in the other 3 studies the non-responsiveness was retrospectively obtained through patient self-reports.

Exhibit 11: Use of alternative triptans in patients who fail to respond to a single triptan

Guideline	Recommendation
American Academy of Neurology (2000): ²⁰	Not assessed in review.
British Association for the Study of Headache Guidelines (2010): ²⁵	Evidence from several trials confirms the common clinical observation that patients with a poor response to one triptan can benefit from another in subsequent attacks. Ideally, each triptan should be tried in three attacks before it is rejected for lack of efficacy. Not only a different triptan but also dosage and a different route of administration should be considered.
ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013): ²²	Not assessed in review.
Canadian Headache Society Guideline (2013): ¹⁰	If a patient does not respond well to one triptan or tolerates it poorly, other triptans should be tried over time in subsequent attacks. It is recommended that patients wait 24 hours before trying another triptan.
NICE (2012): ²³	When prescribing a triptan, start with the one that has the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans.

Triptans in Pregnancy

For many women, migraine frequency may decrease during pregnancy, but in about 5-30% of women, migraine frequency remains unchanged.^{25;31} Although the role of triptans in pregnancy has not been well-defined, there is some data suggesting that sumatriptan may be used during pregnancy if triptan use is absolutely indicated.¹⁰ A summary of statements relating to the use of triptans in pregnancy is provided in Exhibit 12.

Exhibit 12: Use of Triptans as Option during Pregnancy

Guideline	Recommendation
American Academy of Neurology (2000): ²⁰	Not assessed in review.
British Association for the Study of Headache Guidelines (2010): ²⁵	Use of triptans during pregnancy cannot be recommended as routine. Most of the available information relates to sumatriptan, and suggests that exposure during pregnancy leads to no higher risk of birth defects than is recorded in the general population.
ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013): ²²	Not assessed in review.
Canadian Headache Society Guideline (2013): ¹⁰	Sumatriptan is a potential option for acute migraine treatment in pregnancy, but is not recommended for routine use. There is much less information available regarding the safety of other triptans during pregnancy; therefore, they should be avoided.

NICE (2012): ²³	Offer pregnant women acetaminophen for acute treatment of migraine. Consider use of a triptan or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy.
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Summary

1. Early vs. late treatment of migraines: Guidelines that have addressed this have all stated that patients should take triptans as early as possible during their migraine attacks.
2. Prevention of over-use headache: Guidelines are consistent in the definition of medication over-use headache associated with triptans i.e., regular use of triptans (or combinations of triptans with opioids) on 10 days a month or more on a regular basis for greater than 3 months places the patient at risk for the development of medication over-use headache.
3. Prophylactic medication: The Canadian Headache Society Guideline and the ICS (Institute for Clinical Systems Improvement) Migraine Guidelines state that prophylactic therapy should be considered for patients with greater than 3 moderate or severe headache days a month that fail to respond to symptomatic therapy.
4. Menstrually-related migraine: Triptans given cyclically (e.g., 6 days/month) have been recommended as an option for the management of women and girls with menstrually-related migraine.
5. Triptans in pregnancy: Although not considered a routine choice for pregnant women with migraines, sumatriptan can be considered after assessing the need for treatment and potential risks.

Part C: Impact of different drug reimbursement schemes for triptans

Methods

A literature search was conducted in Pubmed using the terms: triptans OR tryptamines OR migraine disorders AND health services accessibility OR treatment outcome OR drug utilization review OR managed care programs. Bibliographies of identified articles were scanned for additional relevant articles relating to the impact of different triptan drug reimbursement schemes (e.g. quantity limits, restricted access) on patient access and/or utilization and costs.

Results

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. In addition, since more than 85% of migraine patients experience four or fewer headache occurrences per month, the use of quantity limits would only affect a small majority of migraine sufferers.⁶ Finally, use of quantity limits can result in cost-savings for the payee. A quantity limit of 12 tablets 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.³²

Impact of Quantity Limits on Medical and Economic Outcomes

There have been five published studies, all of which were of a retrospective, observational design, that have investigated the impact of quantity limits on pharmacy and medical outcomes (see Exhibit 13).³³⁻³⁷ These studies were all conducted by health maintenance organizations in the United States. In each of these studies, the total cost and utilization of triptan prescriptions was decreased after implementation of quantity limits. In two of the studies that reported total costs of migraine care (e.g., all medications and medical care), costs decreased by 11% and 26%^{34;36}; however, one of these studies showed no significant difference in overall costs.³⁵

Although quantity limits may help to reduce overall costs, the evidence that they help to reduce the risk of development of medication overuse headache is scarce. A randomized, parallel group study of 6 months duration enrolled 197 subjects with a frequency of 3-8 migraines per month who were randomly assigned to receive 9 (formulary limit: FL) or 27 (clinical limit: CL) tablets of rizatriptan 10mg orally disintegrating tablet per month.³⁸ The primary endpoint was change in the mean number of migraine days from baseline to treatment period. At the end of 3 months, there was no statistically significant difference between the two groups. Subjects in the CL group treated attacks at lower headache severity; this resulted in the mean number of doses of study medication used per month in the CL group increasing significantly from 6.5 to 8.6 tablets/month, whereas there was no change in the FL group. No significant difference was associated between the two groups in elimination of associated symptoms and functional impairment at 2 hours, responder rate (50% reduction in number of attacks per month), attack severity or attack duration. The authors concluded that providing a greater quantity of rizatriptan

tablets did not reduce the number of migraine days per month.

In addition, due to quantity limits that various drug plans impose, it has been suggested 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.^{32;39} In one multicenter, cross-sectional, observational study, the most frequent external factor that patients identified with delaying treatment with a triptan was concern that the triptan prescription would not last all month (30.8%).³⁹ In another cross-sectional, observational study, the most commonly stated reason for not treating a migraine headache early was the desire to reserve medication for a severe migraine (51.2%) followed by not having medication on hand (34.9%) and health plan quantity limit on drugs (27%).⁴⁰ This is important since treatment of headache in the early phase is recommended to minimize adverse events and headache recurrence. Conversely, when quantity limits are not severely restricted, patients will treat mild migraine headaches more often than those with more severely restricted limits.³⁸ In an observational study, patients receiving 27 tablets/month (clinical limit: CL) increased their treatment of mild headaches by 7% and patients receiving 9 tablets/month (formulary limit: FL) decreased their treatment of mild headaches by 0.5% ($p < 0.0001$ for FL vs CL groups).³⁸

Use of prophylactic (preventative) therapy to decrease triptan usage

In order to decrease triptan usage, one reimbursement strategy that has been employed is use of prophylactic migraine therapy in patients who experience a pre-specified number of migraine headaches per month. Evidence suggests that there is an overall decrease in the use of abortive treatments, in particular triptans, after initiation of prophylactic migraine treatment.⁴¹⁻⁴³

Triptan therapy is the preferred treatment in patients who have failed to respond to conventional analgesics such as nonsteroidal anti-inflammatories (NSAIDs) or ASA. Preventive care should be considered for patients who have more than 3 moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than eight headache days a month even when acute medications are effective because of the risk of medication overuse headache. However, prophylactic medications for migraine are underused.¹⁰ In one study, 38% of patients met the study guidelines for being offered or considered for prophylactic medication, but only 12% indicated that they were taking a migraine preventive medication.⁶

There are a number of different agents that are used as preventive treatment including: beta-adrenergic blockers (e.g., metoprolol, propranolol, atenolol), anti-epileptic drugs (valproic acid, topiramate, gabapentin), calcium channel blockers (e.g., verapamil), tricyclic antidepressants (e.g., amitriptyline)⁴⁴ and serotonin antagonists (e.g., pizotifen, methysergide). For the treatment of chronic migraine, topiramate has been the best studied agent although approximately 30-50% of patients develop paresthesias. Other agents that have been used for chronic migraine include botulinum toxin.^{26;45}

One study examined the pharmacy and medical utilization and costs of migraine patients in a managed care population and compared health services utilization trends of patients who are treated with prophylaxis with those who might be candidates but do not receive migraine prophylaxis (3 or more

migraines/month).⁴⁶ Overall patients receiving drug prophylaxis had lower migraine-related costs than those using acute treatment alone. The average treatment effect of drug prophylaxis in moderate-to-severe migraine patients was a decrease of \$560 per patient per year (21% in total migraine cost versus no prophylaxis).

Another study found that there was an overall decrease in the use of abortive treatments, in particular triptans, after initiation of prophylactic migraine treatment. The decrease in the number of triptan prescriptions following initiation of prophylactic therapy ranged from 38.6% for patients started on topiramate to 18.6% for patients initiated on amitriptyline.⁴¹ Similarly, a retrospective study concluded that sumatriptan use decreased after initiation of prophylactic therapy. The decrease in sumatriptan usage was greatest in patients receiving highest number of units at baseline. Reductions were also noted in office visits, ED visits and other healthcare utilization (e.g., CT scans, MRI scans) costs.⁴²

Using data from two US claims databases with data for a total of 4394 patients with migraine, a statistically significant decrease in triptan use of up to 20% was noted in the 12 month period after starting topiramate therapy.⁴⁷ As well, in one of these analyses, significant reductions were noted in the proportion of patients using concomitant non-opioid analgesics and NSAIDs during the 6 months after topiramate initiation. A non-significant reduction was noted in the use of opioids.⁴³

Use of a preferred triptan

In some jurisdictions, use of a preferred triptan has been employed in order to reduce expenditures associated with triptans. Often the preferred triptan is chosen based on economic concerns (e.g., drug contracts), and not on any clinical evidence. However, limited studies have shown there are issues to implementing such a strategy.^{48;49}

A retrospective cohort study conducted in a managed care organization investigated the conversion success, migraine drug utilizations and patient satisfaction with a clinical pharmacist-managed conversion program from sumatriptan to rizatriptan ODT.⁴⁸ Due to changes in drug purchase contracts, it was economically advantageous to consider the use of rizatriptan over sumatriptan in a managed care organization. Both drugs remained on the formulary and there was no incentive for members to convert to rizatriptan from sumatriptan. Conversion was attempted in 457 patients with 47% successfully converted. The patients who failed conversion had a higher mean number of sumatriptan doses per patient per month compared with the successful conversions. Rizatriptan ODT was preferred by 68% and 8.5% of successful and failed conversion subjects, respectively ($p < 0.001$). Using representative group purchase prices, triptan expenditures for successful conversion subjects were reduced by a median of -\$2 (6%) PPPM while triptan expenditures for unsuccessful conversions increased by a median of \$8 ($P < 0.001$). There were no differences in changes in migraine-related office visits in either group.

In a retrospective database analysis of 292 patients who were switched from sumatriptan to another triptan, 54% of patients returned to sumatriptan within 15 months.⁴⁹ Switching from sumatriptan to another triptan resulted in a significant increase in costs of £53 per patient compared to patients continuing on sumatriptan over a 15-month period. The authors suggest that switching patients already

established on sumatriptan to another triptan is not economically rational.

Disease management programs

Migraine quality-of-care programs have been introduced in some US healthcare plans in order to reduce utilization of triptans and improve clinical management of patients with migraines. These programs include: provision of appropriate physician and patient education about the signs and symptoms of migraine; use of migraine diaries for recording the frequency of migraine attacks; use of patient feedback reports; and the provision of telephone disease management support units.⁴⁷

A prospective, observational study showed that group educational sessions on management of migraine headaches had the potential to decrease medical costs (but not triptan costs) and improve quality of care for patients.⁵⁰ The 6-month triptan costs increased by 19%, but the number of headache-related office visits and emergency department visits was reduced by 32% and 49%, respectively.

Summary

1. All studies have shown a decrease in triptan costs when quantity limits have been imposed. In two of three studies, there was an overall decrease in medical costs associated with migraines when quantity limits were implemented.
2. There is no direct evidence that imposing quantity limits for triptans reduces the risk of development of medication overuse headache.
3. 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.
4. Use of prophylactic medication for migraine has been shown to decrease triptan use.
5. Use of a preferred triptan (based on economic reasons) may not be a viable option as studies have indicated that many patients revert back to their original triptan.

Part D: Rapid Review of Selected Topics

Medication Overuse Headache and Triptans

Medication overuse headache (also known as rebound or drug-induced headache) results from the overuse of opioids, other analgesics or triptans. The International Headache Society defines medication overuse headache (MOH) as a chronic headache occurring on 15 or more days per month after regular overuse for more than 3 months of ergotamine, triptans, opioids or combined analgesic medications on 10 days or more days per month, or simple analgesics alone (acetaminophen, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs on 15 days a month or more.²⁷ The prevalence of MOH is approximately 1% of adults in the general population.⁵¹

Studies have investigated the proportion of migraineurs who are considered overusers. A population-based observational study in the Netherlands concluded that 10% of users of triptans were overusers (defined as 18 single doses or more per month for 3 or more consecutive months). As well, the overusers were responsible for nearly half of the total costs for triptans.⁵² In the Canadian Headache Outpatient Registry and Database (CHORD) study, 21% of patients referred to headache specialists in Canada who received a migraine diagnosis had acute medication overuse.⁵³

The overuse of any acute headache treatment including ergotamine, triptans, opioids and NSAIDs, can result in MOH.^{11;54} Case series have identified triptans as a cause for the development of MOH, although the frequency of use for the triptans ranged from 0.1 to 56%.⁵⁵ Other risk factors for the development of medication overuse headache include gender (women are more prone to develop MOH)⁵⁶, caffeine (often found in combination containing analgesics), regular use of tranquilizers, psychologic comorbidities such as depression and anxiety, low socioeconomic status⁵⁷ and presence of other body pains (e.g., chronic back pain, fibromyalgia).⁵⁴ Use of combination analgesics and triptans result in higher headache frequency and greater intensity than overuse of triptans alone.⁵⁸

Overuse of triptans has been identified as a significant risk factor for the development of MOH. In a prospective study of 98 patients, triptan overuse led to medication over-use headache more quickly and at lower dose levels than did overuse of ergots or analgesics.⁵⁹ All eligible patients underwent inpatient medication withdrawal. Patient diaries and interview were used to compare the features of MOH associated with the overuse of acute treatments. The onset of daily headache was shortest for triptans (approximately 1.7 years), 2.7 years for ergots and 4.8 years for simple analgesics. As well, the number of doses associated with the development of MOH in this study was lowest for the triptans (18 single doses per month), 37 single doses per month for ergots and 114 single doses per month for analgesics. Although the mean number of doses associated with the development of MOH with triptans was 18, it was as low as 10 single doses per month in some patients.

Some patients with episodic migraine may develop chronic migraine (sometimes referred to as transformed migraine) over several months or years. Chronic migraine is defined as migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse.²⁷ The transition to chronic migraine (known as migraine chronification) is influenced by a variety of factors including lifestyle, comorbid conditions and possible medication overuse.⁶⁰ Although

MOH is considered a separate diagnosis from chronic migraine, some authors consider MOH a complication of chronic migraine.⁶¹ Although triptans were associated with migraine progression in those with 10-14 days of headache at baseline, overall, triptans did not induce chronic daily headache.⁶² In a cross-sectional study surveying approximately 24,000 patients with a diagnosis of migraine, triptans did not increase the risk of chronic migraine overall (OR=1.07, 95% CI=0.89-1.29).⁶³

Prevention of MOH associated with triptans includes education of patients to the hazards of MOH, limiting the number of doses of triptans per month, avoidance of drugs that contain barbiturates, caffeine, codeine or tranquilizers, and early and appropriate migraine prophylaxis.⁵⁴

Summary: The International Headache Society defines a triptan medication overuse headache as headache present on fifteen or more days per month with regular overuse of triptans for 10 or more days per month on a regular basis for more than 3 months. The evidence for the diagnostic criteria is based primarily on one observational study that showed that 10 single doses per month (mean 18 single doses/month) may place some patients at risk for the development of MOH.⁵⁹

Health Canada Warnings/Alerts and US Food Drug Administration Warnings

In 2000, Health Canada issued a warning regarding the possibility of an increased risk of serotonin syndrome during concomitant administration of serotonergic antidepressants or triptans and St. John's Wort products.⁶⁴

In 2006, the 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.⁶⁵ In 2010, the American Headache Society reviewed the literature and published a position paper on the potential risk of serotonin syndrome with the use of triptan, and SSRI or SNRI. In this review, they 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.⁶⁶

Use of Triptans and Workplace Productivity

The prevalence of migraine is approximately 10% of the adult population in Canada; the highest prevalence occurs during peak employment years (between the ages of 25-54).⁷ The burden of migraine is substantial and impacts patients (e.g., decreased quality of life), family, employers (e.g., lost workdays and productivity) and society.⁶⁷

Direct costs related to migraine include the use of medical resources, emergency room visits, diagnostic procedures and medications. Indirect costs include temporary disability, reduced functionality and lost productivity (either as absenteeism or presenteeism). Presenteeism can be described as loss of productivity that occurs when employees come to work but perform below par due to any kind of illness.⁶⁸ The impact of migraine symptoms on health care use and work loss in Canada was assessed in 134 patients. Patients reported an average of 6.5 days absent from work, 44 days working with migraine headache and 10.4 reduced workday equivalents due to ineffectiveness at work with

migraine.⁶⁹

A study published in 1999 estimated the indirect costs of migraine in the United States at \$13.3 billion.⁷⁰ These costs were primarily based on missed work days (approximately \$8 billion or 60% of total indirect costs) and impaired work performance. In another study conducted in the United States, patients with migraine incurred significantly higher indirect costs compared with a cohort of patients without migraine including absence, short-term disability and worker's compensation. The annual indirect expenditures were significantly higher in the migraine group compared with the control group (\$4453 vs \$1619; $p < 0.001$). The total estimated indirect burden, excluding presenteeism, was \$12 billion.⁷¹

Triptans have been shown to reduce migraine-associated lost workplace productivity by their ability to provide freedom from pain and associated symptoms and restoration of functional ability.^{72,73} In a randomized, double-blind placebo-controlled trial, 135 migraineurs used injectable sumatriptan to treat migraines that started in the first 4 hours of an 8 hour shift.⁷⁴ Overall, sumatriptan was superior to placebo in reducing productivity loss due to migraine. For example, significantly more sumatriptan-treated patients vs. placebo treated patients experienced shorter return to normal work performance at 2 hours (52 vs 9%, respectively; $p < 0.001$).

In an observational study conducted in a large California health plan, initiation of sumatriptan therapy was associated with improved productivity outcomes. Total lost workplace productivity (encompassing both absenteeism and presenteeism) decreased by 70% from 9.72 lost days per 3 months before initiation of sumatriptan to 2.87 lost days per 3 months after sumatriptan was started.⁷⁵ An economic model was developed for two US companies to estimate productivity costs of migraine and impact of triptan use on productivity. For the major financial services corporation with over 87,000 employees, the value of annual work loss avoided if migraine is treated with rizatriptan was projected at \$10.3 million (versus baseline cost of \$23.8 million).⁷⁶

Summary: Migraine disorder impacts the workplace significantly through absenteeism and presenteeism. Triptans have been shown to significantly impact the total lost workplace productivity.

Triptan formulations and patient preference

Triptans are available in various dosage forms including conventional tablet, oral disintegrating tablet, nasal spray and injectable formulations. Factors to consider in terms of patient preference with triptan formulations include^{10,77}:

- Non-oral routes can be considered for patients with migraine associated with severe nausea or vomiting. An injectable formulation may be useful for patients with migraine attacks that progress very rapidly and/or are characterized by early vomiting.¹⁰
- A nasal spray may provide a fast onset of action than oral formulations but may be associated with bad taste. In one study, zolmitriptan nasal spray was preferred in 36% of subjects compared to zolmitriptan oral disintegrating tablet (preferred by 50% of subjects) and conventional tablet (preferred by 14% of subjects).⁷⁸
- Oral disintegrating tablets (ODT or wafers) can be taken without water. Oral disintegrating

tablets do not have a faster onset of action, as they are not absorbed through the buccal mucosa but rather are swallowed and absorbed in the gastrointestinal tract.¹⁰

- Frovatriptan has the longest half-life but the slowest onset of action. Naratriptan also has a slow onset of action and longer half-life (see Exhibit 13)
- Triptans with longer half-lives and greater 5-HT_{1B} receptor potency had the lowest rates of headache recurrence. Recurrence rates were lowest for frovatriptan, eletriptan and naratriptan.^{79;80}

A comparison of the triptans, including dose, pharmacokinetic data and drug interactions is found in Exhibit 13.

Exhibit 13: Comparison of Available Triptans

Drug	Route	Usual Dose*	Maximum dose (per 24hrs)	Age recommendations**	Onset	Tmax	Half-life	Bioavailability	Significant drug Interactions
Almotriptan (Axert) ⁸¹	Oral	12.5mg	25mg	Pediatrics: 12-17 yrs Adults: >18yrs Geriatrics (>65): caution	0.5-2hr	1-3hr	3-4hr	~70%	Other triptans, ergot derivatives
Eletriptan (Relpax) ⁸²	Oral	20-40mg	80mg	Adults: >18yrs Geriatrics (>65): not recommended	0.5hr	2hr	4hr	50%	Other triptans, ergot derivatives Potent CYP3A4 inhibitors (e.g., ketoconazole) may inhibit metabolism of eletriptan and increase risk of adverse effects
Frovatriptan (Frova) ⁸³	Oral	2.5mg	5mg	Adults: >18yrs (limited clinical experience in elderly)	2-3hr	2-4hr	26hr	20-30%	Other triptans, ergot derivatives CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin) can increase half-life
Naratriptan (Amerge) ⁸⁴	Oral	2.5mg	5mg	Elderly (>65 yrs): not recommended	1-3hr	2-3hr	6hr	70%	Other triptans, ergot derivatives
Rizatriptan (Maxalt) ⁸⁵	Oral	10mg	20mg	Adults: >18yrs Pediatrics: not recommended Geriatrics (>65): not recommended	30min-2hr	1-1.5hr (tab); 1.6-2.5hr (ODT)	2-3hr	45%	Other triptans, ergot derivatives MAOIs (avoid use within 14 days) Use 5mg if taken concurrently with propranolol
Sumatriptan (Imitrex) ⁸⁶	Oral	50-100mg	200mg	Adults: >18yrs Pediatrics: not recommended Geriatrics (>65): not recommended	20-30min	2.5hr	2.5hr	~15%	Other triptans, ergot derivatives MAOIs (avoid use within 14 days)
	Nasal spray	20mg	40mg		15 min (20mg)	1hr	2hr	~17%	
	Injectable	6mg	12mg		10-15min	0.25hr	2hr	97%	
Zolmitriptan (Zomig) ⁸⁷	Oral	2.5mg	10mg	Adults: >18yrs Pediatrics: not recommended Geriatrics (>65): not recommended	45min	2hr (tab); 3hr (ODT)	3 hr	40%	Other triptans, ergot derivatives MAOIs (avoid use within 14 days) CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin) can increase half-life (maximum dose 5 mg/24hours recommended when used concurrently)
	Nasal spray	5mg	10mg		15min	3hr	3hr	41%	

*Based on product monograph recommendations, neurologist survey and literature review; dose can be repeated (up to the maximum dose) in a 24 hour period if headache returns

**Based on product monograph recommendations. Adapted from Reference⁸⁸⁻⁹⁰

Discussion

Part A: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Availability in Canada

- There are seven triptans available in Canada: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan.
 - Sumatriptan was the first triptan introduced onto the Canadian market in 1992.
 - All triptans are available as oral formulations. Sumatriptan is available as an injectable solution. Sumatriptan and zolmitriptan are available as nasal sprays.
- Most oral triptans available as generic formulations. Injectable sumatriptan also available generically.
- The cost of six tablets for brand-name oral triptans varies from \$82.57-105.69. Wholesale generic prices range from 46-75% of brand name prices.
- The most common package size is 6 for the majority of oral dosage forms. The nasal sprays are available in packages of 2 sprays (Imitrex and Zomig); in addition, Zomig is packaged as 6 sprays (i.e., 3x2 sprays). Sumatriptan injectable is packaged as 2 syringes.

Public Plan Listing in Canada

- Triptans are available as benefits on public drug programs in Canada.
 - General benefits without restrictions: British Columbia, Yukon, Quebec
 - General benefits with quantity limits: NIHB/NT/NU
 - Restricted (passive): Manitoba, Alberta (Alberta Health Restricted Benefit)
 - Restricted (enforced): Alberta (Alberta Health Special Authorization), Saskatchewan, Ontario, Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland
- Restriction criteria include:
 - Quantity limits (12 doses for NIHB and Manitoba; 6 doses for Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland)
 - Previously failed other therapies such as NSAIDs, acetaminophen, DHE spray (Alberta, Manitoba, Ontario, Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland)
 - Use of prophylactic medication (Ontario)
 - Previously failed other triptans (e.g., zolmitriptan)

EAP Listing in Ontario

1. Between 67% and 70% of EAP requests for almotriptan, naratriptan, rizatriptan and sumatriptan are approved.
2. Approval for zolmitriptan, which has more restrictive EAP criteria (patients must have failed or demonstrated intolerance to other triptans), is rare. This may reflect lack of awareness of these criteria among prescribers.
3. The majority of requests that were not approved had missing information or had no description of

migraine headaches, use of preventative therapy or intolerance to oral triptan.

Selected International Jurisdictions

- Managed care organizations in the United States use quantity limits for triptans. If the patient requires quantities in excess of the prespecified limits, then prior authorization utilizing specific criteria is required.
- The Pharmaceutical Benefits Scheme in Australia sets a limit of 4 oral dosage forms in a 20-day period (i.e., 6 oral dosage forms in 30 days). As well, use of triptans is restricted to those patients with migraines who have not responded to analgesics.
- In the UK and Germany, several oral triptans (sumatriptan, naratriptan, almotriptan) are available as over-the-counter medication.

Part B: Guidelines for the management of acute migraine

- Five guidelines were reviewed: American Academy of Neurology (2000), British Association for the Study of Headache Guidelines (2010), ICS (Institute for Clinical Systems Improvement) Migraine Guidelines (2013), Canadian Headache Society Guideline (2013) and NICE (2012).
- Early vs. late treatment of migraines: Guidelines that have addressed this have all stated that patients should take triptans as early as possible during their migraine attacks. Use of a “stratified” care approach, where the first acute medication recommended is tailored to the patient’s attack severity or degree of disability, is recommended by most guidelines.
- Prevention of over-use headache: Guidelines are consistent in the definition of medication over-use headache associated with triptans i.e., regular use of triptans (or combinations of triptans with opioids) on 10 days a month or more on a regular basis for greater than 3 months places the patient at risk for the development of medication over-use headache.²⁷
- Prophylactic medication: The Canadian Headache Society Guideline and the ICS (Institute for Clinical Systems Improvement) Migraine Guidelines state that prophylactic therapy should be considered for patients with greater than 3 moderate or severe headache days a month that fail to respond to symptomatic therapy.
- Management of Menstrually-associated Migraine with Triptans: Triptans given cyclically (e.g., 6 days/month) have been recommended as an option for the management of women and girls with menstrually-related migraine.

Part C: Impact of different drug reimbursement schemes for triptans

- Quantity limits:
 - Most studies have shown a decrease in overall medical costs (including triptan drug costs, prophylactic medications, other acute drug costs, office visits, emergency room visits) when quantity limits have been imposed with triptans.
 - There is no direct evidence that imposing quantity limits for triptans reduces the risk of development of medication overuse headache.
 - 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.
- Use of prophylactic migraine treatments:
 - Limited studies have shown that patients receiving drug prophylaxis had lower migraine-related costs than those using acute treatment alone.
- Use of a preferred triptan:
 - Use of a preferred triptan (based on economic reasons) may not be a viable option as studies have indicated that many patients revert back to their original triptan.
- Educational programs:
 - Educational programs have been used in conjunction with other strategies to improve patient outcomes. For example, an educational intervention to increase use of migraine prophylaxis in appropriate patients resulted in a trial of a migraine prophylactic drug initiated in about one-third of candidates. Migraine quality-of-care programs (including provision of physician and patient education material) have been introduced in order to reduce utilization of triptans and improve clinical management of patients with migraines.

Part D: Rapid Reviews of Selected Topics

- Medication overuse headache:
 - A triptan medication overuse headache is defined as headache present on fifteen or more days per month with regular overuse of triptans for 10 or more days per month on a regular basis for more than 3 months.
 - The evidence for the diagnostic criteria is based primarily on one observational study that suggested that 10 single doses per month may place some patients at risk for the development of MOH.
- Health Canada warnings/alerts and FDA warnings:
 - Possibility of an increased risk of serotonin syndrome during concomitant administration of serotonergic antidepressants or triptans and St. John's Wort products (Health Canada: 2000)
 - Potential for serotonin syndrome in patients taking triptans and selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) concomitantly (FDA: 2006).
- Patients may prefer certain dosage formulations such as:
 - Non-oral routes for migraines associated with severe nausea or vomiting
 - A nasal spray may provide a fast onset of action (but may be associated with bad taste)
 - Oral disintegrating tablets (wafers) can be taken without water

Health Equity

No major health equity issue was identified in this analysis. Triptans are available across Canada through public health plans, albeit some plans are more restricted in coverage than others. Migraines can occur in adolescent patients. However, some plans restrict the use of triptans in patients over the age of 18. It should be noted that almotriptan is indicated in adolescents 12-17 years of age.

No specific issues regarding health equity were identified in the literature review. However, it should be noted that quantity limits imposed by drug plans may not have taken into consideration women with menstrual migraines. In women with refractory menstrual migraines, use of a triptan twice daily for six days/month (i.e., 12 tablets) is a treatment option.¹⁰ It should be noted that women with menstrually-related migraine may also suffer from migraine attacks at other times of the cycle, thereby requiring greater than 12 tablets/month.

Access to triptans was restricted in some provinces (e.g., Alberta, Saskatchewan, Prince Edward Island) to migraineurs under the age of 65 prior to 2009. However, after reviews were conducted in each of these provinces, all public plan beneficiaries, regardless of age, now have access to triptans.

Triptans are costly drugs, especially for patients suffering from multiple migraines every month. Unfortunately, for patients without access to public drug coverage or other private insurance, triptans may be inaccessible.

Conclusion

There are seven triptans available on the Canadian market in various dosage forms including oral tablet, oral disintegrating tablets, nasal sprays and injectable. In Canada, triptans are covered in all public drug programs; however, various reimbursement schemes are used including general benefit with no restrictions, general benefit with quantity limit, restricted (passive) benefit with quantity limits and restricted (enforced) benefit with various criteria, including quantity limits, use of previous acute medications and use of concurrent prophylactic medications. In Ontario, triptans are available under the Exceptional Access Program (EAP), but no quantity limits are in place. Quantity limits are used in many of the public health plans in Canada, as well as by private and public payers in the United States and public payers internationally.

Quantity limits for triptans are imposed for economic as well as clinical benefits. A review of the literature suggests that implementation of quantity limits decreases triptan utilization and cost. From a clinical perspective, quantity limits have been implemented to prevent medication overuse headaches. Other reimbursement schemes that are employed include step therapy (e.g., use of other non-triptan medications prior to triptan use) and prophylactic migraine medication in patients who exceed the defined quantity limit.

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Appendix A: Triptans available in Canada

Information obtained from Health Canada Drug Product Database ⁹¹

Generic name	Trade Name	Dosage forms	Generic available	DIN	Package size
Almotriptan	Axert	Tablets (6.25mg, 12.5mg)	Yes	Axert 6.25 02248128 Axert 12.5 02248129 Apotex 6.25 02405792 Apotex 12.5 02405806 Mylan 6.25 02398435 Mylan 12.5 02398443 Sandoz 12.5 02405334	6 tabs 6 tabs 6 tabs 6 tabs 6 tabs 6 tabs 6 tabs
Eletriptan	Relpax	Tablets (20mg, 40mg)	Yes	Relpax 20 02256290 Relpax 40 02256304 Apotex 20 02386054 Apotex 40 02386062 Genmed 20 02342235 Genmed 40 02342243 Teva20 02382091 Teva 40 02382105	6 tabs 6 tabs 6 tabs 6 tabs 6 tabs 6 tabs 6 tabs 6 tabs
Frovatriptan	Frova	Tablets (2.5 mg)	No	Frova2.5mg 02257084	7 tabs
Naratriptan	Amerge	Tablets (1 mg, 2.5 mg)	Yes	Amerge 1 02237820 Amerge 2.5 02237821 Sandoz 2.5 02322323 Teva 1 02314290 Teva 2.5 02314304	2 tabs 2 tabs, 6 tabs 6, 8 tabs 8 tabs 8 tabs
Rizatriptan	Maxalt	Tablets (5mg, 10mg)	Yes	Maxalt10mg 02240521 Apo 5mg 02393468 Apo 10mg 02393476 Cobalt 10mg 02381702 Jamp 5 02380455 Jamp 10 02380463 Marcn 10 02379678	12 tabs 6 tabs 6 tabs 6 tabs, 12 tabs 6 tabs 6 tabs, 30 b 12 tabs
	Maxalt RPD	Wafers (oral disintegrating tablet) (5 mg, 10mg)	Yes	Maxalt 5 02240518 Maxalt 10 02240519 Apo 5mg 02393484 Apo 10mg 02393492 Cobalt 5 02374730 Cobalt 10 02374749 Dom 10mg 02396203 Mylan 5 02379198 Mylan 10 02379201 PMS 5 02393360 PMS 10 02393379 Sandoz 5 02351870 Sandoz 10 02351889	12 tabs 12 tabs 6 tabs 6 tabs 6 tabs, 12 tabs 6 tabs 12 tabs 6 tabs, 12 tabs 6 tabs 6 tabs 6 tabs 6 tabs 6 tabs 6 tabs

Sumatriptan	Imitrex	Tablets (25 mg, 50mg, 100mg)	Yes	Apo 50 02279399 Apo 100 02268396 Avanstra 50 02366258 Avanstra 100 02366266 Cobalt 25 02257882 Cobalt 50 02257890 Cobalt 100 02257904 Dom 25 02270749 Dom 50 02270757 Dom 100 02270765 Imitrex DF 50 02212153 Imitrex DF 100 02212161 Mylan 25 02268906 Mylan 50 02268914 Mylan 100 02268922 Pharmel 25 02270714 Pharmel 50 02270722 Pharmel 100 02270730 PMS 25 02256428 PMS 50 02256436 PMS 100 02256444 Sandoz 50 02263025 Sandoz 100 02263033 Sanis 25 02286513 Sanis 50 02286521 Sanis 100 02286548 ProDoc 50 02324652 ProDpc 100 02324660 Sivem DF 50 02385570 Sivem DF 100 02385589 Teva 100 02239367 Teva DF 25 02286815 Teva DF 50 02286823 Tev DF 100 02286831	6t 6t 6t 6t 6t, 100b 6t, 100b 6t, 100b 6t, 30b 6t, 30b 6t, 30b 6t 6t 6t 6t 6t, 30b 6t, 30b 6t, 30b 6t, 30b 6t, 30b 6t 6t 6t 6t, 50 b 6 t 6 t 6 t 6 t
	Imitrex	Injection (12 mg/mL)	No	Imitrex 6 02212188 Taro 6 02361698	2 syringes 2 syringes
	Imitrex	Nasal spray (5 mg/dose, 20 mg/dose)	No	Imitrex 5 02230418 Imitrex 20 02230418	2 sprays 2 sprays
Zolmitriptan	Zomig	Tablets (2.5 mg)	Yes	Dom 2.5 02389525 Mylan 2.5 02369036 PMS 2.5 02324299 Riva 2.5 02401304 Sandoz 2.5 02362988 Teva 2.5 02313960 ProDoc 2.5 02379929 Zomig 2.5 02238660	6t 6t 6t, 30b 6t, 30b 2t, 6t 2t, 6t 6t 3t, 6t
	ZomigRapimelt	Oral disintegrating tablet (2.5 mg)	Yes	Mylan 2.5 02387158 PMS 2.5 02324768 Sandoz 2.5 02362996 Teva 2.5 02342545 ProDoc 2.5 02379988 Zomig 2.5 02243045	6t 6t 2t, 6t 2t, 6t 6t 2t, 6t
	Zomig	Nasal spray (2.5 mg/spray, 5 mg/spray)	No	Zomig 2.5 02248992 Zomig 5 02248993	2 sprays 6 sprays

Appendix B: Webpages for Provincial Drug Formularies

Province	Webpage for Drug Formulary
British Columbia	http://www.health.gov.bc.ca/pharmacare/benefitslookup/faces/Search.jsp
Alberta	https://idbl.ab.bluecross.ca/
Saskatchewan	http://formulary.drugplan.health.gov.sk.ca/
Manitoba	http://web6.gov.mb.ca/eFormulary/
Ontario	https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp
Quebec	http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
New Brunswick	http://www.gnb.ca/0212/nbpdpformulary-e.asp
Nova Scotia	http://novascotia.ca/dhw/pharmacare/formulary.asp
Prince Edward Island	http://healthpei.ca/formulary
Newfoundland	http://www.health.gov.nl.ca/health/nlpdp/fmlsearch.asp
Yukon Territories	https://apps.gov.yk.ca/pls/apex40p/f?p=161:9000:4324580815029961:::~:
NIHB (Non-insured Health Benefits) Program	http://www.hc-sc.gc.ca/fniah-spnia/nihb-ssna/provide-fourrir/pharma-prod/med-list/index-eng.php

Appendix C: Restriction Criteria for Triptans in Canada

Province	Criteria
Alberta ⁹²	<p>ALBERTA HEALTH RESTRICTED BENEFIT This product is a benefit for patients 18 to 64 years of age inclusive for the treatment of acute migraine attacks in patients where other standard therapy has failed. (Refer to Criteria for Special Authorization of Select Drug Products of the List for eligibility in patients 65 years of age and older, and Criteria for Special Authorization of Select Drug Products in the Alberta Human Services Drug Benefit Supplement for eligibility in Alberta Human Services clients.)</p> <p>ALBERTA HEALTH SPECIAL AUTHORIZATION (Refer to 28:32.28 of the Alberta Drug Benefit List for coverage of patients 18 to 64 years of age inclusive.) "For the treatment of acute migraine attacks in patients 65 years of age and older where other standard therapy has failed." "For the treatment of acute migraine attacks in patients 65 years of age and older who have been using [the specific triptan] prior to turning 65." "Special authorization for both criteria may be granted for 24 months."</p> <p>In order to comply with the first criteria, information is required regarding previous medications utilized and the patient's response to therapy.</p> <p>The following product(s) are eligible for auto-renewal.</p> <p>ALBERTA HUMAN SERVICES SPECIAL AUTHORIZATION "For the treatment of acute migraine attacks in patients where other standard therapy has failed. Special authorization may be granted for 24 months." Information is required regarding previous medications utilized and the patient's response to therapy. The following product(s) are eligible for auto-renewal.</p>
Saskatchewan ⁹³	<p>For treatment of migraine headaches in patients over 18 years of age. The maximum quantity that can be claimed through the Drug plan is limited to 6 doses per 30 days within a 60-day period</p> <p>Patients requiring more than 12 doses in a consecutive 60-day period should be considered for migraine prophylaxis therapy if they are not already receiving such therapy.</p>

<p>New Brunswick⁹⁴</p>	<p>ALMOTRIPTAN (AXERT) 6.25mg and 12.5mg tablets</p> <p>For the treatment of migraine¹ headache of moderate² intensity when other therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective AND patients have not responded to oral sumatriptan, zolmitriptan, rizatriptan and naratriptan.</p> <p>For the treatment of migraine¹ headache of severe² or ultra severe² intensity when patients have not responded to oral sumatriptan, zolmitriptan, rizatriptan and/or naratriptan.</p> <p>Coverage limited to 6 doses / 30 days³ patients with >3 migraines/month on average despite prophylactic therapy may be considered for up to a maximum of 12 doses / 30 days</p> <p>¹As diagnosed based on current Canadian guidelines. ²Definitions: Moderate - pain is distracting causing need to slow down and limit activities; Severe - pain affects ability to concentrate and very difficult to continue with daily activities; Ultra severe - unable to speak or think clearly; not able to function; likely lying down or sleeping</p> <p>³ Reimbursement will be available for a maximum quantity of triptan doses as outlined in criteria per 30 days regardless of the agent(s) used within the 30 day period.</p> <p><i>Special authorization for the products almotriptan 6.25mg and 12.5mg tablets, naratriptan 1mg and 2.5mg tablets, rizatriptan 5mg and 10mg tablets and wafers, sumatriptan 5mg and 20mg nasal spray and zolmitriptan 2.5mg tablets and orally dispersible tablets, 2.5mg and 5mg nasal spray will be considered as a set. Approvals will include all products in this list, however reimbursement will be available for a maximum quantity of one agent per month.</i></p> <p>NARATRIPTAN, RIZATRIPTAN, SUMATRIPTAN</p> <p>For the treatment of migraine¹ headache when:</p> <p>Migraines are moderate² in severity and other therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective, or Migraine attacks are severe or ultra severe</p> <p>Coverage limited to 6 doses / 30 days³ patients with >3 migraines/month on average despite prophylactic therapy may be considered for up to a maximum of 12 doses / 30 days</p> <p>SUMATRIPTAN (IMITREX NASAL SPRAY) 5mg and 20mg nasal spray</p> <p>For the treatment of migraine¹ headache of moderate² intensity when other therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective AND patients have not responded to oral sumatriptan, zolmitriptan, rizatriptan and naratriptan.</p> <p>For the treatment of migraine¹ headache of severe² or ultra severe² intensity when patients have not responded to oral sumatriptan, zolmitriptan, rizatriptan and/or naratriptan.</p> <p>SUMATRIPTAN (IMITREX INJECTION and generic brand) 6mg injection</p> <p>For the treatment of migraine¹ headache of moderate² intensity when other therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective AND oral and nasal triptans are not appropriate.</p> <p>For the treatment of migraine¹ headache of severe² or ultra severe² intensity when oral and nasal triptans are not appropriate.</p> <p>ZOLMITRIPTAN (ZOMIG NASAL SPRAY) 2.5mg and 5mg nasal spray</p>
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	<p>For the treatment of migraine¹ headache of moderate² intensity when other therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective AND patients have not responded to oral sumatriptan, zolmitriptan, rizatriptan and naratriptan.</p> <p>For the treatment of migraine¹ headache of severe² or ultra severe² intensity when patients have not responded to oral sumatriptan, zolmitriptan, rizatriptan and/or naratriptan.</p>
Nova Scotia⁹⁵	<p>SELECTIVE 5HT1 - RECEPTOR AGONISTS (Almotriptan Tablet, Naratriptan Tablet, Rizatriptan Tablet & Wafer, Sumatriptan Nasal Spray, Zolmitriptan Tablet & Nasal Spray) Sumatriptan 50mg & 100mg Tablet, Naratriptan Tablet, Rizatriptan Tablet & Wafer, Zolmitriptan Tablet - for the treatment of migraine¹ headache when: migraines are moderate in severity and other therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective, or migraine attacks are severe or ultra severe</p> <p>Almotriptan Tablet, Zolmitriptan Nasal Spray, Sumatriptan Nasal Spray for the treatment of migraine headache of moderate intensity when: other therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective AND patients have not responded to oral sumatriptan, zolmitriptan, rizatriptan and naratriptan. for the treatment of migraine headache of severe or ultra severe intensity when patients have not responded to oral sumatriptan, zolmitriptan, rizatriptan, and/or naratriptan.</p> <p>Sumatriptan 6mg/Syringe Injection for the treatment of migraine headache of moderate intensity when: other therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective AND oral and nasal triptans are not appropriate. for the treatment of migraine headache of severe or ultra severe intensity when oral and nasal triptans are not appropriate.</p> <p>NOTE: Coverage limited to 18 doses/3 months - patients with >3 migraines/month on average despite prophylactic therapy may be considered for up to a maximum of 12 doses/30 days</p> <p>1 As diagnosed based on current Canadian guidelines. 2 Definitions: Moderate - pain is distracting causing need to slow down and limit activities; Severe - pain affects ability to concentrate and very difficult to continue with daily activities; Ultra severe - unable to speak or think clearly; not able to function; likely lying down or sleeping. 3 Reimbursement will be available for a maximum quantity of 18 triptan doses per quarter (e.g., Jan to Mar) regardless of the agent(s) used within the 90 day period.</p>

<p>PEI⁹⁶</p>	<p>Almotriptan, tablet, 6.25mg, 12.5mg (Axert-JAN) For the treatment of migraine headaches where other standard therapies, such as oral analgesics have failed AND the patient has not responded to oral Sumatriptan. Coverage is limited to 6 tablets per 30 day period. Anyone requiring more than 6 doses per 30 day period should be considered for migraine prophylaxis therapy if not already receiving such therapy.</p> <p>NaratriptanHCl, tablet, 1mg, 2.5mg (Amerge-GSK) For the treatment of migraine headaches where other standard therapies, such as oral analgesics have failed AND the patient has not responded to oral Sumatriptan. Coverage is limited to 6 tablets per 30 day period. Anyone requiring more than 6 doses per 30 day period should be considered for migraine prophylaxis therapy if they are not already receiving such therapy.</p> <p>Sumatriptan, tablet, 25mg, 50mg, 100mg; nasal spray, 5mg, 20mg; injection 6mg/0.5mL (Imitrex DF-GSK and generics) For the treatment of migraine headaches where other standard therapies, such as oral analgesics have failed. Coverage for the injectable form will only be considered if the tablet and nasal dosage forms are not appropriate. Coverage is limited to 6 tablets or 6 sprays or 6 syringes per 30 day period. Anyone requiring more than 6 doses per 30 day period should be considered for migraine prophylaxis therapy if they are not already receiving such therapy.</p> <p>Zolmitriptan, tablet, 2.5mg (Zomig-AZE) For the treatment of migraine headaches where other standard therapies, such as oral analgesics have failed AND the patient has not responded to oral Sumatriptan. Coverage is limited to 6 tablets per 30 day period. Anyone requiring more than 6 doses per 30 day period should be considered for migraine prophylaxis therapy if they are not already receiving such therapy.</p>
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Newfoundland ⁹⁷	<p>Almotriptan malate (Axert 6.25mg, 12.5mg) For the treatment of migraine headache of moderate intensity when 2 or more therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective AND patients have not responded to oral sumatriptan, oral zolmitriptan, oral rizatriptan and oral naratriptan</p> <p>Naratriptan (Amerge 1mg and 2.5mg tablet & generics), Sumatriptan (Imitrex 50mg, 100mg tablet, Imitrex DF 50mg, 100mg, and generics), Zolmitriptan (Zomig 2.5mg tablet, Rapiment tablets and generics), Rizatriptan (Maxalt 5 and 10mg tablets, 5 and 10mg wafers & generics)</p> <p>Sumatriptan nasal spray (Imitrex 5mg, 20mg nasal spray) For the treatment of migraine headache of moderate intensity when 2 or more therapies (e.g. NSAIDs, acetaminophen, DHE spray) are not effective AND patients have not responded to oral sumatriptan. For the treatment of migraine headache of severe or ultra severe intensity when patients have not responded to oral sumatriptan.</p> <p>Coverage limited to 6 doses / 30 days >6 doses / 30 days considered for patients with >3 migraines/month on average despite prophylactic therapy (up to a maximum of 12 doses / 30 days). As diagnosed based on current Canadian guidelines.</p> <p>Definitions: Moderate -pain is distracting causing need to slow down and limit activities; Severe -pain affects ability to concentrate and very difficult to continue with daily activities; Ultra severe -unable to speak or think clearly, not able to function, likely lying down or sleeping.</p> <p>Reimbursement will be available for a maximum quantity of 6 triptan doses per 30 days regardless of the agent(s) used within the 30 day period</p>
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Appendix D: Ontario EAP Criteria (June 2013)

Information obtained from Ontario Public Drug Programs ⁹⁸

Drug name	Brands reimbursed	Dosage form/strength	Reimbursement criteria	Standard approval duration
Almotriptan	Axert	6mg, 12.5mg tablet	<p>For the treatment of migraines with or without aura in patients who failed adequate trials of other medications for migraines (e.g. acetaminophen, NSAIDs) and where the following information is provided:</p> <p>Details of migraine prophylactic regimens (e.g. amitriptyline, beta-blockers) tried or rationale why they are inappropriate; and</p> <p>The number of attacks, duration, and severity of migraines.</p> <p>Renewal requests may be considered for patients who continue to benefit from treatment.</p> <p>The physician must provide the frequency of triptan use.</p>	5 years
Naratriptan	Amerge	1mg, 2.5 mg tablet		
Rizatriptan	Maxalt Maxalt RPD	5mg, 10mg tablet and wafer		
Sumatriptan	Imitrex	50mg, 100mg tablet		
Sumatriptan	Imitrexinj	12 mg/mL SC injection	<p>For the treatment of migraines with or without aura in patients who failed adequate trials of other medications for migraines (e.g. acetaminophen, NSAIDs) and has documented intolerance* to an oral triptan. The following information must also be provided:</p> <p>Details of migraine prophylactic regimens (e.g. amitriptyline, beta-blockers) tried or rationale why they are inappropriate; and</p> <p>The number of attacks, duration, and severity of migraines.</p> <p>* The nature of intolerance or why oral sumatriptan cannot be used must be specified.</p> <p>Renewal requests for sumatriptan may be considered for patients who continue to benefit from treatment. The physician must provide the frequency of triptan use.</p>	5 years
		Imitrex Nasal Spray		
Zolmitriptan	Zomig ZomigRapimelt	2.5mg tablet 2.5 mg dispersible tablet	<p>For the treatment of migraines with or without aura in patients who have failed an adequate trial of or experienced intolerance to all other oral triptans considered under the Exceptional Access Program.</p> <p>Renewal requests may be considered for patients who continue to benefit from treatment. The physician must provide the frequency of triptan use.</p>	5 years

Appendix E: Interview Questions

How long have you listed triptans in your provincial formulary? How are they listed (e.g., restricted, general benefit)?
Why did you decide to list triptans this way?
What was the basis for this listing (e.g., quantity limits, general listing)?
Do you have any studies comparing usage/costs before and after implementation of this listing?
Have you had any positive/negative feedback?
<ul style="list-style-type: none">• From patients?
<ul style="list-style-type: none">• From healthcare providers?
Why are certain triptans NOT funded?
Do you restrict prescribing to certain specialties (or are certain specialties exempt from restrictions)?

Appendix F: Drug-specific milligram quantity limit

Drug name (strength)	Maximum quantity	Milligram maximum (mg)
Sumatriptan 25 mg	36	900
Sumatriptan50mg	18	900
Sumatriptan100mg	9	900
Sumatriptan nasal spray 20mg	9	180
Sumatriptan nasal spray 5mg	36	180
Sumatriptaninjectable6mg	9	54
Naratriptan1mg	25	25
Naratriptan2.5mg	10	25
Zolmitriptan2.5mg	18	45
Zolmitriptan5mg	9	45
Rizatriptan5mg	24	120
Rizatriptan10mg	12	120
Almotriptan6.25mg	24	150
Almotriptan12.5mg	12	150

From Hoffman et al ³⁶